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(71) Applicant: **ABBVIE INC.** [US/US]; 1 North Waukegan Road, North Chicago, Illinois 60064 (US).

(72) Inventors: **QIU, Yihong**; 1634 Lake Charles Drive, Vernon Hills, Illinois 60061 (US). **ZHOU, Deliang**; 271 Congressional Court, Vernon Hills, Illinois 60061 (US). **SHEBLEY, Mohamad**; 7606 Cascade Way, Gurnee, Illinois 60031 (US). **NG, Juki Wing-Keung**; 1661 Cavell Avenue, Highland Park, Illinois 60035 (US). **MOHAMED, Ahmed**; 31218 Prairie Ridge Road, Libertyville, Illinois 60048 (US). **HAN, Jian-Hwa**; 1012 Creek View Drive, Vernon Hills, Illinois 60061 (US). **METZGER, David**; 6325 58th Avenue, Kenosha, Wisconsin 53142 (US). **RUGGLES, Alexander**; 175 Washington Circle, Lake Forest, Illinois 60045 (US). **ZU, Hui**; 996 Green Meadow Avenue, Vernon Hills, Illinois 60060 (US). **SHAO, Xi**; 39746 North Environ Circle, Lake Bluff, Illinois 60044 (US). **GONG, Yuchuan**; 1600 Cypress Pointe Drive, Vernon Hills, Illinois 60061 (US). **CHEN, Yisheng**; 1 Guangxing Lu, NETDA Nantong, Jiangsu 226009 (CN). **GONG, Jian**; 1 Guangxing Lu, NETDA Nantong, Jiangsu 226009 (CN). **LI, Min**; 1 Guangxing Lu, NETDA Nantong, Jiangsu 226009 (CN).

(74) Agent: **AHMED, Aamer** et al.; 1 North Waukegan Road, North Chicago, Illinois 60064 (US).

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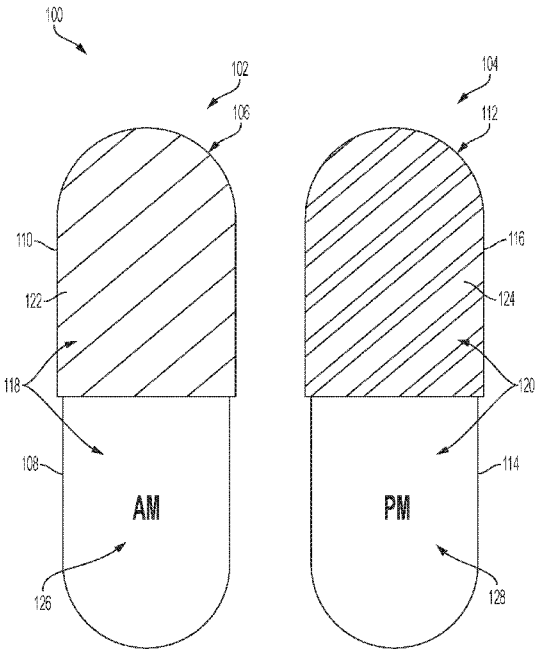

FIG. 1

(57) Abstract: A multi-drug delivery system includes a first capsule including a first capsule body that includes a first interior, and a first tablet and a second tablet within the first interior. The first tablet includes a first drug, and the second tablet includes at least a second drug different from the first drug. The first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient. The system also includes a second capsule including a second capsule body that includes a second interior, and a third tablet within the second interior. The third tablet includes the first drug.

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SYSTEM AND METHOD OF MULTI-DRUG DELIVERY

BACKGROUND

[1] The field of the present disclosure relates generally to medicinal products and, more specifically, to a drug dosage form that enables simultaneous, immediate release of more than one drug enclosed within a capsule upon ingestion by a patient, and a delivery system for the drug dosage that ensures compliance with intake instructions by the patient.

[2] Oral administration of medicaments such as drugs, supplements, and other nutritional or therapeutic agents is typically done with tablet and capsule dosage forms. A capsule generally includes a hollow shell having an interior for storing powder or liquid-based drugs therein, and a tablet may be fabricated from a compressed powder of the medicinal substance. For at least some known ailments, it may be beneficial to administer more than one type of medicament to the patient. As such, tablets and capsules may be fabricated to enable administration or intake of two or more drugs to the patient in a single dose or single dosage form. For example, at least some known capsules contain a mixture of drugs in liquid or powder form within the interior of the hollow shell. In addition, at least some known tablets include a first drug encapsulated within a second drug. However, encapsulating the first drug within the second drug may hinder dissolution of the first drug, and may reduce the dissolution of the first and second drugs. In addition, drugs administered in powder or liquid form may dissolve at a rate unsuitable for a desired efficacy.

[3] In addition, many known prescription medicines have complicated instructions and dosing regimens. For example, some prescriptions require the oral administration of multiple drug forms containing different types of drugs and/or require administration at different times in the day. Other medicines are to be taken in the morning, afternoon, or evening, some with or without food, some

with or without certain types of food, and in particular quantities. As such, it may be difficult for a patient to remember and comply with the administration instructions for a drug or a group of drugs. Failure to comply with such administration instructions can result in suboptimal efficacy.

SUMMARY

[4] In one aspect, a multi-drug delivery system is provided. The system includes a first capsule including a first capsule body having a first interior, and a first tablet and a second tablet included within the first interior. The first tablet includes a first drug, and the second tablet includes at least a second drug different from the first drug. For example, the second tablet may include a second and third drug, each of which are different from the first drug and each other. The first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient. The system also includes a second capsule, co-packaged with the first capsule, including a second capsule body having a second interior, and a third tablet included within the second interior. The third tablet may include either the first drug, the second drug and/or one or more other drugs. At least 75%±10% of the first drug in the first tablet dissolves after 60 minutes and at least 70%±10% or 70%±20% or 70%±30% or 70%±40% of the second and third drugs in the second tablet dissolve after 30 minutes when using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C.

[5] In some embodiments, the first tablet may include a gonadotropin-releasing hormone antagonist. For example, the first tablet may include elagolix, relugolix, another gonadotropin-releasing hormone antagonist and/or a combination of gonadotropin-releasing hormone antagonists. In some embodiments, the first tablet may include elagolix.

[6] In some embodiments, the first tablet may include between about 175 mg to about 325 mg of the gonadotropin-releasing hormone antagonist and

the second tablet may include between about 0.75 mg and about 1.25 mg of estradiol; the second tablet may further include between about 0.1 mg and about 1 mg of norethindrone acetate; after about 15 minutes, the release of estradiol is equal to or greater than 70%±10% or 70%±20% or 70%±30% or 70%±40%.

[7] In some examples, the first capsule may be marked with a first identifier and the second capsule may be marked with a second identifier different from the first identifier such that the first capsule and the second capsule are visually distinguishable; the first identifier may be configured to indicate the first capsule is intended for administration within a first time window in the day, and the second identifier may be configured to indicate the second capsule is intended for administration within a second time window in the day different from the first time window. In some examples, the first identifier may be configured to indicate the first capsule is intended for administration at the first time window that is before noon, and the second identifier may be configured to indicate the second capsule is intended for administration at the second time window that is after noon; the first identifier may be a first color included on the first capsule, and the second identifier may be a second color included on the second capsule.

[8] In some examples, the system may include a package having a plurality of compartments configured to house the first capsule and the second capsule. The package may include a blister card that defines the plurality of compartments, wherein the first capsule and the second capsule housed in the plurality of compartments are accessible by puncturing a seal in the blister card; the package may have information printed thereon related to when to administer the first capsule and the second capsule to the patient; the blister card may have a first row of the plurality of compartments and a second row of the plurality of compartments, wherein the first capsule is housed in the first row, wherein the second capsule is housed in the second row, and wherein the first row and the second row are visually distinct.

[9] In another aspect, a capsule for use in delivering drugs to a patient is provided. The capsule includes a capsule body having an interior, and at least one first tablet and a second tablet included within the interior. The at least one first tablet includes a first drug, and the second tablet includes at least a second drug different from the first drug. The at least one first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule body within the patient.

[10] In some embodiments, the first tablet may include between about 175 mg and about 325 mg of a gonadotropin-releasing hormone antagonist, such as elagolix, and the second tablet comprises between about 0.75 mg and about 1.25 mg of estradiol; the second tablet may further comprise between about 0.1 mg and about 1.0 mg of norethindrone acetate. In some examples, wherein after 16 minutes, the release of estradiol is equal to or greater than 70%±10% or 70%±20% or 70%±30% or 70%±40%; the capsule body may be oblong to define a longitudinal axis, wherein the at least one first tablet and the second tablet are arranged in a serial relationship along the longitudinal axis within the interior; the at least one first tablet and the second tablet may be distinct tablets that have been formed separately from each other and then secured within the interior; the capsule body may not contain drugs in powder form; the capsule body may not include a barrier extending between the first tablet and the second tablet, and wherein the first tablet and the second tablet are not bonded together within the interior; the first capsule may include gelatin.

[11] In yet another aspect, a method of delivering drugs to a patient is provided. The method includes delivering a first capsule to the patient, wherein the first capsule includes a first capsule body having a first interior, and a first tablet and a second tablet included within the first interior. The first tablet includes a first drug, and the second tablet includes at least a second drug different from the first drug. The first tablet and the second tablet are configured for

simultaneous release upon dissolution of the first capsule body within a patient. The method also includes delivering a second capsule, which is co-packaged with the first capsule, to the patient after a predetermined amount of time has elapsed after administration of the first capsule. The second capsule includes a second capsule body having a second interior, and a third tablet included within the second interior. The third tablet includes the first drug.

[12] In some embodiments, the first tablet comprises the first tablet comprises between about 175 and 325 mg of gonadotropin-releasing hormone antagonist and the second tablet comprises between about 0.75 mg and 1.25 mg of estradiol and between about 0.1 mg and 1.0 mg of norethindrone; after 20 minutes, the release of estradiol is equal to or greater than 70%±10% or 70%±20% or 70%±30% or 70%±40%; delivering a second capsule includes delivering the second capsule at least 5 hours after administration of the first capsule; includes providing a package comprising a plurality of compartments configured to house the first capsule and the second capsule therein; and/or further includes housing a plurality of first capsules and a plurality of second capsules within the package, such that the number of first capsules and the number of second capsules housed within the package are each a multiple of the number of days in a week.

[13] In some embodiments, a multi-drug tablet includes a first tablet and a second tablet coated on the first tablet; the second tablet may be positioned in the center of the first tablet; and/or the multi-tablet includes crospovidone.

[14] In some embodiments, a medication container assembly includes a first set of a plurality of compartments each compartment configured to support a first capsule; a second set of a plurality of compartments each compartment configured to support a second capsule; wherein, the first capsule comprises a first interior; a first tablet within the first interior, the first tablet comprising a first drug; and a second tablet within the first interior, the second tablet comprising at

least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient; and the second capsule comprises a second capsule body comprising a second interior; and a third tablet within the second interior, the third tablet comprising the at least one drug selected from the group consisting of: the first drug, the second drug, or a third drug.

[15] In some embodiments, a multi-drug capsule includes a first tablet, the first tablet comprising a first drug; a second tablet co-packaged with the first tablet and, the second tablet comprising at least a second drug different from the first drug; and a third drug different from the first and second drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule within a patient; wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75%±10% of the first drug in the first tablet dissolves after 60 minutes and at least 70%±10% or 70%±20% or 70%±30% or 70%±40% of the second and third drugs in the second tablet dissolve after 30 minutes.

[16] In some embodiments, a multi-drug capsule includes a first tablet, the first tablet comprising a first drug; a second tablet co-packaged with the first tablet and, the second tablet comprising at least a second drug different from the first drug; and a third drug different from the first and second drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule within a patient; wherein using USP apparatus 1 at 100 rpm, pH 6.8, and 37.5±0.5°C, at least 75%±10% of the first drug in the first tablet dissolves after 45 minutes and at least 90%±10% or 90%±20% or 90%±30% or 90%±40% of the second and third drugs in the second tablet dissolve after 30 minutes.

[17] In some examples, the first tablet comprises elagolix, the first tablet has between about 175 mg to about 325 mg of elagolix and the second tablet has between about 0.75 mg and about 1.25 mg of estradiol.

[18] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and following administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration (Cmax) for said elagolix of about 1218.4 ng/mL to about 2185 ng/mL; a mean peak concentration (Cmax) for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL; a mean peak concentration (Cmax) for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL; a mean Area Under the Curve ($AUC_{(t)}$) for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve ($AUC_{(t)}$) for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve ($AUC_{(t)}$) for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[19] In another aspect, a multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/ml to about 2185 ng/mL; a mean peak concentration, Cmax for said estradiol of about 0.0424 ng/ml to about 0.0775 ng/ml; and a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng/ml to about 8.0 ng/ml.

[20] In one example, the multi-drug composition has a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3296.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[21] In one aspect, multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and administration of a single dose of the composition to healthy adult subjects results in a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[22] In one example, administration of the multi-drug capsule to healthy adult subjects results in a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/mL to about 2185 ng.hr/mL; a mean peak concentration, Cmax for said estradiol of about 0.0424 ng.hr/mL to about 0.0775 ng/mL ng/ml; and a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng.hr/mL to about 8.0 ng/ml.

[23] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes. In another aspect, a method of safely treating heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in a pre-menopausal female patient is provided. The method comprising once daily oral administration to said patient of: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate, wherein said method results in a mean Cmax for said elagolix of about 1218.4 ng.hr/mL to about 2185 ng/mL; for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL; for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL, and a mean $AUC_{(t)}$ for said elagolix of about 3293.6ng.hr/mL to about 5892.5 ng.hr/mL; for

said estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL, and wherein, after a treatment duration of about 6 months, said patient achieves equal to or greater than about 2 g/dL increase in hemoglobin as compared to baseline where the patient did not receive elagolix, estradiol, and norethindrone.

[24] In another aspect, an oral capsule for use in delivering drugs to a patient comprises: a capsule body comprising an interior; a first tablet within the interior, the at least one first tablet comprising a first drug; and a second tablet within the interior, the second tablet comprising at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule body within the patient, wherein using USP apparatus 1 at 100 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 45 minutes and at least 90% of the second and third drugs in the second tablet dissolve after 30 minutes.

[25] In another aspect, an oral multi-drug capsule composition is provided that is bioequivalent to any of the foregoing compositions.

[26] In another aspect, a method of delivering co-packaged drugs to a patient for oral use is provided. The method comprises delivering a first capsule to the patient, wherein the first capsule includes: a first capsule body including a first interior; a first tablet within the first interior, the first tablet including a first drug; and a second tablet within the first interior, the second tablet including at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within the patient; and delivering a second capsule, co-packaged with the first capsule, to the patient after a predetermined amount of time has elapsed after administration of the first capsule, wherein the second capsule includes: a second capsule body including a second interior; and a third tablet within the second interior, the third tablet including the first drug.

BRIEF DESCRIPTION OF THE DRAWINGS

[27] FIG. 1 is an illustration of an example multi-drug delivery system that includes a first capsule and a second capsule of drugs.

[28] FIG. 2 is an internal view of an example capsule housing two tablets.

[29] FIG. 3 is an internal view of an example capsule housing a single tablet.

[30] FIG. 4A is an internal view of a first example multi-drug tablet having a first tablet encapsulating a second tablet.

[31] FIG. 4B is an internal view of a second example multi-drug tablet having a first tablet encapsulating a second tablet.

[32] FIG. 5 is internal view of a third example multi-drug tablet having a bilayer, the bilayer having a first layer of a first drug and a second layer of a second and third drug.

[33] FIG. 6 is an internal view of a fourth example multi-drug tablet having a first tablet coated with a mixture of a third and fourth drug.

[34] FIG. 7 internal view of a fifth example multi-drug tablet having a bilayer, the bilayer having a first layer of a first drug and a second layer of an embedded tablet.

[35] FIG. 8 is an internal view of an example capsule according to FIG. 1 having a first tablet, and four mini-tablets.

[36] FIG. 9 is an internal view of an example capsule according to FIG. 1 containing melt granules and a tablet.

[37] FIG. 10 is a flow chart showing Process of Examples 1 E2/NETA tablet-in-elagolix tablet and Example 2 E2/NETA tablet embedded on the surface of elagolix tablet.

[38] FIG. 11A is a flow chart showing Process of Example 3-1: bilayer tablet E2/NETA layer: fluid-bed granulation, spraying API solution onto lactose.

[39] FIG. 11B is a flow chart showing the process of Example 3-2: bilayer tablet E2/NETA layer: fluid-bed granulation, spraying binder onto API mixture.

[40] FIG. 11C is a flow chart showing the process of Example 3-3: bilayer tablet, direct blend of E2/NETA layer, with disintegrant.

[41] FIG. 11D is a flow chart showing the process of Example 3-4: bilayer tablet, direct blend of E2/NETA layer without disintegrant.

[42] FIG. 12 is a flow chart showing the process of Example 4: Coating of elagolix core tablet with solution of E2/NETA.

[43] FIG. 13 is a flow chart showing the process of Example 5: bilayer tablet, E2/NETA embedded in the placebo layer.

[44] FIG. 14 is a flow chart showing the process of Example 6: Elagolix tablet and E2/NETA tablet in a capsule.

[45] FIG. 15 is a flow chart showing the process of Example 7: minitablets of elagolix and one E2/NETA tablet in a capsule.

[46] FIG. 16 is a flow chart showing the process of Example 8: elagolix granules and one E2/NETA tablet filled in a capsule.

[47] FIG. 17 is a perspective view of an example package that may be used to house and transport the multi-drug delivery system shown in FIG. 1.

[48] FIG. 18 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 4A and Example 1.

[49] FIG. 19 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 4B and Example 2.

[50] FIG. 20A is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 5 and Example 3-1.

[51] FIG. 20B is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 5 and Example 3-2.

[52] FIG. 20C is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 5 and Example 3-3.

[53] FIG. 20D is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 5 and Example 3-4

[54] FIG. 21 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 6 and Example 4

[55] FIG. 22 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 7 and Example 5.

[56] FIG. 23 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the capsule shown in FIG. 2 and Example 6.

[57] FIG. 24 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the capsule shown in FIG. 8 and Example 7.

[58] FIG. 25 is a diagram illustrating the dissolution rates of drugs administered according to various embodiments of the present disclosure, and according to the capsule shown in 9 and Example 8.

[59] FIG. 26 is a graphical representation of the percent change from baseline in lumbar spine bone mineral density (BMD) in Women with Uterine Fibroids who received 12 months of the System described in Example 10 and had follow-up BMD 12 months off therapy in studies UF-1, UF-2, UF-3.

[60] FIG. 27 is a graphical representation of monthly change from Baseline in MBL Volume in Women with Uterine Fibroids in the UF-1 study.

[61] FIG. 28 is a graphical representation of monthly change from Baseline in MBL Volume in Women with Uterine Fibroids in the UF-2 study.

[62] FIG. 29A is a diagram illustrating the dissolution rates of elagolix administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 6 using USP apparatus 1.

[63] FIG. 29B is a diagram illustrating the dissolution rates of E2 administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 6 using USP apparatus 1.

[64] FIG. 29C is a diagram illustrating the dissolution rates of NETA administered according to various embodiments of the present disclosure, and according to the multi-drug tablet shown in FIG. 6 using USP apparatus 1.

DETAILED DESCRIPTION

[65] The following detailed description illustrates the disclosure by way of example and not by way of limitation. The description enables one skilled in the art to make and use the disclosure, describes several embodiments, adaptations, variations, alternatives, and use of the disclosure.

[66] Embodiments of the present disclosure relate to a drug dosage form that enables substantially simultaneous, immediate release of more than one drug enclosed within a capsule upon administration by a patient, and a delivery system for the dosage that facilitates compliance of administration instructions by a patient. The drug delivery system includes a first capsule and also may include a second capsule intended to be administered within different and non-overlapping time windows in the day. For example, in one embodiment, the first capsule is intended to be administered during morning hours (e.g., before noon), and the second capsule is intended to be administered at least 5 hours after administration of the first capsule (e.g., during the afternoon or evening hours). The first capsule and the second capsule may contain different drugs, or combinations of drugs, and may be marked with identifiers that facilitate compliance with the administration instructions of a prescription, for example. The surfaces of the first capsule and the second capsule may have distinct identifying colors and/or surface characteristics. The first capsule and the second capsule may also include symbolic and/or textual markings that indicate in which time window the respective capsule should be administered. In addition, a plurality of first capsules and a plurality of second capsules may be housed in a package that includes symbolic and/or textual markings that likewise indicate in which time window the respective capsules should be administered. Thus, the first capsule

and the second capsule are conspicuously and prominently marked or marked and arranged to enable the patient to easily distinguish the capsules.

[67] In some embodiments, the system co-packages multiple capsules and may include a single capsule containing two or more different drugs, for example, a first tablet containing a first drug and a second tablet containing a second and third drug. In some examples, the first drug may be elagolix or other gonadotropin-releasing hormone (GnRH) releasing antagonists. Oral dosage size is an important component for patient compliance. Larger oral dose sizes create a reluctance for patients to comply with dosing recommendations. In one embodiment, the first capsule contains at least two distinct tablets, with the first tablet including a first drug and the second tablet including a second drug and a third drug different from the first drug. The first, second, and third drugs have different efficacies and, in the example embodiment, the second and third drugs are included in the capsule to at least partially counteract the undesirable adverse effects of the first drug on the patient. As such, the first and second tablets are formed separately from each other and then secured within the first capsule to facilitate simultaneous, immediate release of the drugs in the first tablet and the second tablet upon dissolution of the outer shell of the capsule within the patient. That is, securing the distinct tablets within the capsule enables the tablets to dissolve simultaneously to result in a desirable bioavailability for a patient. Thus, the dosage form provided by the first capsule facilitates desirable dissolution of the drugs and bioavailability within the patient.

[68] As used herein, a bioequivalent composition or formulation is one that is bioequivalent as defined by the U.S. Food and Drug Administration (FDA).

[69] Furthermore, co-administration of the tablets in a capsule may provide a presentation that is easy for a patient to swallow and simpler to manufacture. In addition, the presentation allows the co-administration of the first, second, and third drugs. This co-administration allows for the desired balance

between the therapeutic effect and safety of the first drug in the first tablet with at least the second drug or the third drug in the second tablet. As such, the co-administration of the first drug in the first tablet and the second and third drugs in the second tablet facilitates potential reduction of the undesired effects of the first drug. In one example, the first drug in the first tablet may be elagolix or another GnRH antagonist, and the second and third drugs in the second tablet may be a combination of estradiol (E2) and norethindrone (NETA) (e.g. Activella® tablet). Thus, the E2/NETA facilitate the add-back therapy that counters certain undesirable impact of hormone regulation that is caused by the exogenous introduction of a GnRH antagonist, such as elagolix, relugolix and the like.

[70] In any of the various aspects of the present disclosure, the first drug may suitably be a GnRH antagonist, such as elagolix, and/or relugolix, the second drug may suitably be estradiol, and the third drug may suitably be norethindrone acetate. Elagolix is commonly available as elagolix sodium. For these particular drugs, it is important that a delivery mechanism be used that facilitates achieving improved and desirable dissolution of the drugs and desirable bioavailability within the patient. For example, it has been found that the dissolution of the drugs is likely increased when the drugs are administered in powder form or likely decreased when the drugs are in an embedded multi-drug tablet form having a first tablet embedded within a second tablet. When in powder form, the dissolution rate of the drugs and resulting bioavailability within the patient may be undesirably high and therefore may not be ideal for dosing under certain conditions. When in the embedded multi-drug tablet form, it has been found that the drugs in the first and second tablets do not dissolve together as a result of the second tablet slowing down the release of the drug in the first tablet.

[71] The total amount of elagolix contained in the first capsule or the second capsule may suitably be the free acid equivalent of elagolix, administered as a sodium salt. The free acid equivalent of elagolix may be provided as 100

milligrams (mg), 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 450 mg, or 500 mg, and ranges constructed therefrom, such as about 100 mg to about 500 mg, about 150 mg to about 400 mg, and about 175 mg to about 325 mg. The total amount of estradiol contained in the first capsule may suitably be 0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg, or 1.5 mg, and ranges constructed therefrom, such as about 0.5 mg to about 1.5 mg, about 0.5 mg to about 1.25 mg, about 0.75 mg to about 1.5 mg, or about 0.75 mg to about 1.25 mg. The total amount of base equivalent of norethindrone, available as norethindrone acetate that is contained in the first capsule may suitably be 0.05 mg, 0.1 mg, 0.25 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.75 mg, or 1.0 mg, and ranges constructed therefrom, such as about 0.1 mg to about 1.0 mg, about 0.25 mg to about 0.75 mg, or about 0.4 mg to about 0.6 mg.

[72] Tablets within the scope of the present disclosure comprise the active drug and one or more excipients, including but not limited to, binders, fillers, disintegrants, surfactants, efficacy/bioavailability enhancing agents, glidants, and lubricants.

[73] Binders promote the bonding and cohesiveness of granules and tablets and function to improve hardness. Some non-limiting examples of binders include: pregelatinized starch, hydroxypropyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, copovidone, povidone, crospovidone, and combinations. Other examples include polyethylene glycol, polyvinyl pyrrolidone, and polyvinyl alcohols. In some aspects, the binder is copovidone, povidone, HMP, pregelatinized starch, and combinations thereof. In some further aspects, the binder is copovidone.

[74] Fillers that may be used, include non-limiting examples such as sugars and sugar alcohols, cellulosics, and other fillers. Non-limiting examples of suitable sugars and sugar alcohols include dextrates, dextrin, dextrose, lactose, maltodextrin, mannitol, isomalt, sorbitol, sucrose, sugars spheres, xylitol, fructose, lactitol, erythritol, maltitol, xylose, glucose, mannose, galactose, maltose,

cellobiose, trehalose and raffinose. Non-limiting examples of cellulosics include microcrystalline cellulose ("MCC") and silicified MCC. Non-limiting examples of other fillers include calcium carbonate, calcium sulphate, calcium silicate, chitin, chitosan, dibasic calcium phosphate dihydrate, glyceryl palmitostearate, hydrogenated vegetable oil, kaolin, magnesium aluminum silicate, magnesium carbonate, magnesium oxide, polymethacrylates, potassium chloride, powdered cellulose, pregelatinized starch, sodium chloride, starch, talc, and di- and tri-basic calcium phosphate. Combinations of the above-listed fillers are within the scope of the present disclosure.

[75] Disintegrants that may be used include, non-limiting examples such as modified starches such as sodium carboxymethyl starch (sodium starch glycolate); cross-linked polyvinylpyrrolidones such as crospovidone; modified celluloses such as croscarmellose sodium; cross-linked alginic acid; gums such as gellan gum and xanthan gum; calcium silicate; and combinations thereof.

[76] Surfactants may function to increase the concentration of the drug in the diffusion layer formed at the interface of the drug surface and the aqueous medium after administration and/or increase wettability of the drug/formulation. Non-limiting examples of surfactants include, vitamin E d-alpha tocopheryl polyethyleneglycol succinate, sodium dodecyl sulfate, polysorbate, poloxamer, Tween® type, and combinations thereof.

[77] Lubricants that may be used include, non-limiting examples such magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oils, polyethylene glycol (4000-6000), sodium lauryl sulfate, and combinations thereof.

[78] Glidants that may be used include, non-limiting examples such colloidal silicon dioxide (e.g., highly dispersed silica (Aerosil®)), animal or vegetable fats, waxes, and combinations thereof.

[79] Other excipients may be present include an acidifying agent or an alkalizing agent. Acidifying agents may be organic acids for pH adjustment and/or control after administration, such as, for instance and without limitation, fumaric acid, citric acid, and tartaric acid.

[80] Selection of excipients and weight/weight concentrations or active to excipient ratios thereof in tablets may be made to increase drug solubility in an aqueous medium (e.g., the stomach and/or intestine) and thereby improve dissolution rate and bioavailability. Further, in the case of co-administration of a first tablet having a first drug and a second tablet having a second drug, selection of excipients and weight over weight concentrations or active to excipient ratios thereof may be made to both increase drug bioavailability and minimize any interaction between the first and second tablets that could adversely affect bioavailability of either drug.

[81] Tablets of the present disclosure may be formed utilizing pharmaceutical operations, such as, but not limited to, screening, blending, dry granulation, compression, and optional film coating. In some aspects, the excipient may be blended, the blend may be roller compacted and milled, and the resulting material may be tableted by compression in tableting equipment known in the art. In some such aspects, the roller compacted, and milled material may be termed “intragranular” and said material may then be blended with one or more additional excipients described above prior to tableting. The one or more additional excipients would be present as an “extragranular” component in the tablet.

[82] The uncoated tablets of the present disclosure (e.g., tablet cores) may be optionally coated with a film-coating to provide for tablets that are predominantly tasteless and odorless and are easy to swallow. Further, film coating prevents dust formation during packaging and ensures robustness during transportation. Commercial coating compositions are suitable for purposes of the

present disclosure and include, without limitation, Opadry® YS-1-7003, Opadry® YS-1-18202, and Opadry® II White 85F18422.

[83] Tablets containing elagolix sodium are commercially available as Orilissa®. Manufacturing of different strengths of elagolix is described in AbbVie Inc's applications US201900540088 and US 20190054027, both of which are incorporated in its entirety by reference. Other manufacturers also provide various manufacturing of elagolix active ingredient and elagolix containing drug product, as described in applications WO2017/221144, WO2018/189213, and WO2018/224063. Tablets containing varying strengths of E2/NETA are commercially available as Activella®.

[84] Referring now to the drawings, FIG. 1 is an illustration of an example multi-drug delivery system 100 that includes a first capsule 102 and a second capsule 104 of drugs. First capsule 102 includes a first capsule body 106 including a first body portion 108 and a first cap portion 110, and second capsule 104 includes a second capsule body 112 including a second body portion 114 and a second cap portion 116. In the example embodiment, first capsule 102 is marked with a first identifier 118, and second capsule 104 is marked with a second identifier 120 that is different from first identifier 118 to facilitate rendering first capsule 102 and second capsule 104 visually distinguishable from each other to a patient. First capsule 102 and second capsule 104 may include any suitable identifier that enables multi-drug delivery system 100 to function as described herein. The identifier may include, but is not limited to, shading, coloring, a symbolic marking, and/or a textual marking.

[85] For example, in the example embodiment, a first color 122 (as illustrated by a first pattern) is included on first capsule 102, and a second color 124 (as illustrated by a second pattern) is included on second capsule 104. More specifically, first cap portion 110 is first color 122 and second cap portion 116 is second color 124. First color 122 is different from second color 124. Thus, first

cap portion 110 is visually distinguishable from first body portion 108, second body portion 114, and second cap portion 116, and second cap portion 116 is visually distinguishable from first body portion 108, first cap portion 110, and second body portion 114.

[86] First identifier 118 and second identifier 120 may also be configured to indicate when a respective capsule is intended to be administered. For example, in the example embodiment, first identifier 118 includes a first textual marking 126 and second identifier 120 includes a second textual marking 128. First textual marking 126 is configured to indicate that first capsule 102 is intended for administration within a first time window in the day, and second textual marking 128 is configured to indicate that second capsule 104 is intended for administration within a second time window in the day that is different from the first time window. More specifically, first textual marking 126 ("AM") indicates that first capsule 102 is intended for administration before noon, and second textual marking 128 ("PM") indicates that second capsule 104 is intended for administration after noon. As will be described in more detail below, first capsule 102 and second capsule 104 may contain different types of drugs. As such, first textual marking 126 and second textual marking 128 facilitate quick and easy identification of the capsules and compliance with administration instructions.

[87] FIG. 2 is a cross-sectional views of examples of first capsule 102 that may be used in multi-drug delivery system 100 (shown in FIG. 1), and FIG. 8 is a cross-sectional view of an additional first capsule 102 that may be used in multi-drug delivery system 100.

[88] FIG. 3 is a cross-sectional view of an example second capsule 104 that may be used in multi-drug delivery system 100 (shown in FIG. 1). In the example embodiment, second capsule body 112 includes a second interior 140 sized to receive at least one first tablet 132 therein. While illustrated as housing a single first tablet 132, it should be understood that any number of first tablets 132

may be included within second interior 140 that enables multi-drug delivery system 100 to function as described herein. Second capsule body 112 includes second body portion 114 and second cap portion 116. Second body portion 114 includes an open end 142 sized to enable insertion of first tablet 132 therethrough. After insertion of first tablet 132 into second body portion 114, second cap portion 116 may be engaged with second body portion 114 to enclose open end 142, and to define and seal second interior 140.

[89] First capsule body 106 (shown in FIGS. 2 and 3) and second capsule body 112 may be fabricated from any material that enables multi-drug delivery system 100 to function as described herein. Example capsule body materials include, but are not limited to, gelatin (in the form of hard gelatin capsules or soft elastic gelatin capsules), starch, carrageenan and hydroxypropylmethylcellulose. First capsule body 106 and second capsule body 112 can additionally be prepared with coatings that ease swallowing, provide a taste barrier, or provide other functions.

[90] As described above, first capsule 102 and second capsule 104 may each contain a different drug, or a different combination of drugs, such that first capsule 102 and second capsule 104 are intended for administration at different times of the day. As such, second capsule 104 only contains first tablet 132 therein, and does not contain second tablet 134 therein.

[91] FIG. 17 is a perspective view of an example package 144 that may be used to house and transport multi-drug delivery system 100 (shown in FIG. 1). In the example embodiment, package 144 includes a carton 146, and a blister card 148 positioned within carton 146. Carton 146 includes a first wall 150 having an access opening 152 defined therein. Access opening 152 is sized to provide access to blister card 148 and, more specifically, to a plurality of compartments 154 of blister card 148 that are each configured to house an individual first capsule 102 or second capsule 104 therein. As such, a plurality of first capsules

102 and a plurality of second capsules 104 are housed within package 144. In one embodiment, the number of first capsules 102 and the number of second capsules 104 housed within package 144 in compartments 154 are each a multiple of the number of days in a week (e.g., 7, 14, or 21), and each compartment 154, or groupings of compartments 154, are labeled according to respective days of the week. In addition, first wall 150 includes informational markings 156 thereon that may be either symbolic or textual markings to easily distinguish the capsules 102 and 104 from each other. Informational markings 156 are printed on package 144 and include information related to when to administer first capsule 102 and second capsule 104 to the patient. As such, including compartments 154 as a multiple of the number of days in the week in package 144, and including informational markings 156 on first wall 150, facilitates compliance of administration instructions by a patient.

[92] The invention further provides a multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix which is administered twice daily; (b) 1 mg of estradiol which is administered once daily; and (c) 0.5 mg of norethindrone acetate which is administered once daily. Table A7, provides the mean peak concentration Cmax and mean Area Under the Curve AUC(t) for this formulation when the composition is administered to healthy volunteers. The invention further includes the mean peak concentration Cmax and the mean Area Under the Curve, AUC_T that is 80%-125% of the Cmax or AUC_T provided in Table A7. Therefore, mean peak concentration, Cmax for said elagolix is about 80% to about 125% of 1200±45% ng/mL or about 528-2175 ng/mL The mean peak concentration, Cmax for said estradiol is about 80% to about 125% of 0.06±52% ng/ml or 0.023-0.114 ng/mL The mean peak concentration, Cmax for said norethindrone acetate is about 80% to about 125% of 6.1±35% ng/ml or 3.172-10.294 ng/mL. Moreover, the mean Area Under the Curve, AUC_T for said elagolix is about 80% to about 125% of 2826±44% ng.hr/mL or 1266.0-5086.8 ng.hr/mL. The mean Area Under the Curve, AUC_T for said estradiol is about 80% to about

125% of 0.86±38% ng.hr/mL or 0.4266-1.4835 ng.hr/mL. The mean Area Under the Curve, AUC_T for said norethindrone acetate is about 80% to about 125% of 23.8±48% ng.hr/mL or 9.90-44.03 ng.hr/mL.

[93] The invention further provides a multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix which is administered twice daily; (b) 1 mg of estradiol which is administered once daily; and (c) 0.5 mg of norethindrone acetate which is administered once daily. Table A7, provides the mean peak concentration Cmax and mean Area Under the Curve AUC (t) for this formulation when the composition is administered to healthy volunteers. The invention further includes the mean peak concentration Cmax and the mean Area Under the Curve, AUC_T that is 80%-125% of the Cmax AUC_T provided in Table A7. Therefore, mean peak concentration, Cmax for said elagolix is about 80% to about 125% of 1200 ng/mL or about 960-1500 ng/mL The mean peak concentration, Cmax for said estradiol is about 80% to about 125% of 0.06 ng/ml or 0.048-0.075 ng/mL The mean peak concentration, Cmax for said norethindrone acetate is about 80% to about 125% of 6.1 ng/ml or 4.88-7.625 ng/mL. Moreover, the mean Area Under the Curve, AUC_T for said elagolix is about 80% to about 125% of 2826 ng.hr/mL or 2260.8-3532.5 ng.hr/mL. The mean Area Under the Curve, AUC_T for said estradiol is about 80% to about 125% of 0.86 ng.hr/mL or 0.688-1.075 ng.hr/mL. The mean Area Under the Curve, AUC_T for said norethindrone acetate is about 80% to about 125% of 23.8 ng.hr/mL or 19.04-29.75 ng.hr/mL.

[94] The invention further provides a multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix which is administered twice daily; (b) 1 mg of estradiol which is administered once daily; and (c) 0.5 mg of norethindrone acetate which is administered once daily. Table A7, provides the mean peak concentration Cmax and mean Area Under the Curve AUC (t) for this formulation when the composition is administered to healthy volunteers. The

invention further includes the mean peak concentration Cmax and the mean Area Under the Curve, AUC_T that is 80%-125% of the Cmax AUC_T provided in Table A7. Therefore, mean peak concentration, Cmax for said elagolix is about 80% to about 125% of 629-1770 ng/mL or about 503-2212.5 ng/mL. The mean peak concentration, Cmax for said estradiol is about 80% to about 125% of 0.053-0.062 ng/ml or 0.0424-0.0775 ng/mL. The mean peak concentration, Cmax for said norethindrone acetate is about 80% to about 125% of 5.7-6.4 ng/ml or 4.56-8.0 ng/mL. Moreover, the mean Area Under the Curve, AUC_T for said elagolix is about 80% to about 125% of 1534-4118 ng.hr/mL or 1227.2-5147.5 ng.hr/mL. The mean Area Under the Curve, AUC_T for said estradiol is about 80% to about 125% of 0.81-0.91 ng.hr/mL or 0.688-1.1375 ng.hr/mL. The mean Area Under the Curve, AUC_T for said norethindrone acetate is about 80% to about 125% of 22-26.3 ng.hr/mL or 17.6-33.125 ng.hr/mL.

[95] In some examples, the current invention provides an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate.

[96] When the composition is administered as depicted on Table 7 (d) to healthy adult subjects, it results in a steady state concentration $Cmax_{ss}$ for said elagolix of about 503-2212.5 ng/mL; mean peak concentration Cmax for said estradiol of about 0.0424-0.0775 ng/mL ng/ml; mean peak concentration Cmax for said norethindrone acetate of about 4.56-8.0 ng/ml; a mean Area Under the Curve, (AUC_T) for said elagolix of about 1227.2-5147.5 ng.hr/mL; a mean Area Under the Curve AUC(t) for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC(t) for said norethindrone acetate of about 17.6-33.125 ng.hr/mL. In another embodiment, when the composition is administered as depicted on Table 7 (d) to healthy adult subjects, it results in a mean peak concentration Cmax for said elagolix of about 1218.4-2185 ng/mL; Cmax for said estradiol of about 0.0424-0.0775 ng/mL ng/ml; Cmax for said norethindrone acetate of about 4.56-8.0

ng/ml; a mean Area Under the Curve, (AUC(t)) for said elagolix of about 3293.6-5892.5 ng.hr/mL; AUC(t) for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC(t) for said norethindrone acetate of about 17.6-33.125 ng.hr/mL.

[97] In another embodiment, the current invention provides an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate. When the composition is administered based on Table A7(c) or Table A7(d), to healthy adult subjects, it results in a mean steady state concentration, $Cmax_{ss}$ for said elagolix of about 503-2212.5 ng/mL; mean peak concentration Cmax for said estradiol of about 0.0424-0.0775 ng/mL; and mean peak concentration, Cmax for said norethindrone acetate of about 4.56-8.0 ng/ml.

[98] In one example, the oral multi-drug capsule composition has a steady state Area Under the Curve, AUC_{τ} for said elagolix of about 1227.2-5147.5 ng.hr/mL; AUC_{τ} for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC_{τ} for said norethindrone acetate of about 17.6-33.125 ng.hr/mL.

[99] In another embodiment, the current invention provides an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate. When the composition is administered based on Table A7(c) or Table A7(d), to healthy adult subjects, it results in a mean peak concentration, Cmax for said elagolix of about 1218.4-2185 ng/mL; mean peak concentration Cmax for said estradiol of about 0.0424-0.0775 ng/ml; and mean peak concentration, Cmax for said norethindrone acetate of about 4.56-8.0 ng/ml.

[100] In one example, the oral multi-drug capsule composition has a mean Area Under the Curve, AUC(t) for said elagolix of about 3293.6-5892.5 ng.hr/mL; AUC(t) for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC(t) for said norethindrone acetate of about 17.6-33.125 ng.hr/mL.

[101] In another embodiment, the current invention provides an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate; further when the composition is administered as shown in Table A7(c) and Table A7(d) to healthy adult subjects, it results in a mean Area Under the Curve, AUC_T for said elagolix of about 1227.2-5147.5 ng.hr/mL; AUC_T for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC_T for said norethindrone acetate of about 17.6-33.125 ng.hr/mL.

[102] In another example, the oral multi-drug capsule composition results in a steady state peak concentration, $Cmax_{ss}$ for said elagolix of about 503-2212.5 ng/mL; mean peak concentration, $Cmax_{ss}$ for said estradiol of about 0.0424-0.0775 ng/mL ng/ml; and mean peak concentration, $Cmax_{ss}$ for said norethindrone acetate of about 4.56-8.0 ng/ml

[103] In another embodiment, the current invention provides an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate; further when the composition is administered as shown in Table A7(c) and Table A7(d) to healthy adult subjects, it results in a mean Area Under the Curve, AUC(t) for said elagolix of about 3293.6-5892.5 ng.hr/mL; AUC(t) for said estradiol of about 0.0.688-1.1375 ng.hr/mL; and AUC(t) for said norethindrone acetate of about 17.6-33.125 ng.hr/mL.

[104] In another example, the oral multi-drug capsule composition results in a mean peak concentration, Cmax for said elagolix of about 1218.4-2185 ng/mL; mean peak concentration, Cmax for said estradiol of about 0.0424-0.0775 ng/mL ng/ml; and mean peak concentration, Cmax for said norethindrone acetate of about 4.56-8.0 ng/ml.

[105] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix which is administered twice daily; 1 mg of estradiol which is administered once daily; and 0.5 mg of norethidrone acetate which is administered once daily; administration of the composition to healthy subject results is shown in Table A7 (a) or Table A7 (b). For this administration the steady state concentration, $Cmax_{ss}$ for said elagolix of about 528-2175 ng/mL; a mean peak concentration, Cmax for said estradiol of about 0.023-0.114 ng/mL; a mean peak concentration, Cmax for said norethindrone acetate of about 3.172-10.294 ng/ml; a mean Area Under the Curve, AUC_T for said elagolix of about 1266.0-5086.8 ng.hr/ml, a mean Area Under the Curve, AUC_T for said estradiol of about 0.4266-1.4835 ng.hr/mL; and a mean Area Under the Curve, AUC_T for said norethindrone acetate of about 9.90-44.03 ng.hr/mL.

[106] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix which is administered twice daily; 1 mg of estradiol which is administered once daily; and 0.5 mg of norethidrone acetate which is administered once daily; further wherein administration of the composition to healthy subject results in a mean steady state concentration, $Cmax_{ss}$ for said elagolix of about 960-1500 ng/mL; a mean peak concentration, $Cmax_{ss}$ for said estradiol of about 0.048-0.075 ng/mL; a mean peak concentration, $Cmax_{ss}$ for said norethindrone acetate of about 4.88-7.625 ng/ml; a mean Area Under the Curve, AUC_T for said elagolix of about 2260.8-3532.5 ng.hr/ml, a mean Area Under the Curve, AUC_T for said estradiol of about 0.688-1.075 ng.hr/mL; and a mean Area Under the Curve, AUC_T for said norethindrone acetate of about 19.04-29.75 ng.hr/mL.

[107] In one example, the oral multi-drug capsule may have a mean Area Under the Curve, AUC_T for said elagolix of about 1266.0-5086.8 ng.hr/mL; a mean Area Under the Curve, AUC_T for said estradiol of about 0.4266-1.4835

ng.hr/mL; and a mean Area Under the Curve, AUC_T for said norethindrone acetate of about 9.90-44.03 1.4835 ng.hr/mL.

[108] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix which is administered twice daily; 1 mg of estradiol which is administered once daily; and 0.5 mg of norethindrone acetate which is administered once daily; further wherein administration of the composition to healthy adult subjects results in a mean Area Under the Curve, AUC_T for said estradiol of about 0.4266-1.4835 ng.hr/mL; and a mean Area Under the Curve, AUC_T for said norethindrone acetate of about 9.90-44.03 ng.hr/mL.

[109] In one example, administration of the multi-drug capsule composition to healthy adult subjects may further result in a mean steady state concentration, $Cmax_{ss}$ for said elagolix of about 528-2175 ng/mL; a mean peak concentration, $Cmax_{ss}$ for said estradiol of about 0.023-0.114 ng/mL; and a mean peak concentration, $Cmax_{ss}$ for said norethindrone acetate of about 3.172-10.294 ng/ml.

[110] In one example, an oral multi-drug capsule composition is provided comprising: (a) 300 mg of free acid equivalent of elagolix which is administered twice daily; (b) 1 mg of estradiol which is administered once daily; and (c) 0.5 mg of norethindrone acetate which is administered once daily; wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

[111] In one example, an oral multi-drug capsule composition is provided comprising: (a) 200 mg of free acid equivalent of elagolix which is administered twice daily; (b) 1 mg of estradiol which is administered once daily; and (c) 0.5 mg of norethindrone acetate which is administered once daily; wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in

the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

[112] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and following administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration (Cmax) for said elagolix of about1218.4 ng/mL to about 2185 ng/mL; a mean peak concentration (Cmax) for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL; a mean peak concentration (Cmax) for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL; a mean Area Under the Curve ($AUC_{(t)}$) for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve ($AUC_{(t)}$) for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve ($AUC_{(t)}$) for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[113] In another aspect, a multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/ml to about 2185 ng/mL; a mean peak concentration, Cmax for said estradiol of about 0.0424 ng/ml to about 0.0775 ng/ml; and a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng/ml to about 8.0 ng/ml.

[114] In one example, the multi-drug composition has a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3296.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[115] In one aspect, multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and administration of a single dose of the composition to healthy adult subjects results in a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

[116] In one example, administration of the multi-drug capsule to healthy adult subjects results in a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/mL to about 2185 ng.hr/mL; a mean peak concentration, Cmax for said estradiol of about 0.0424 ng.hr/mL to about 0.0775 ng/mL ng/ml; and a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng.hr/mL to about 8.0 ng/ml.

[117] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate; and using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

[118] The invention further provides an oral multi-drug capsule composition that is bioequivalent to any of the multi-drug capsules described herein.

[119] In another aspect, an oral multi-drug capsule composition includes 300 mg of free acid equivalent of elagolix; 1 mg of free acid equivalent estradiol; and 0.5 mg of free acid equivalent norethindrone acetate may be useful for

reducing uterine fibroid volume prior to surgery (pre-surgery) for removal of uterine fibroids.

[120] In another aspect, certain doses of elagolix plus estradiol and norethindrone acetate therapy may be useful for treating pain associated with endometriosis. For example, in one embodiment, 200 mg of free acid equivalent of elagolix plus 1 mg free acid equivalent of estradiol, and 0.5 mg free acid equivalent of norethindrone may be useful for treating pain associated with endometriosis.

[121] In another aspect, a method of treating heavy menstrual bleeding associated with uterine leiomyomas (fibroids) includes once daily oral administration to an adult human female patient suffering from uterine leiomyomas (fibroids) of a capsule comprising 300 mg of free acid equivalent of elagolix; 1 mg of estradiol; and 0.5 mg of norethindrone acetate, and the method results in a mean Cmax for the elagolix of about 1218.4 ng.hr/mL to about 2185 ng/mL; for the estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL; for the norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL, and a mean AUC(t) for the elagolix of about 3293.6ng.hr/mL to about 5892.5 ng.hr/mL; for the estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and for the norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

EXAMPLES

Example 1: Estradiol (E2) and norethindrone (NETA) tablet with elagolix compression overcoat. As shown in FIG. 4A

[122] Elagolix/E2/NETA tablets 400 were prepared by coating commercially sourced E2/NETA tablets 403 with compression coating using elagolix granules 401 as shown in FIG. 4A. The composition of the tablets 400 is provided in Table 1 and the granule composition is in Table 2 and the process is shown in FIG. 10.

Table 1: Composition of Example 1

Component	Amount per Unit
Elagolix Layer	
Intragranular	
Elagolix Sodium	310.5 mg [a]
Sodium Carbonate Monohydrate	155.3 mg
Polyethylene Glycol 3350	25.0 mg
Crospovidone	25.0 mg
Colloidal Silicon Dioxide	5.2 mg
Extragranular	
Mannitol	70 mg
Colloidal Silicon Dioxide	3.0 mg
Magnesium Stearate	6.0 mg
Total Elagolix Layer	600 mg
Activella® Core	
Activella® tablet, (estradiol/norethindrone acetate, 1.0/0.5 mg)	1 Tablet (approx. 80 mg)
Approximate total weight	680 mg

a: (300 mg of free acid elagolix is equivalent to about 310.5 mg elagolix sodium)

Table 2: Composition of Elagolix Melt Granule

Component	% w/w
Elagolix Sodium	59.67%
Sodium Carbonate Monohydrate	29.75%
Polyethylene Glycol 3350	4.80%
Crospovidone	4.80%
Colloidal Silicon Dioxide	0.97%
Total	100%

Table 3: Melt Granulation Temperature Settings.

	Temperature (°C)
Barrel 1	20
Barrel 2	40

Barrel 3	55
Barrel 4	60
Barrel 5	60
Barrel 6	60
Die	70

Example 2: Elagolix tablets containing E2/NETA tablets. As shown in FIG. 4B.

[123] The Elagolix/E2/NETA tablets were prepared according to the process shown in FIG. 10. The tablets 410 of Example 2 were prepared by first loading of the final blend and subsequently placing the Activella® tablets 403 on the surface of the powder bed followed by compression manually. The composition of the tablets 410 is provided in Table 4 and the tablet 410 is shown in FIG. 4B.

Table 4: Composition of Example 2 Tablet.

Component	Amount per Tablet
Elagolix Blend	
Intragranular	
Elagolix Sodium	310.5 mg
Sodium Carbonate Monohydrate	155.3 mg
Polyethylene Glycol 3350	25.0 mg
Crospovidone	25.0 mg
Colloidal Silicon Dioxide	5.2 mg
Extragranular	
Mannitol	70 mg
Colloidal Silicon Dioxide	3.0 mg
Magnesium Stearate	6.0 mg
Total Elagolix Layer	600 mg
Activella®	
Activella® tablet, (estradiol/norethindrone acetate, 1.0/0.5 mg)	1 Tablet (approx.80 mg)
Approximate total weight	680 mg

Example 3: Elagolix and E2/NETA bilayer tablets. As shown in FIG. 5.

[124] The bilayer tablets 500 consisting of elagolix 501 and E2/NETA layers 503 as shown in FIG. 3 were prepared using following examples:

Example 3-1

[125] Elagolix/E2/NETA tablets 500 were prepared according to the process shown in FIG. 11A.

[126] (The composition of the tablets is provided in

[127] Table 6.

Table 5: Extrusion Melt Granulation Temperature Settings.

	Temperature (°C)
Barrel 1	20
Barrel 2	40
Barrel 3	55
Barrel 4	90
Barrel 5	110
Barrel 6	70
Die	70

Table 6: Composition of Example 3-1 Tablet.

Component	**Amount per Unit**
Elagolix Layer	
Intragranular	
Elagolix Sodium	207.0 mg [a]
Sodium Carbonate Monohydrate	103.5 mg
Polyethylene Glycol 3350	16.7 mg
Crospovidone	16.7 mg
Colloidal Silicon Dioxide	3.5 mg
Extragranular	
Colloidal Silicon Dioxide	2.0 mg
Magnesium Stearate	3.3 mg
Total Elagolix Layer	352.7 mg
E2/NETA Layer	
Estradiol hemihydrate	1.0 mg
Norethindrone Acetate	0.5 mg
Lactose Monohydrate, 316	69.2 mg
Polysorbate 80	0.3 mg
Magnesium Stearate	0.4 mg
Total E2/NETA Layer	71.4 mg
Total weight	424.1 mg

a: (200 mg of free acid elagolix is equivalent to about 207.0 mg elagolix sodium)

Example 3-2

[128] Elagolix/E2/NETA tablets 500, were prepared according to the process shown in FIG. 11B.

[129] The composition of the tablets 500 is provided in Table 7.

Table 7: Composition of Example 3-2 Tablet.

Component	**Amount per Unit**
Elagolix Layer	
Intragranular	
Elagolix Sodium	207.0 mg
Sodium Carbonate Monohydrate	103.5 mg
Polyethylene Glycol 3350	16.7 mg
Crospovidone	16.7 mg
Colloidal Silicon Dioxide	3.5 mg
Extragranular	
Colloidal Silicon Dioxide	2.0 mg
Magnesium Stearate	3.3 mg
Total Elagolix Layer	352.7 mg
E2/NETA Layer	
Estradiol hemihydrate	1.0 mg
Norethindrone Acetate	0.5 mg
Lactose Monohydrate, 316	67.4 mg
Povidone K-29/32	2.1 mg
Magnesium Stearate	0.4 mg
Total E2/NETA Layer	71.4 mg
Total weight	424.1 mg

Example 3-3

[130] Elagolix/E2/NETA tablets 500 were prepared according to the process shown in FIG. 11C.

[131] The composition of the tablets 500 is provided in Table 8.

Table 8: Composition of Example 3-3 Tablet.

Component	**Amount per Unit**
Elagolix Layer	
Intragranular	
Elagolix Sodium	207.0 mg
Sodium Carbonate Monohydrate	103.5 mg
Polyethylene Glycol 3350	16.7 mg
Crospovidone	16.7 mg
Colloidal Silicon Dioxide	3.5 mg
Extragranular	
Colloidal Silicon Dioxide	2.0 mg
Magnesium Stearate	3.3 mg
Total Elagolix Layer	352.7 mg
E2/NETA Layer	
Estradiol hemihydrate	1.0 mg
Norethindrone Acetate	0.5 mg
Lactose Monohydrate, 316	65.9 mg
Crospovidone XL-10	3.6 mg
Magnesium Stearate	0.4 mg
Total E2/NETA Layer	71.4 mg
Total weight	424.1 mg

Example 3-4

[132] Elagolix/E2/NETA tablets were prepared according to the process shown in FIG. 11D.

[133] The composition of the tablets is provided in Table 9.

Table 8: Composition of Example 3-4 Tablet.

Component	**Amount per Unit**
Elagolix Layer	
Intragranular	
Elagolix Sodium	207.0 mg
Sodium Carbonate Monohydrate	103.5 mg
Polyethylene Glycol 3350	16.7 mg
Crospovidone	16.7 mg
Colloidal Silicon Dioxide	3.5 mg
Extragranular	
Colloidal Silicon Dioxide	2.0 mg
Magnesium Stearate	3.3 mg
Total Elagolix Layer	352.7 mg
E2/NETA Layer	
Estradiol hemihydrate	1.0 mg
Norethindrone Acetate	0.5 mg
Lactose Monohydrate, 316	69.5 mg
Magnesium Stearate	0.4 mg
Total E2/NETA Layer	71.4 mg
Total weight	424.1 mg

Example 4: Elagolix tablets with E2/NETA overcoat. As shown in FIG. 6.

[134] Elagolix/E2/NETA tablets were prepared by coating elagolix tablets 601 using layering of E2/NETA formulation as shown in FIG. 4. elagolix tablets 601 were first compressed using the final blend described in Example 3-1 on a tablet press with the target tablet weight of 352.7 mg. The tablets were prepared using the process shown in FIG. 12. The composition of the tablets 600 is provided in Table 9.

Table 9: Composition of Example 4 Tablet.

Component	Amount per Unit
Elagolix Tablet	
Intragranular	
Elagolix Sodium	207.0 mg
Sodium Carbonate Monohydrate	103.5 mg
Polyethylene Glycol 3350	16.7 mg
Crospovidone	16.7 mg
Colloidal Silicon Dioxide	3.5 mg
Extragranular	
Colloidal Silicon Dioxide	2.0 mg
Magnesium Stearate	3.3 mg
Total Elagolix Tablet	352.7 mg
E2/NETA Layer	
Estradiol hemihydrate	1.0 mg
Norethindrone Acetate	0.5 mg
Polysorbate 80	0.3 mg
Povidone K-29/32	10.0 mg
Total E2/NETA Layer	11.8 mg
Total weight	364.5 mg

Example 5: Elagolix and E2/NETA bilayer tablets. As shown in FIG. 7.

[135] Bilayer tablets consist of one layer of elagolix formulation 701 and a rapidly disintegrating layer 705 with embedded E2/NETA tablets 703, as shown in FIG. 7, were prepared for dissolution test. The compositions of each layer are provided in Table 10 and prepared according to the process shown in FIG. 13.

[136] Additionally, the barrel temperature setup is shown in Table 11.

[137] The rapidly disintegrating layer 705 contains commercially sourced excipient composite of Prosolv EASYtab (JRS Pharma) and one commercially sourced E2/NETA tablet 703 (Breckenridge Pharmaceutical Inc.). The bilayer tablet 700 was prepared individually by sequential filling into the die of tooling

A2310: (1) 80 mg EASYtab, (2) one E2/NETA tablet, (3) 80 mg EASYtab and (3) 529 mg Elagolix granules, followed by compression into the final tablet.

Table 10: Composition of Example 5 Tablet.

Component	**Amount per Unit**
Elagolix layer	
Intragranular	
Elagolix	310.5 mg
Anhydrous sodium carbonate	155.3 mg
PEG 3350	25 mg
Crospovidone	25 mg
Silicon dioxide	5.2 mg
Extragranular	
Silicon dioxide	3 mg
Magnesium stearate	0.92 mg
Total Elagolix Tablet	529 mg
E2/NETA layer	
E2/NETA tablet, (estradiol/norethindrone acetate, 1.0/0.5 mg)	1 tablet (approx. 80 mg)
Prosolv Easytab	160 mg
Total E2/NETA Layer	240 mg
Approximate total weight	769 mg

Table 11: Extruder temperature setup for melt granules used in Example 5.

	Temperature (°C)
Barrel 1	20
Barrel 2	80
Barrel 3	110
Barrel 4	130
Barrel 5	130
Barrel 6	130
Die	120

Calender Roller	25
Conveyer Belt	15
Liquid Dose - Line	80

Example 6: Elagolix and E2/NETA Capsules. As shown in FIG. 2

[138] The capsule of example 6, as shown in FIG. 2, provides a presentation that is easy for a patient to swallow and simpler to manufacture. The capsule was prepared according to the process shown in FIG. 14. This formulation allows for desirable co-administration of Elagolix/E2/NETA, which in turn provides the desired balance between the therapeutic and safety effect of elagolix E2 and NETA. Exogenous addition of a GnRH antagonist, such as elagolix regulates the hormones that may create certain adverse effects. These adverse effects may be effectively counterbalanced by administration by appropriate dosage and formulation of E2/NETA which is provided with elagolix such that the patient is not negatively impacted by competitive antagonism of the elagolix administration. The composition of this capsule is shown in Table 12. The use of the preformed E2/NETA tablet 134 in the capsule of example 6 avoids further handling of the estradiol (E2) hormone.

Table 12: Composition of Example 6 Capsules.

Component	Amount per Unit
Elagolix Tablet	
Intragranular	
Elagolix Sodium	310.5 mg
Sodium Carbonate Monohydrate	155.3 mg
Polyethylene Glycol 3350	25.0 mg
Crospovidone	25.0 mg
Colloidal Silicon Dioxide	5.2 mg
Extragranular	
Colloidal Silicon Dioxide	3.0 mg
Magnesium Stearate	6.0 mg
Total Elagolix Layer	529.0 mg
Activella® Tablet	
Activella® tablet, (estradiol/norethindrone acetate, 1.0/0.5 mg)	1 Tablet (approx. 80 mg)
Capsule, Gelatin, No. 0, Light Gray Opaque	1 Capsule

Example 7: Elagolix tablets in capsules. As shown in FIG. 8.

[139] The elagolix granules were manufactured as described before (see Example 1). Furthermore, the capsules were prepared according to the process shown in FIG. 15.

Table 13: Composition of Example 7 Elagolix Tablets.

Component	Amount per Unit
Intragranular	
Elagolix Sodium	77.9 mg [a]
Sodium Carbonate Monohydrate	38.8 mg
Polyethylene Glycol 3350	6.3 mg
Crospovidone	6.3 mg
Colloidal Silicon Dioxide	1.3 mg
Extragranular	
Colloidal Silicon Dioxide	0.8 mg
Magnesium Stearate	1.3 mg
Total Elagolix Tablet	132.5 mg

[a]: (75 mg of free acid elagolix is equivalent to about 77.9 mg elagolix sodium)

Example 8: Elagolix Melt Granules and E2/NETA Tablet in capsules. As shown in FIG. 9.

[140] The capsules 900 containing elagolix melt granules 901 and E2/NETA tablets 903 were prepared according to the process shown in FIG. 16. Example 6 and one E2/NETA tablet (Activella®) 903 into a size 00 capsule 901, as shown in FIG. 9, for dissolution test. The capsule 900 may include air, or any other suitable filler in interior space 910. In some examples, the elagolix melt granules 901 and E2/NETA tablets 903 may be mixed/placed together in the capsule 900.

Example 9A: Dissolution test of Examples 1-8

[141] Gelling properties of amorphous elagolix creates unpredictability in a formulation that contains both elagolix and E2/NETA. It is unclear how the elagolix in the presence of an anti-gelling agent such as sodium carbonate will interact with E2/NETA.

[142] In vitro dissolution of elagolix dosage forms for examples 1-8 were tested using USP apparatus 2 at 50 rpm in a 900 mL of 0.05M pH 6.8 phosphate buffer at 37.5±0.5°C and shown in Table 15-25. The filtrate was analyzed by HPLC. Elagolix, E2 and NETA were determined by a multiple wavelength detector at 310, 220 or 241 nm, respectively.

Table 15: Dissolution Data for Example 1 (mean ±SD). As shown in FIG. 4A.

Description	15 min	30 min	45 min	60 min
Elagolix Release	58 (7.5)	89 (8.1)	100 (3.5)	103 (2.0)
E2 Release	4 (6.4)	67 (17.2)	85 (1.5)	93 (0.6)
NETA Release	4 (7.5)	77 (21.0)	99 (1.5)	101 (1.5)

Table 16: Dissolution Data of Example 2 (mean ±SD). As shown in FIG. 4B.

Description	15 min	30 min	45 min	60 min
Elagolix Release	47 (5.3)	79 (8.7)	96 (4.0)	100 (0.0)

E2 Release	47 (18.6)	78 (9.1)	89 (4.5)	89 (0.6)
NETA Release	54 (22.6)	90 (10.0)	98 (4.0)	96 (0.6)

Table 17: Dissolution Data of Example 3-1 (mean ±SD). As shown in FIG. 5.

Description	15 min	30 min	45 min	60 min
Elagolix Release	61 (6.6)	92 (5.3)	101 (0.5)	102 (0.5)
E2 Release	91 (4.2)	93 (1.7)	94 (1.2)	95 (1.1)
NETA Release	94 (4.7)	96 (0.8)	97 (1.1)	96 (1.0)

Table 18: Dissolution Data for Example 3-2 (mean ±SD). As shown in FIG. 5.

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	54 (9.6)	86 (8.4)	100 (2.8)	102 (0.5)	103 (0.6)
E2 Release	39 (9.7)	79 (5.1)	88 (2.8)	90 (1.0)	90 (1.1)
NETA Release	41 (9.7)	82 (6.2)	91 (2.1)	93 (1.0)	93 (0.7)

Table 19: Dissolution Data of Example 3-3 (mean ±SD). As shown in FIG. 5.

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	62 (2.0)	92 (1.9)	99 (0.6)	100 (0.6)	100 (0.5)
E2 Release	72 (2.4)	76 (1.6)	79 (2.1)	80 (2.1)	82 (1.9)
NETA Release	92 (2.3)	93 (1.3)	93 (1.5)	93 (1.4)	93 (1.2)

Table 20: Dissolution Data for Example 3-4 (mean ±SD). As shown in FIG. 5.

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	60 (8.9)	90 (7.2)	100 (1.3)	101 (0.4)	101 (0.5)
E2 Release	80 (5.3)	84 (2.4)	86 (1.2)	88 (1.5)	89 (2.6)
NETA Release	93 (4.4)	96 (1.3)	96 (1.0)	96 (0.9)	96 (0.9)

Table 21: Dissolution Data for Example 4 (mean ±SD). As shown in FIG. 6.

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	57 (7.1)	91 (6.1)	102 (2.2)	104 (0.9)	104 (0.9)
E2 Release	98 (3.5)	98 (3.7)	98 (3.8)	98 (3.6)	98 (3.6)
NETA Release	100 (3.6)	100 (3.5)	100 (3.6)	100 (3.5)	100 (3.6)

Table 22: Dissolution Results of Example 5 (mean ±SD). As shown in FIG. 7

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	31 (4)	55 (5)	73 (4)	85 (5)	97 (5)
E2 Release	22 (13)	43 (18)	60 (12)	70 (6)	78 (2)
NETA Release	16 (13)	41 (23)	56 (11)	60 (1)	63 (5)

Table 23: Dissolution Data of Example 6 (mean ±SD). As shown in FIG. 2

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	11 (3.9)	43 (6.9)	73 (6.7)	91 (4.2)	102 (1)
E2 Release	78 (17.3)	95 (1.4)	96 (1.4)	97 (1.1)	97 (1.2)
NETA Release	79 (18.1)	96 (1.3)	97 (1.7)	98 (1.2)	98 (1.5)

Table 24: Elagolix Dissolution Data of Example 7 (mean ±SD). As shown in FIG. 8

Description	15 min	30 min	45 min	60 min
4 mini-tablets in HG capsule	14 (1.4)	68 (4.2)	97 (7.1)	101 (0.7)
4 mini-tablets in HPMC capsule	5 (2.8)	26 (3.5)	52 (2.1)	71 (1.4)
4 mini-tablets	85 (0.7)	103 (0.7)	103 (0.7)	103 (0.7)

Table 25: Dissolution Data of Example 8 (mean ±SD). As shown in FIG. 9

Description	15 min	30 min	45 min	60 min	90 min
Elagolix Release	23 (5.6)	76 (4.9)	96 (4.7)	99 (2.7)	99 (2.3)
E2 Release	6 (14.3)	66 (29.9)	93 (2.2)	93 (2.9)	95 (1.0)
NETA Release	6 (15.1)	71 (31.0)	99 (1.6)	100 (1.5)	101 (1.0)

Example 9B: Dissolution test of Example 6

[143] In vitro dissolution of elagolix dosage form for example 6 was tested using USP apparatus 1 at 100 rpm with 900 mL of 0.05 M sodium phosphate buffer, pH 6.8 maintained at 37°C. The dissolution release shown was measured and the release at various time intervals is shown in Table 26 and FIGS. 29A (Elagolix release), 29B (E2 release), and 29C (NETA release). The filtrate was analyzed by HPLC. Elagolix, E2 and NETA were determined by a multiple wavelength detector at 310, 220 or 241 nm, respectively.

Table 26: Dissolution Data of Example 6 (mean ±SD). As shown in FIGS. 29A, 29B, and 29C n=6.

Description	10 min	15 min	30 min	45 min	60 min	90 min
Elagolix Release	NA	9 (3.4)	49 (8.2)	87 (5.7)	100 (1.1)	101 (0.9)
E2 Release	34 (24.9)	NA	100 (2.1)	100 (1.8)	NA	NA
NETA Release	35 (24.7)	NA	99 (1.9)	99 (1.8)	NA	NA

Example 10: Dosage Forms and Administration

[144] The drug delivery system 100 includes a morning capsule 102 labelled “AM” 126. Capsule 102 is white and yellow and includes additional identifying labelling “EL300.” Capsule 102 includes about 300 mg elagolix, about 1 mg estradiol, and about 0.5 mg norethindrone acetate. Capsule 104 is labelled “PM” is white and light blue, and also is labelled “EL300.” In some examples, capsule 104 may include about 300 mg elagolix. Each capsule 102, 104 should be administered orally daily at approximately the same time each day (e.g. 102 taken in the morning and capsule 104 taken in the evening). In one embodiment, each of the capsules may be taken with or without food and the capsules may be administered daily for about 48 months. In another embodiment, each of the capsules may be taken with or without food and the capsules may be

administered daily for about 60 months. In another embodiment, each of the capsules may be taken with or without food and the capsules may be administered daily for about 72 months. In another embodiment, each of the capsules may be taken with or without food and the capsules may be administered daily for about 6 months, for about 12 months, for about 12-24 months, for about 24-36 months, for about 36-48 months, for about 48-60 months, or for about 60-72 months. Duration of treatment may be extended based on assessment of bone mineral density loss or any other adverse effect, for example, if a woman is treated for a duration of 24 months, and continues to have a positive benefit-risk profile, the duration of treatment may be extended to 36 months or longer. The bone mineral density loss may be assessed using any suitable methods, including radiographic techniques e.g. DXA scan for continued treatment. If a patient has missed a dose, the patient should be instructed to take the missed dose within 4 hours of the time the dose was supposed to be taken and them the next dose may be taken and the usual time. If, however, more than 4 hours have passed since the missed dose would have usually been taken, the patient should not take the missed dose and take the next dose at the usual time. Only one morning and one evening capsule should be taken per day.

Example 11: Adverse Reactions Clinical Trials Experience

[145] The safety of system of Example 10 was evaluated in two randomized, double-blind, placebo-controlled studies [UF-1 (NCT02654054) and UF-2 (NCT02691494)] in which 790 premenopausal women received elagolix, elagolix 300 mg twice daily, or placebo for 6 months. Elagolix 300 mg twice daily was included as a reference arm to characterize the impact of estradiol/norethindrone acetate (E2/NETA) on safety and efficacy. Women who completed the 6-month treatment period in either UF-1 or UF-2 and met eligibility criteria entered an uncontrolled blinded 6-month extension study [UF-EXTEND

(NCT02925494)] for a total treatment duration of up to 12 months receiving either elagolix or elagolix 300 mg twice daily.

Common Adverse Reactions

[146] The most commonly reported adverse reaction for women treated with the system of Example 10 (incidence of at least 10%) in UF-1 and UF-2 was hot flush and/or night sweats (see Table A1). In UF-1 and UF-2, discontinuation from therapy due to any adverse event occurred in 9.6% (n=38) of women treated with elagolix and 6.6% (n=13) in those who received placebo. Adverse reactions reported in ≥ 5% of women receiving the system of Example 10 and at a greater frequency than placebo is shown in Table A1.

Table A1: Adverse Reactions Occurring in at Least 5% of Women with Uterine Fibroids Receiving the System of Example 10 in Studies UF-1 and UF-2 and at a Greater incidence Than Placebo

Adverse Reaction	**System of Example 10 N=395**	**Placebo N= 196 %**	**Elagolix 300 mg Twice Daily N=199** %
Hot Flush	22%	9%	56%
Headache	9%	7%	15%
Fatigue	6%	4%	2%
Metrorrhagia	5%	1%	1%

[147] In Studies UF-1 and UF-2, discontinuation from therapy due to any adverse reaction occurred in 9.6% (n=38) of women treated with the System of Example 10 and 6.6% (n=13) in those who received placebo.

Less Common Adverse Reactions

[148] In Studies UF-1 and UF-2, adverse reactions reported in ≥ 3% and < 5% in the System of Example 10 group and greater incidence than the placebo group included: libido decreased, arthralgia, hypertension, alopecia, mood swings, abdominal distension, menorrhagia, influenza, upper respiratory tract

infection, vomiting, and weight increased. The most commonly reported adverse reactions in the extension trial (Study UF-EXTEND) were similar to those in the placebo-controlled trials.

Bone Loss

[149] The effect of the System of Example 10 on BMD was assessed by dual-energy X-ray absorptiometry (DXA). In Studies UF-1 and UF-2, there was a greater decrease in BMD in women treated with the System of Example 10 compared to placebo. The mean change from baseline in lumbar spine BMD at Month 6 and Month 12 for women who received the system of Example 10 compared to women who received placebo was -0.6% and -1.5%, respectively, and are presented in Table A2.

Table A2: Percent Change from Baseline in Lumbar Spine BMD at Month 6 in UF-1 and UF-2

	Studies UF-1 and UF-2 Treatment Month 6	
	Placebo	System of Example 10
Number of Subjects	150	305
Percent Change from Baseline	-0.1	-0.7
Treatment Difference, % (95% CI)		-0.6 (-1.0, -0.1)

[150] In the extension study, UF-EXTEND, continued bone loss was observed with 12 months of continuous treatment with the System of Example 10. The proportion of women who experienced a greater than 8% BMD decrease in

lumbar spine, total hip or femoral neck at treatment month 6 in Studies UF-1 and UF-2 and at treatment month 12 in Study UF-EXTEND are presented in Table A3.

Table A3: Percent of Subjects with Greater than 8% BMD Decrease in Women with Uterine Fibroids in Studies UF-1, UF-2, and UF-EXTEND

	Studies UF-1 and UF-2			**Study UF-EXTEND**	
	Treatment Month 6			Treatment Month 12	
BMD Location	System of Example 10 %	Placebo %	Elagolix 300 mg BID %	System of Example 10 %	Elagolix 300 mg BID %
Lumbar Spine	0%	0%	2.9%	1.7%	14.8%
Total Hip	0%	0%	0.7%	0%	4.9%
Femoral neck	1.6%	0.7%	1.4%	1.7%	12.3%

[151] To assess for recovery, the change in lumbar spine BMD over time was analyzed for women who received continuous treatment with the System of Example 10 for up to 12 months and who were then followed after cessation of therapy for an additional 12 months (Figure 19). Twelve months after cessation of the System of Example 10, continued bone loss was observed at the spine, total hip, and femoral neck in 24%, 32%, and 38% of women, respectively. Of these women, all but one woman had ≤3% decline in BMD at the lumbar spine, and all had ≤5% decline at either hip site. Full recovery of bone loss was observed in 31%, 36% and 24% of women who lost bone following 12 months of treatment with System of Example 10 at the spine, total hip, and femoral neck, respectively. The remaining women had partial recovery, and the time to maximum recovery in these women is unknown.

[152] Overall, the presence of E2/NETA in the current 300 mg BID elagolix formulation (System of Example 10) reduces the BMD loss as compared to 300 mg BID of elagolix alone without E2/NETA.

Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

[153] In the placebo-controlled trials (Studies UF-1 and UF2), the System of Example 10 was associated with adverse mood changes. Depression, depressed mood, and/or tearfulness were reported in 3% of women receiving the System of Example 10 compared with 1% in the placebo group.

Hepatic Transaminase Elevations

[154] In Studies UF-1 and UF-2, asymptomatic elevations of serum ALT to at least 3- times the upper limit of the reference (ULN) range occurred in 1.1% (4/379) of women receiving System of Example 10, 2.2% (4/184) receiving elagolix 300 mg twice daily, and none receiving placebo. . Elevations in ALT, up to 8-times the ULN were reported. Concurrent elevations in bilirubin were not reported.

Changes in Lipid Parameters

[155] Increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), serum triglycerides, and apolipoprotein B were noted during the System of Example 10 treatment in UF-1 and UF-2. In UF-1 and UF-2, 16.7% and 0% of subjects women with mildly elevated LDL-C (130-159 mg/dL) at baseline had an increase in LDL-C concentrations to 190 mg/dL or higher during treatment with System of Example 10 and placebo, respectively, none receiving placebo had such increase in LDL-C. In UF-1 and UF-2, 1.5% and 5.6% of subjects with mildly elevated serum triglycerides (150-300 mg/dL) at baseline had an increase in serum triglycerides to higher than 500 mg/dL during treatment with System of Example 10 and placebo, respectively. The highest measured serum triglyceride

concentration during treatment with System of Example 10 was 852 mg/dL. In women receiving System of Example 10 , lipid changes were reversible and elevated lipid levels returned to near Baseline baseline levels within 3 months after cessation of treatment. No cases of pancreatitis were reported in the clinical trials.

[156] After cessation of six months of therapy with the System of Example 10, resumption of menses was reported by 39.0%, 687.8% and 732.9% of women within 1, 2, and 6 months respectively for UF-1 and 39.0%, 84.75% and 91.52% within 1, 2, and 6 months respectively for UF-2. After 12 months of therapy with the System of Example 10 (UF-1 or UF2 then UF-EXTEND), During the second 6 months of treatment in UF-EXTEND, the incidence of amenorrhea ranged from 60.0% to 71.6% monthly for the System of Example 10 and resumption of menses was reported by 40.8X%, 79.3X% and 89.7X% of women within 1, 2, and 6 months after stopping treatment, respectively. Whether the subject who did not resume having menses transitioned to a peri-postmenopausal status is unknown.

Endometrial Effects

[157] In UF-1, UF-2 and UF-EXTEND, endometrial biopsies were performed at Month 6. There were no abnormal biopsy findings, including no endometrial hyperplasia or cancer, in women treated with the System of Example 10. Based ultrasound, the System of Example 10 treatment in UF-1 and UF-2 resulted in a decrease from baseline to Month 6 in mean endometrial thickness (-1.65 mm).

Example 12: Drug Interactions

Potential for the System of Example 10 to Affect Other Drugs

[158] Elagolix is a weak to moderate inducer of cytochrome P450 (CYP) 3A). Coadministration with the System of Example 10 may decrease plasma concentrations of drugs that are substrates of CYP3A. Elagolix is a weak inhibitor of CYP2C19. Co-administration with the System of Example 10 may increase plasma concentrations of drugs that are substrates of CYP2C19 (e.g., omeprazole and esomeprazole) ([see Table A5)]

[159] Elagolix is an inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with the System of Example 10 may increase plasma concentrations of drugs that are substrates of P-gp (e.g., digoxin) ([see Table A5]).

Drug Interactions- Examples and Clinical Management

[160] The effect of co-administration of The System of Example 10 on concentrations of concomitant drugs and the effect of concomitant drugs on the System of Example 10 the clinical recommendations for these drug interactions are summarized in Table A5.

Table A5: Drug Interactions: Effects of The System of Example 10 on Other Drugs

Concomitant Drug Class: Drug Name	**Effect on Plasma Exposure of Elagolix Or Concomitant Drug**	**Clinical Recommendations**
Cardiac glycosides digoxin	↑ digoxin	Increased monitoring of digoxin concentrations and potential sign and symptoms of clinical toxicity when initiating or discontinuing the system of example 10 in patients who are taking digoxin.

Benzodiazepines oral midazolam	↓ midazolam	Consider increasing the dose of midazolam by no more than 2 folds and individualize midazolam therapy based on the patient's response.
Statins rosuvastatin	↓ rosuvastatin	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
Proton pump inhibitors omeprazole	↑ omeprazole	No dose adjustment needed for omeprazole 40 mg once daily when co-administered with the system of example 10. When the System of Example 10 is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole.
The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑= increase, ↓ = decrease).		

Example 13: Use in Specific Populations

[161] Exposure to the System of Example 10 early in pregnancy may increase the risk of early pregnancy loss. Use of the System of Example 10 is contraindicated in pregnant women. The System of Example 10 should be discontinued if pregnancy occurs during treatment. When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, post implantation loss was observed in pregnant rats at doses 12 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss were observed in rabbits at doses 4 and 7 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 25 and 7 times the MRHD for the rat and rabbit, respectively.

Human Data

[162] There was one pregnancy reported out of the 453 women who received the System of Example 10 in the Phase 3 uterine fibroids clinical trials. The pregnancy resulted in a spontaneous abortion and the estimated fetal exposure to the System of Example 10occurred during the first 18 days of pregnancy.

Animal Data

[163] Embryofetal development studies were conducted in the rat and rabbit. Elagolix was administered by oral gavage to pregnant rats (25 animals/dose) at doses of 0, 300, 600 and 1200 mg/kg/day and to rabbits (20 animals/dose) at doses of 0, 100, 150, and 200 mg/kg/day, during the period of organogenesis (gestation day 6-17 in the rat and gestation day 7-20 in the rabbit). In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased post implantation losses were present in the mid dose group, which was 12 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 7 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 4 times the MRHD. No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity.

[164] At the highest doses tested, the exposure margins were 25 and 7 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential non-target-related

effects of elagolix. In a pre- and postnatal development study in rats, elagolix was given in the diet to achieve doses of 0, 100 and 300 mg/kg/day (25 per dose group) from gestation day 6 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, and one failed to deliver. Pup survival was decreased from birth to postnatal day 4. Pups had lower birth weights and lower body weight gains were observed throughout the pre-weaning period at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at 300 mg/kg/day. Post-weaning growth, development and behavioral endpoints were unaffected. Maternal plasma concentrations in rats on lactation day 21 at 100 and 300 mg/kg/day (47 and 125 ng/mL) were 0.04-fold and 0.1-fold the maximal elagolix concentration (Cmax) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.

Lactation

Risk Summary

[165] the System of Example 10 is not recommended during lactation. There is limited information on the presence of the System of Example 10 in human milk, the effects on the breastfed child, or the effects on milk production.

Data

[166] There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen and progestin combinations. There are no adequate animal

data on excretion of elagolix in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the System of Example 10 and any potential adverse effects on the breastfed infant from the System of Example 10 or from the underlying maternal condition.

Example 14: Clinical Pharmacology

Mechanism of Action

[167] the System of Example 10 combines elagolix, a GnRH receptor antagonist, and estradiol/norethindrone acetate (E2/NETA), an exogenous combination of estrogen and progestin. Elagolix inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Estrogens such as E2 act through binding to nuclear receptors in estrogen-responsive tissues. Progestins such as NETA enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes.

Pharmacodynamics

[168] Effect on Gonadotropin and Ovarian Hormones. Administration of elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone. The E2/NETA component supplements endogenous estrogen and progesterone. In Phase 3 trials in women with uterine fibroids administered the System of Example 10 for 6 months, LH and FSH was approximately 0.40 to 0.70 mIU/mL and 1.8 to 2.5 mIU/mL respectively, resulting in median concentrations of estradiol of

approximately 42 to 51 pg/mL, and progesterone of approximately 0.37 to 0.38 nM.

[169] In a multiple-ascending dose study in premenopausal healthy female subjects, elagolix 150 mg QD or 100, 200, 300, or 400 mg BID or placebo was administered for 21 days. Dose-dependent suppression of sex hormones was achieved rapidly within hours after administration of the first dose on day 1 and continued through day 21, with maximum E2 suppression achieved with elagolix doses of 200 mg BID or higher. At elagolix doses ≥100 mg BID, P concentrations remained at anovulatory levels throughout 21 days of dosing. Dose-dependent suppression of FSH and LH was also observed, with maximal or near-maximal suppression achieved at elagolix doses of 300 mg BID and 200 mg BID, respectively. LH and FSH were suppressed compared to placebo, however, LH suppression was more pronounced than that of FSH in all groups except the 150 mg QD group. When elagolix administration was stopped, LH and FSH levels rose within 24 hours after the last dose, and E2 levels began to rise 24 hours after the last dose was administered. The effects of different doses and dosing regimens of elagolix alone or with the hormonal add-back therapy dose of Activella® (E2/norethindrone acetate, 1/0.5 mg) on ovulation, ovarian activity and ovarian reserve were evaluated in an open-label study in healthy adult premenopausal females.

[170] During the 3-month treatment phase, with three-times-a-week hormone sampling, suppression of gonadotropins and ovarian hormones were observed in a dose-dependent manner. Mean E2 levels were observed at the 150 mg QD dose were approximately 40 to 50 pg/mL, consistent with partial E2 suppression. On the other hand, and consistent with the previous study, near maximal suppression was observed with the 200 mg BID and 300 mg BID regimens, with mean E2 levels of approximately 20 to 40 pg/mL. However, when said dose of Activella was administered with elagolix 300 mg BID regimen, mean

E2 levels appeared to increase to slightly above the levels observed with the 150 mg QD regimen due to exogenous E2 administration.

Effect on Ovulation

[171] In a 3-menstrual cycle study of the System of Example 10 in healthy women, approximately 10% ovulated.

Cardiac Electrophysiology

[172] The effect of elagolix on the QTc interval was evaluated in a randomized, placebo- and positive-controlled, open-label, single-dose, crossover thorough QTc study in 48 healthy adult premenopausal women. Elagolix concentrations in women given a single dose of 1200 mg was 9-times higher than the concentration in women given elagolix 300 mg twice daily. There was no clinically relevant prolongation of the QTc interval.

Pharmacokinetics

[173] The pharmacokinetic properties of the System of Example 10in healthy subjects are summarized in Table A6. The steady-state pharmacokinetic parameters under fasting conditions are summarized in Table A7.

Table A6: Pharmacokinetic Properties of the System of Example 10 in Healthy Subjects

Absorption			
	Elagolix	**Estradiol[a]**	**Norethindrone**
Tmax (h)[b,c]	1.5 (1.0 – 4.0)	2.0 (0.0 - 10.0)	1.0 (0.5 - 2.0)
High-fat meal[d] (relative to fasting)	AUC: ↓25%, C_{max}: ↓36%	AUC: no change, C_{max}: ↓23%	AUC: ↑23%, C_{max}: ↓50%
Distribution			
% Bound to human plasma proteins	80	98	97
Blood-to-plasma	0.6	NA	NA

ratio			
Metabolism			
Metabolism	CYP3A (major) Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)	CYP3A (partial) Other pathways include: sulfation and glucuronidation	CYP3A (partial)
Elimination			
Major route of elimination	Hepatic metabolism	Hepatic metabolism	Hepatic metabolism
Terminal phase elimination half-life ($t_{1/2}$) (h)[c, e]	2.9 ± 0.8	14.5 ± 6.6	9.2 ± 4.0
% of dose excreted in urine	< 3	NA	NA
% of dose excreted in feces	90	NA	NA
NA=not available			
[a]Baseline adjusted unconjugated estradiol [b]Median and range [c]Following administration of a single dose under fasting conditions [d]High-fat meal is approximately 826 kcal, 52% fat. [e]Mean ± SD			

Table A7 (a): Mean (%CV) Pharmacokinetic Parameters of the System of Example 10

Pharmacokinetic Parameter (Units)	**Elagolix 300 mg Twice Daily[a] N = 8**	**Estradiol[b] 1 mg N = 163**	**Norethindrone[b] 0.5 mg N = 163**
C_{max} (ng/mL)	1200 (45)	0.06 (52)	6.1 (35)
AUC_T (ng•hr/mL)	2826 (44)	0.86 (38)	23.8 (48)
[a]Data obtained at steady state (Day 21); AUC_T represents the area under the plasma concentration-time curve from 0 to 12 hours post dose. [b]Data obtained following single dose administration; AUC_T represents AUC from 0 to 24 hours post dose; Estradiol: baseline adjusted unconjugated estradiol. CV: Coefficient of variation			

C_{max}: plasma peak concentration

Table A7 (b): Mean (±SD) Pharmacokinetic Parameters of the System of Example 10 with 90% confidence intervals around the mean Cmax or AUC ratios of 0.8-1.25.

Pharmacokinetic Parameter (Units)	**Elagolix 300 mg Twice Daily N = 8**	**Estradiol[a] 1 mg N = 163**	**Norethindrone[a] 0.5 mg N = 163**
C_{max} (ng/mL)	1200 ± 544	0.06 ± 0.03	6.1 ± 2.1
AUC_T (ng•hr/mL)	2826 ± 1231	0.86 ± 0.33	23.8 ± 11.4

Table A7 (c): 95% confidence intervals around the mean for Cmax and AUC of elagolix, E2 and NETA of the System of Example 10, as well as the 80-125% of the geometric mean.

	Cmax ng/ml		**AUC ng.hr/ml**	
	mean and 95% CI	**80-125% of the geometric mean**	**mean and 95% CI**	**80-125% of the geometric mean**
Elagolix (300 mg BID steady state)	1200 (629, 1770)	869 - 1359	2826 (1534, 4118)*	2075 - 3242*
Elagolix (300 mg single dose)	1640 (1523, 1748)	1200 - 1875	4420 (4117, 4714)^	3536 - 5525^
E2 (1 mg single dose)	0.058 (0.053 - 0.062)	0.042 - 0.065	0.86 (0.81, 0.91)^	0.63 - 991^
Norethindrone (0.5 mg single dose)	6.1 (5.7, 6.4)	4.6 - 7.1	23.8 (22.0, 26.5)^	17.0 - 26.5^
*AUC(tau); AUC during the dosing interval (i.e. 12 hours for BID) ^AUC(t); AUC from '0' to time of the last measured concentration				

Table A7 (d): depicting 80%-125% of mean Cmax and mean AUCT for System of Example 10.

	Cmax ng/ml		AUCT ng.hr/ml	
	mean and 95% CI	**80-125% of the mean**	**mean and 95% CI**	**80-125% of the mean**
Elagolix (300 mg BID steady state	1200 (629, 1770)	503-2212.5	2826 (1534, 4118)*	1227.2-5147.5*
Elagolix (300 mg single dose)	1640 (1523, 1748)	1218.4-2185	4420 (4117, 4714)^	3293.6-5892.5^
E2 (1 mg single dose	0.058 (0.053 - 0.062)	0.0424-0.0775	0.86 (0.81, 0.91)^	0.688-1.1375^
NETA (0.5 mg single dose)	6.1 (5.7, 6.4)	4.56 – 8.0	23.8 (22.0, 26.5)^	17.6-33.125^
*AUC(tau); AUC during the dosing interval (i.e. 12 hours for BID) ^AUC(t); AUC from '0' to time of the last measured concentration				

Specific Populations

Renal Impairment

[174] Elagolix exposures (Cmax and AUC) were not altered by renal impairment. The elagolix mean plasma exposures were similar for women with moderate to severe or end stage renal disease (including women on dialysis) compared to women with normal renal function. The effect of renal impairment on the pharmacokinetics of E2/NETA has not been studied.

Patients with Hepatic Impairment

[175] Elagolix exposures (Cmax and AUC) were similar between women with normal hepatic function and women with mild hepatic impairment. Elagolix exposures in women with moderate and severe hepatic impairment were approximately 3- fold and 7-fold, respectively, higher than exposures from women with normal hepatic function. The effect of hepatic impairment on the pharmacokinetics of E2/NETA has not been studied.

Racial or /Ethnic Groups

[176] No clinically meaningful difference in the pharmacokinetics of elagolix between White and Black subjects or between Hispanics and others was observed. There is no clinically meaningful difference in the pharmacokinetics of elagolix between Japanese and Han Chinese subjects. The effect of race/ethnicity on the pharmacokinetics of E2/NETA has not been studied.

Body weight/Body Mass Index

[177] Body weight or body mass index does not affect the pharmacokinetics of elagolix. The effect of body weight/body mass index on the pharmacokinetics of E2/NETA has not been studied.

Drug Interaction Studies

[178] Drug interaction studies were performed with elagolix and other drugs likely to be co-administered and with drugs commonly used as probes for pharmacokinetic interactions. Tables 8 and 9 summarize the pharmacokinetic effects when elagolix was co-administered with these drugs.

Table A8: Drug Interactions: Change in Pharmacokinetics of Elagolix in the Presence of Co-administered Drugs

Co-administered Drug	**Co-administered Drug Regimen**	**Elagolix Regimen**	**N**	**Ratio % (90% CI)***	
Ketoconazole	400 mg once daily	150 mg single[&] dose	11	**Cmax**	**AUC**
				177 (148 - 212)	220 (198 - 244)
Rifampin	600 mg single dose	150 mg single dose[&]	12	437	558

				(362 - 528)	(488 - 637)
	600 mg once daily			200 (166 - 241)	165 (145 - 189)
CI: Confidence interval & The elagolix dose in these studies was 0.5 times the approved dose in system of Example 10) (0.25 times the total approved daily dosage of elagolix in the system of Example 10) *ratios for Cmax and AUC compare co-administration of the medication with elagolix vs. administration of elagolix alone.					

[179] No clinically significant changes in elagolix exposures were observed when elagolix 300 mg was co-administered with rosuvastatin (20 mg once daily), sertraline (25 mg once daily) or fluconazole (200 mg single dose). The effect of co-administered rosuvastatin, sertraline or fluconazole on E2/NETA has not been studied.

Table A9: Drug Interactions: Change in Pharmacokinetics of Co-administered Drug in the Presence of Elagolix

Co-administered Drug	**Co-administered Drug Regimen**	**Elagolix Regimen**	**N**	**Ratio % (90% CI)***	
Digoxin	0.5 mg single dose	200 mg twice daily x 10 days	11	C_{max}	AUC
				171 (153 - 191)	126 (117 - 135)
Rosuvastatin	20 mg once daily	300 mg twice daily x 7 days	10	99 (73 - 135)	60 (50 - 71)
Midazolam	2 mg single dose	300 mg twice daily x 11 days	20	56 (51 - 0.62)	46 (41 - 50)
		150 mg once daily x 13 days	11	81 (74 - 89)	65 (58 - 72)
Omeprazole	40 mg single dose	300 mg twice daily x 9 days	20	195 (150 - 253)	178 (139 - 227)

CI: Confidence interval
*ratios for Cmax and AUC compare co-administration of the medication with elagolix vs. administration of the medication alone.
[a] metabolite of norgestimate

[180] No clinically significant changes in sertraline, fluconazole, bupropion, or transdermal patch E2/NETA 0.51/4.8 mg exposures were observed when co-administered with elagolix 300 mg twice daily.

Pharmacogenomics

[181] Disposition Hepatic uptakedate of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in groups of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C) (these patients are likely to have reduced hepatic uptake of elagolix; and thus, higher plasma elagolix concentrations). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. WomenPatients with this genotype are expected to have approximately 2-fold higher elagolix mean concentrations compared to women with normal transporter function (i.e., SLCO1B1 521T/T genotype). Adverse effects of elagolix have not been fully evaluated in subjects who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C). In one embodiment, for clinical management of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C), the dose of elagolix may be reduced to about 50% of the original dose in order to achieve once daily mean concentration of elagolix. Therefore, for clinical management of patients who have two reduced function alleles of the gene that encodes OATP 1B1, the elagolix dose may be reduced to half the original dose, the dosing interval may be reduced from twice a day to once a day, or the dosing may be reduced from daily dosing to every other day dosing.

Example 15: Nonclinical Toxicology

Elagolix

[182] Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 11.9-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (7.7 to 8.1-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans. Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay. In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 2.9-fold. However, because elagolix has low affinity for the GnRH receptor in the rat and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

E2/NETA

[183] Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Example 16: Clinical Studies

[184] The efficacy of the System of Example 10in the management of heavy menstrual bleeding (HMB) associated with uterine fibroids was demonstrated in two, randomized, double-blind, placebo-controlled studies [UF-1 (NCT02654054) and UF-2 (NCT02691494)] in which 790 premenopausal women

who had at least two menstrual cycles with greater than 80 mL of menstrual blood loss (MBL), as assessed by alkaline hematin (AH) method (an objective, validated measure to quantify MBL volume on sanitary products), received the System of Example 10 or placebo for 6 months. Each study also included an elagolix 300 mg twice daily reference arm to characterize the impact of E2/NETA on efficacy and safety. In UF-1 and UF-2 , the median age was 43 years (ranging from 25 to 53 years); 68% of the women were Black or African American, 29% were White, and 3% were other races; 16% of women had uterine fibroids and coexisting adenomyosis at baseline as evaluated by transvaginal and transabdominal ultrasound (TVU/ TAU) and/or MRI; MBL at baseline ranged from 83.8 mL to 1207.1 mL; uterine volume by TVU/TAU ranged from 71.6 cm3 to 3347.9 cm3; and primary fibroid volume by TVU/TAU ranged from 1 cm3 to 1081.5 cm3.

Menstrual Blood Loss

[185] The primary endpoint in both studies was the proportion of women who achieved successful treatment defined as attaining both, 1) MBL volume less than 80 mL at the Final Month and 2) 50% or greater reduction in MBL volume from Baseline to the Final Month. MBL at baseline was defined as the mean of total MBL volume from at least 2 screening menstrual cycles that are >80 mL. Final month is defined as the last 28 days before and including the last treatment visit date or the last dose date. A higher proportion of women treated with the System of Example 10 achieved successful treatment compared to placebo (see Table A10).

Table A10: Proportion of Women Achieving Successful Treatment in Studies UF-1 and UF-2

	UF-1		**UF-2**	
	System of Example 10	Placebo	System of Example 10	Placebo
	N=206	N=102	N=189	N=94

Women with MBL volume < 80 mL at and ≥ 50% reduction in MBL volume from Baseline to the Final Month	69%	9%	77%	11%
Difference from placebo	60% (51, 69)		66% (57, 75)	
CI: confidence interval				

Changes in MBL Volume

[186] Compared with placebo, the System of Example 10 reduced mean MBL volume from Baseline at Month 1 through Month 6 (see Figures 20 and 21). In Study UF-1, mean baseline MBL was 238.0 mL for the System of Example 10, and 255.3 mL for placebo. In Study UF-2, mean baseline MBL was 2298.5 mL for the System of Example 10, and 254.3 mL for placebo. Women taking the System of Example 10 had a significant mean reduction of MBL volume from baseline to final month in both studies UF-1 and UF-2 compared to women taking placebo (Study UF-1; -176.7 mL for the System of Example 10 and 0.81 mL for placebo; Study UF-2 -168.89 mL for the System of Example 10and -4.3 mL for placebo).

Suppression of Bleeding

[187] In Studies UF-1 and UF-2, a greater proportion (57% and 61%, respectively) of women receiving the System of Example 10 experienced suppression of bleeding, defined as no bleeding (but spotting allowed), at final month, compared to 4% and 5% of women receiving placebo, respectively.

Hemoglobin (Hgb)

[188] Over 90% of women with baseline Hgb ≤ 10.5 g/dL took supplemental iron. In Studies UF-1 and UF-2, a greater proportion of women treated with the System of Example 10 who were anemic with baseline Hgb ≤

10.5 g/dL achieved an increase ≥ 2 g/dL in Hgb from baseline to month 6 compared to women treated with placebo (see Table A11).

Table A11: Proportion of Women with Baseline Hgb ≤10.5 g/dL and Increase ≥ 2 g/dL in Hgb at Month 6

	UF-1		UF-2	
	System of Example 10 n=52	**Placebo n=32**	**The System of Example 10 n=48**	**Placebo n=24**
(%) at Month 6	62%	16%	50%	21%
Between-Group				
CI: confidence interval				

Example B1

[189] PBPK Model Based Virtual Bioequivalence Assessment of Different Elagolix Formulations

[190] Elagolix is approved at doses of 150 mg once daily and 200 mg twice daily for the management of moderate to severe pain associated with endometriosis, with roller compacted (RC2) tablets being used as the commercial formulation. A combination product of elagolix 200 mg and estradiol (E2) 1 mg/norethindrone acetate (NETA) 0.5 mg is being evaluated in endometriosis Phase 3 trials. The phase 3 investigational product consisted of elagolix 200 mg tablet co-administered with E2/NETA tablet, while the proposed commercial product consists of elagolix 200 mg melt granulated (MG) tablet and E2/NETA tablet as a fixed-dose combination (FDC) morning capsule and elagolix 200 mg MG evening capsule. Dissolution tests performed using USP I (basket) apparatus showed dissimilar in vitro dissolution profiles for the Phase 3 and the to-be-marketed (TBM) capsules, thus requiring the evaluation of bioequivalence (BE) with respect to in vivo exposures. Physiologically based pharmacokinetic (PBPK)

modeling was used along with in vitro dissolution data for various formulations to conduct virtual BE simulations in order to demonstrate simulated bioequivalent exposures without conducting clinical BE studies.

Methods

[191] A previously developed PBPK model (Simcyp V17) for elagolix which was verified with clinical PK and drug-drug interaction (DDI) data, served as the base model. (See *Chiney et al.,* 2019, Clinical Pharmacokinetics). The PBPK model was updated by incorporating in vitro dissolution data of the elagolix formulations using the mechanistic ADAM (Advanced Dissolution & Absorption Model) module which captures drug dissolution and absorption in the different regions of the GI tract. Dissolution testing using USP-I apparatus at 100 RPM in 900 mL of 0.05M Sodium Phosphate, pH 6.8 was conducted for the relevant formulations. The PBPK model with in vitro data incorporated was externally validated using clinical data from two clinical bioequivalence studies, where the elagolix capsules at 300 mg dose were evaluated against the reference RC2 tablet for a different indication. Model predicted exposures (Cmax and AUC) in a virtual healthy, female population were compared to clinical observations for each formulation from the BE studies. Model predicted exposure ratios for Cmax and AUC of the test capsule formulations to the reference (RC2) tablet were also compared to clinical observations. The clinically validated PBPK model was used to simulate virtual bioequivalence trials in a cross-over fashion to compare elagolix 200 mg capsules to 200 mg RC2 tablets. The virtual BE trials were conducted 100 times with different virtual subjects to evaluate the effect of inter-occasion or inter-trial variability on bioequivalence of the formulations.

Results

[192] PBPK model predicted exposures for the 300 mg tablet (RC2) and 300 mg capsules formulations compared well with clinical observations from BE studies

with less than 25% predictions errors. Model predictions of relative BE ratios comparing test to reference formulations also compared well with clinical data from the BE studies. These BE study results were not used in model calibration or verification and thus were used as external validation of the PBPK model predictions. This provided confidence in using the PBPK model to predict exposures for clinically untested formulations using their in vitro dissolution data as inputs. Based on results of the virtual BE trials simulations, both capsule formulations at the 200 mg dose met the bioequivalence criteria of 0.80 – 1.25 when compared to the reference RC2 formulation. Both Cmax and AUC ratios of the test to reference formulations were bioequivalent with the geometric mean of Cmax and AUC ratios predicted to be 0.9 and 0.95 respectively. The 90% prediction intervals of the exposure ratios were also within the BE criteria. The results from multiple trial simulations using different virtual subjects also confirmed that the geometric means and 90% confidence intervals of the exposure ratios for all virtual trials met the BE criteria.

Conclusions

[193] This novel work combined in vitro and clinical data for different formulations using PBPK modeling to conduct virtual BE simulations in lieu of clinical trials. The results of the virtual BE simulations from the clinically validated PBPK model were used to justify that the TBM formulations of elagolix are likely to result in exposures similar to that of the formulations tested clinically and justifying the request for an in vivo bioequivalence waiver. This analysis also showed that permeability and not solubility was the determining factor for the absorption of elagolix, which results in bioequivalent in vivo exposures despite dissimilar in vitro dissolution profiles. This work demonstrated the value of combining in vitro and in silico data in the development and evaluation of new formulations.

Example B2

[194] Clinical Pharmacology Challenges in Assessing Bioequivalence for Elagolix Fixed Dose Combination Products

[195] Elagolix is being developed for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF). The investigational drug product being studied in the UF phase 3 trials is elagolix 300 mg twice daily roller compaction 2 (RC2) tablets co-administered with estradiol/norethindrone acetate (E2/NETA) 1 mg/0.5 mg once daily tablet. For patient compliance and convenience, the proposed to-be-marketed (TBM) formulations are a fixed dose combination (FDC) capsule consisting of elagolix/E2/NETA 300/1/0.5 mg for the morning dose, and an elagolix 300 mg capsule for the evening dose. The two formulations exhibited dissimilar for in vitro dissolution profiles, indicating potential different release characteristics in vivo. The purpose of the studies was to assess (1) BE of the TBM elagolix FDC morning capsule formulation compared to elagolix RC2 tablet co-administered with E2/NETA tablet in postmenopausal healthy women; (2) BE of the TBM elagolix evening capsule formulation compared to elagolix RC2 tablet in premenopausal healthy women; and (3) the effect of food (high-fat meal) on bioavailability of elagolix capsules.

Method

[196] The present research included two separate large phase 1 BE studies. The first one is a randomized, single-center, single dose, four sequence, two/three-period, crossover, phase 1 BE study. This study was conducted in healthy pre-menopausal women (N= 57) to assess BE between elagolix 300 mg capsule (test product; T) and elagolix 300 mg RC2 tablet (reference product; R), as well as the food effect on bioavailability of the elagolix capsule. Serial blood samples for assay of elagolix were collected prior to dosing and up to 24 hours after dosing on study days.

[197] A separate randomized, multi-center, single dose, four sequence, two/three-period, crossover, phase 1 BE study was conducted in healthy post-menopausal women (N= 167) to assess BE between elagolix/E2/NETA 300/1/0.5 mg FDC capsule (T) and elagolix 300 mg RC2 tablet co-administrated with E2/NETA 1 /0.5 mg tablet (R). The food effect on bioavailability of elagolix FDC capsules was also evaluated. Serial blood samples for assay of elagolix, total estrone, and norethindrone were collected prior to dosing and up to 72 hours after dosing on study days.

[198] For both BE studies, a non-compartmental analysis (NCA) was performed using the SAS software (Certara, Princeton, NJ, USA). The geometric mean ratio (GMR) (90% confidence interval [CI]) of T/R for maximum observed plasma concentration (Cmax) and the area under the plasma concentration-time curve from time zero to infinity (AUC0-inf) were calculated for BE assessment. The food effect was evaluated by assessing relative bioavailability (90% confidence interval) of the elagolix capsules (both elagolix capsule and FDC capsule) under fasting and fed conditions.

Results

[199] For the elagolix alone study, the GMR (90% CI) of T/R for elagolix Cmax and AUC0-inf under fasting condition were 0.87 (0.81 – 0.94) and 0.97 (0.93 – 1.01), respectively, indicating elagolix 300 mg capsule is bioequivalent to elagolix 300 mg RC2 tablet. Following administration of elagolix 300 mg capsule after a high-fat breakfast, the elagolix Cmax and AUC0-inf were 40% and 28% lower, respectively. Tmax was delayed by approximately 1 hour compared to fasting conditions. The effect of food on elagolix relative bioavailability was not clinically relevant based on exposure-response analyses.

[200] For the elagolix FDC study, the GMR (90% CI) of T/R for Cmax of elagolix, baseline-adjusted total estrone, and norethindrone were 0.91 (0.87 -

0.95), 1.02 (0.96 - 1.08), 1.12 (1.08 - 1.15), respectively, while the GMR (90% CI) of T/R for AUC0-inf of elagolix, baseline-adjusted total estrone, and norethindrone were 0.97 (0.95 - 1.00), 0.93 (0.87 - 1.00), 0.96 (0.94 - 0.98), respectively, under the fasting condition. The additional hormones analytes also achieved BE criteria. These findings indicated that elagolix/E2/NETA 300/1/0.5 mg FDC capsule is bioequivalent to elagolix 300 mg RC2 tablet co-administrated with 1 /0.5 mg E2/NETA tablet. Following administration of elagolix/E2/NETA 300/1/0.5 mg FDC capsule after a high-fat breakfast, the elagolix Cmax and AUC0-inf were 36% and 25% lower, respectively, when compared to exposures under fasting conditions.

Conclusion

[201] The BE studies' results demonstrated that the TBM elagolix FDC (elagolix/E2/NETA 300/1/0.5 mg) morning capsule and elagolix 300 mg evening capsule formulations are bioequivalent to the UF Phase 3 clinical trials formulation (co-administered elagolix 300 mg tablet and E2/NETA 1/0.5 mg tablet) despite the dissimilarity in their in vitro dissolution profiles. The effect of food (high fat meal) on the components of the TBM product was similar to that observed previously with Orilissa™ commercial tablets for elagolix, and as expected for E2/NETA (activella® USPI). Thus, the morning FDC 300/1/0.5 mg and evening elagolix 300 mg capsules can be taken with or without food.

[202] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents.

[203] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of

use of the invention, may be made without departing from the spirit and scope thereof.

WHAT IS CLAIMED IS:

1. A multi-drug delivery system comprising

a first capsule comprising:

a first capsule body comprising a first interior;

a first tablet within the first interior, the first tablet comprising a first drug; and

a second tablet within the first interior, the second tablet comprising at least a second drug different from the first drug, and a third drug different from the first and second drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient; and

a second capsule, co-packaged with the first capsule, comprising:

a second capsule body comprising a second interior; and

a third tablet within the second interior, the third tablet comprising the first drug,

wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

2. The multi-drug delivery system in accordance with Claim 1, wherein the first tablet comprises elagolix.

3. The multi-drug delivery system in accordance with Claim 1 or 2, wherein the first tablet comprises between about 175 mg to about 325 mg of elagolix and the second tablet comprises between about 0.75 mg and about 1.25 mg of estradiol.

4. The multi-drug delivery system in accordance with claim 3, wherein the second tablet further comprises between about 0.1 mg and about 1 mg of norethindrone acetate.

5. The multi-drug delivery system in accordance with claim 3, wherein after about 15 minutes, the release of estradiol is equal to or greater than 70%.

6. The multi-drug delivery system in accordance with Claim 1, wherein the first capsule is marked with a first identifier and the second capsule is marked with a second identifier different from the first identifier such that the first capsule and the second capsule are visually distinguishable.

7. The multi-drug delivery system in accordance with Claim 6, wherein the first identifier is configured to indicate the first capsule is intended for administration within a first time window in the day, and the second identifier is configured to indicate the second capsule is intended for administration within a second time window in the day different from the first time window.

8. The multi-drug delivery system in accordance with Claim 7, wherein the first identifier is configured to indicate the first capsule is intended for administration at the first time window that is before noon, and the second identifier is configured to indicate the second capsule is intended for administration at the second time window that is after noon.

9. The multi-drug delivery system in accordance with any of Claims 6-8, wherein the first identifier is a first color included on the first capsule, and the second identifier is a second color included on the second capsule.

10. The multi-drug delivery system in accordance with any of Claims 1-9 further comprising a package comprising a plurality of compartments configured to house the first capsule and the second capsule.

11. The multi-drug delivery system in accordance with Claim 10, wherein the package comprises a blister card that defines the plurality of compartments, wherein the first capsule and the second capsule housed in the plurality of compartments are accessible by puncturing a seal in the blister card.

12. The multi-drug delivery system in accordance with Claim 10 or 11, wherein the package comprises information printed thereon related to when to administer the first capsule and the second capsule to the patient.

13. The multi-drug delivery system in accordance with Claim 10, wherein the blister card comprises a first row of the plurality of compartments and a second row of the plurality of compartments, wherein the first capsule is housed in the first row, wherein the second capsule is housed in the second row, and wherein the first row and the second row are visually distinct.

14. A capsule for use in delivering drugs to a patient, the capsule comprising:

a capsule body comprising an interior;

a first tablet within the interior, the at least one first tablet comprising a first drug; and

a second tablet within the interior, the second tablet comprising at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule body within the patient,

wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second drug in the second tablet dissolves after 30 minutes.

15. The capsule in accordance with Claim 14, wherein the first tablet comprises between about 175 mg and about 325 mg of elagolix and the second tablet comprises between about 0.75 mg and about 1.25 mg of estradiol.

16. The capsule in accordance with claim 15, wherein the second tablet further comprises between about 0.1 mg and about 1.0 mg of norethindrone acetate.

17. The capsule in accordance with claim 15, wherein after 16 minutes, the release of estradiol is equal to or greater than 70%.

18. The capsule in accordance with Claim 14, wherein the capsule body is oblong to define a longitudinal axis, wherein the at least one first tablet and the second tablet are arranged in a serial relationship along the longitudinal axis within the interior.

19. The capsule in accordance with Claim 14, wherein the at least one first tablet and the second tablet are distinct tablets that have been formed separately from each other and then secured within the interior.

20. The capsule in accordance with Claim 14, wherein the capsule body does not contain drugs in powder form.

21. The capsule in accordance with Claim 14, wherein the capsule body does not include a barrier extending between the first tablet and the second

tablet, and wherein the first tablet and the second tablet are not bonded together within the interior.

22. The capsule in accordance with Claim 14, wherein the second tablet comprises the second drug and a third drug that are both configured to have a dissolution rate of greater than about 80 percent within the first 30 minutes of administration using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C.

23. The capsule in accordance with Claim 14, wherein the first capsule comprises gelatin.

24. A method of delivering drugs to a patient, the method comprising:

delivering a first capsule to the patient, wherein the first capsule includes:

a first capsule body including a first interior;

a first tablet within the first interior, the first tablet including a first drug; and

a second tablet within the first interior, the second tablet including at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within the patient; and

delivering a second capsule, co-packaged with the first capsule, to the patient after a predetermined amount of time has elapsed after administration of the first capsule, wherein the second capsule includes:

a second capsule body including a second interior; and

a third tablet within the second interior, the third tablet including the first drug.

25. The method accordance with Claim 24, wherein the first tablet comprises between about 175 and 325 mg of elagolix and the second tablet

comprises between about 0.75 mg and 1.25 mg of estradiol and between about 0.1 mg and 1.0 mg of norethindrone.

26. The method in accordance with claim 24, wherein after 20 minutes, the release of estradiol is equal to or greater than 70%.

27. The method in accordance with Claim 24, wherein delivering a second capsule comprises delivering the second capsule at least 5 hours after administration of the first capsule.

28. The method in accordance with Claim 24, wherein delivering the first capsule comprises delivering the first capsule at a first time window in the day that is before noon, and wherein delivering a second capsule comprises delivering the second capsule at a second time window in the day that is after noon.

29. The method in accordance with Claim 24 further comprising providing a package comprising a plurality of compartments configured to house the first capsule and the second capsule therein.

30. The method in accordance with Claim 29 further comprising housing a plurality of first capsules and a plurality of second capsules within the package, wherein the number of first capsules and the number of second capsules housed within the package are each a multiple of the number of days in a week.

31. A multi-drug tablet having a first tablet and a second tablet coated on the first tablet.

32. The multi-drug tablet of claim 31, wherein the second tablet is positioned in the center of the first tablet.

33. The multi-drug tablet of claim 32, further comprising crospovidone.

34. A medication container assembly comprising:

a first set of a plurality of compartments each compartment configured to support a first capsule;

a second set of a plurality of compartments each compartment configured to support a second capsule co-packaged with the first capsule;

wherein, the first capsule comprises a first interior;

a first tablet within the first interior, the first tablet comprising a first drug; and

a second tablet within the first interior, the second tablet comprising at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient; and

the second capsule comprises a second capsule body comprising a second interior, and a third tablet within the second interior, the third tablet comprising the at least one drug selected from the group consisting of: the first drug, the second drug, or a third drug.

35. A multi-drug capsule comprising:

a first tablet, the first tablet comprising a first drug;

a second tablet, the second tablet comprising at least a second drug different from the first drug, and a third drug different from the first and second drug,

wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule within a patient;

wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

36. The multi-drug capsule in accordance with Claim 35, wherein the first tablet comprises elagolix.

37. The multi-drug capsule in accordance with Claim 35 or 36, wherein the first tablet comprises between about 175 mg to about 325 mg of elagolix and the second tablet comprises between about 0.75 mg and about 1.25 mg of estradiol.

38. An oral multi-drug capsule composition comprising:

(a) 300 mg of free acid equivalent of elagolix;

(b) 1 mg of estradiol; and

(c) 0.5 mg of norethindrone acetate;

wherein, following administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration (Cmax) for said elagolix of about 1218.4 ng/mL to about 2185 ng/mL;

a mean peak concentration (Cmax) for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL;

a mean peak concentration (Cmax) for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL;

a mean Area Under the Curve ($AUC_{(t)}$) for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL;

a mean Area Under the Curve ($AUC_{(t)}$) for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and

a mean Area Under the Curve ($AUC_{(t)}$) for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

39. An oral multi-drug capsule composition comprising:

(a) 300 mg of free acid equivalent of elagolix;

(b) 1 mg of estradiol which is administered once daily; and

(c) 0.5 mg of norethindrone acetate;

wherein administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/ml to about 2185 ng/mL;

a mean peak concentration, Cmax for said estradiol of about 0.0424 ng/ml to about 0.0775 ng/ml; and

a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng/ml to about 8.0 ng/ml.

40. The oral multi-drug capsule composition of claim 39, wherein

a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3296.6 ng.hr/mL to about 5892.5 ng.hr/mL;

a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and

a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

41. An oral multi-drug capsule composition comprising:

(a) 300 mg of free acid equivalent of elagolix;

(b) 1 mg of estradiol; and

(c) 0.5 mg of norethindrone acetate;

further wherein administration of a single dose of the composition to healthy adult subjects results in

a mean Area Under the Curve, $AUC_{(t)}$ for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL;

a mean Area Under the Curve, $AUC_{(t)}$ for said estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and

a mean Area Under the Curve, $AUC_{(t)}$ for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL.

42. The oral multi-drug capsule composition of claim 41, wherein administration of the composition to healthy adult subjects results in

a mean peak concentration, Cmax for said elagolix of about 1218.4 ng/mL to about 2185 ng.hr/mL;

a mean peak concentration, Cmax for said estradiol of about 0.0424 ng.hr/mL to about 0.0775 ng/mL ng/mL; and

a mean peak concentration, Cmax for said norethindrone acetate of about 4.56 ng.hr/mL to about 8.0 ng/mL.

43. An oral multi-drug capsule composition comprising:

(a) 300 mg of free acid equivalent of elagolix;

(b) 1 mg of estradiol; and

(c) 0.5 mg of norethindrone acetate;

wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

44. A method of safely treating heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in a pre-menopausal female patient comprising once daily oral administration to said patient of:

(a) 300 mg of free acid equivalent of elagolix;

(b) 1 mg of estradiol; and

(c) 0.5 mg of norethindrone acetate,

wherein said method results in a mean Cmax

for said elagolix of about 1218.4 ng.hr/mL to about 2185 ng/mL;

for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL;

for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL, and a mean $AUC_{(t)}$

for said elagolix of about 3293.6ng.hr/mL to about 5892.5 ng.hr/mL;

for said estradiol of about 0.0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and

for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL, and

wherein, after a treatment duration of about 6 months, said patient achieves equal to or greater than about 2 g/dL increase in hemoglobin as compared to baseline where the patient did not receive elagolix, estradiol, and norethindrone.

45. A capsule for use in delivering drugs to a patient, the capsule comprising:

a capsule body comprising an interior;

a first tablet within the interior, the at least one first tablet comprising a first drug; and

a second tablet within the interior, the second tablet comprising at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the capsule body within the patient,

wherein using USP apparatus 1 at 100 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 45 minutes and at least 90% of the second and third drugs in the second tablet dissolve after 30 minutes.

46. An oral multi-drug capsule composition that is bioequivalent to any of the composition of claims 31-34, 36-45.

47. A method of delivering co-packaged drugs to a patient for oral use, the method comprising:

delivering a first capsule to the patient, wherein the first capsule includes:

a first capsule body including a first interior;

a first tablet within the first interior, the first tablet including a first drug; and

a second tablet within the first interior, the second tablet including at least a second drug different from the first drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within the patient; and

delivering a second capsule, co-packaged with the first capsule, to the patient after a predetermined amount of time has elapsed after administration of the first capsule, wherein the second capsule includes:

a second capsule body including a second interior; and

a third tablet within the second interior, the third tablet including the first drug.

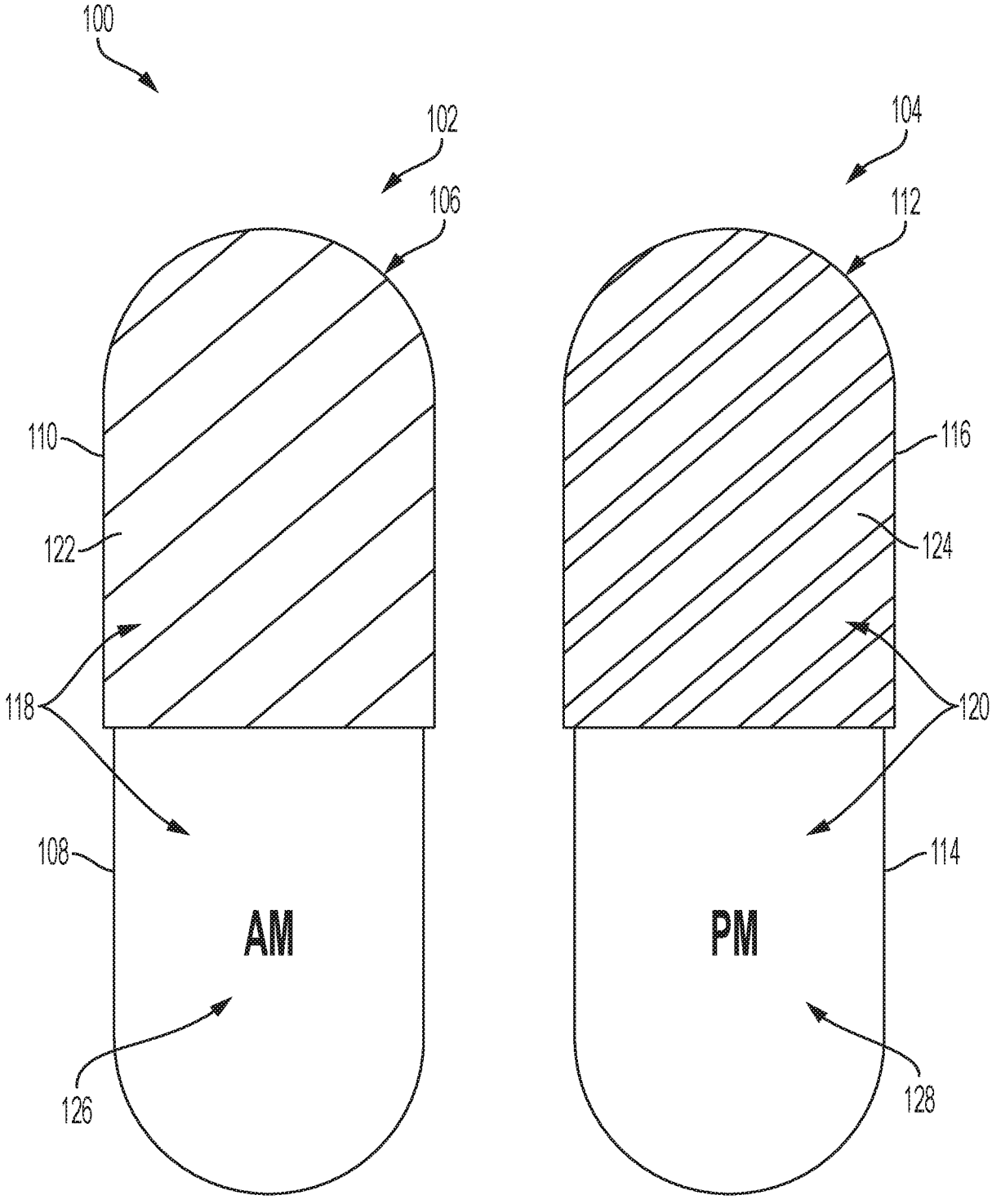

FIG. 1

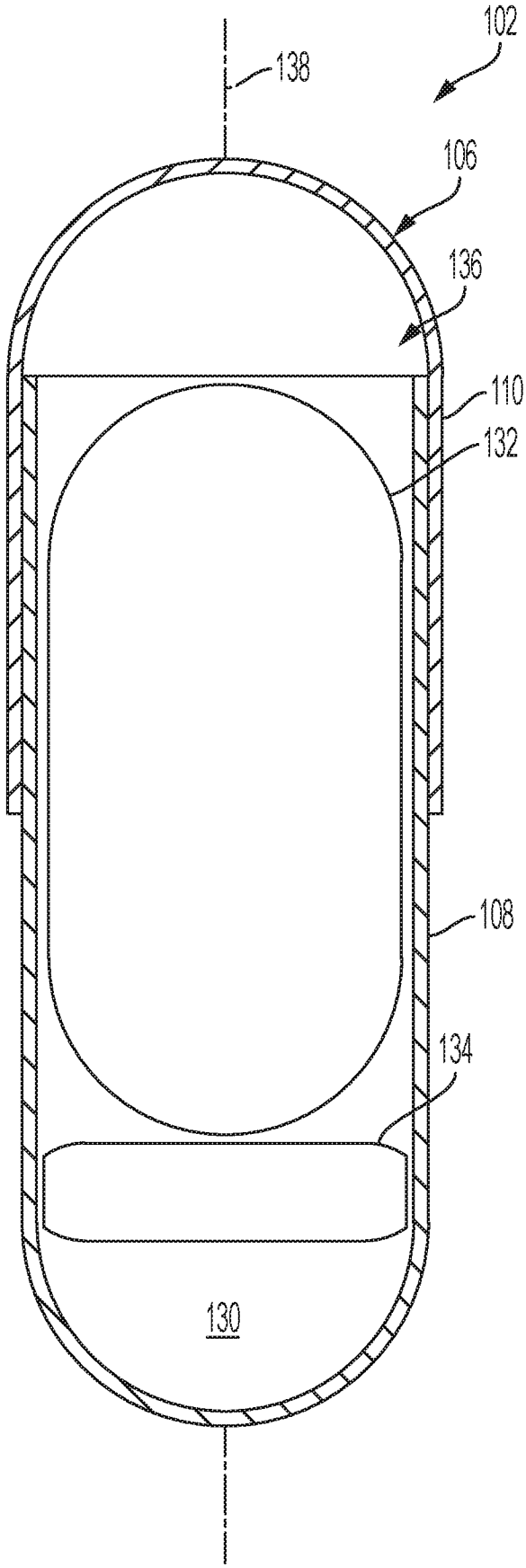

FIG. 2

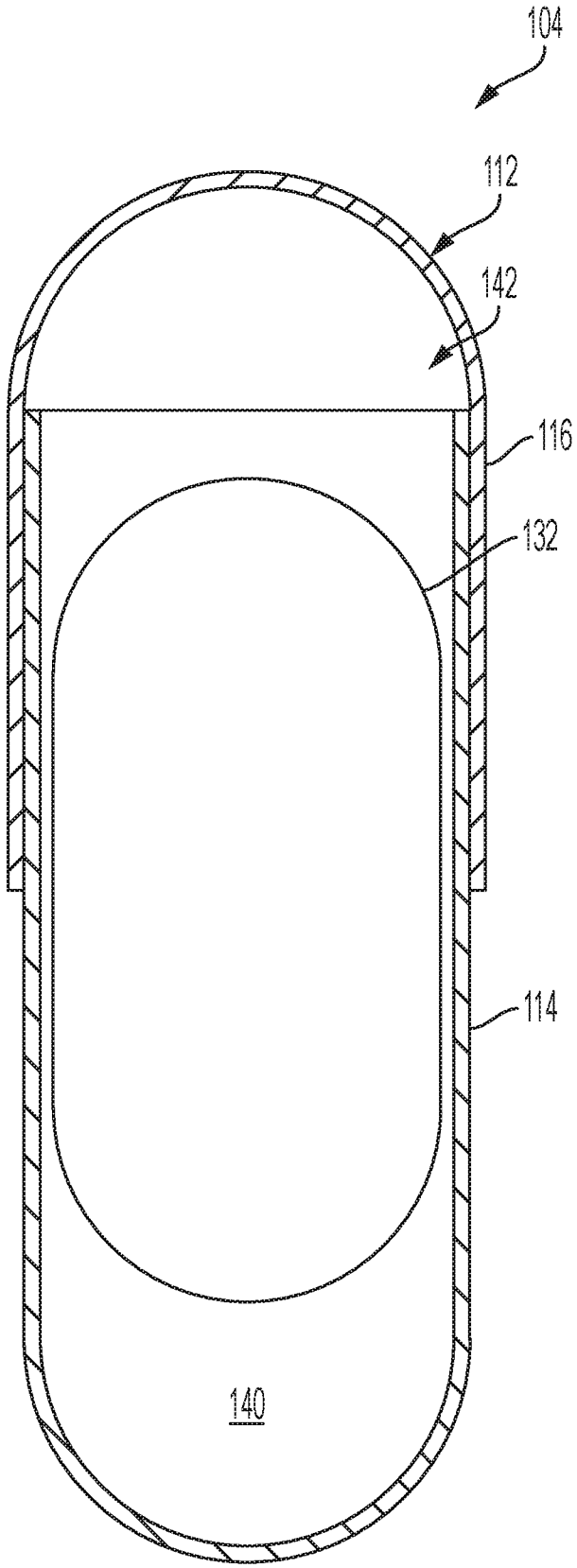

FIG. 3

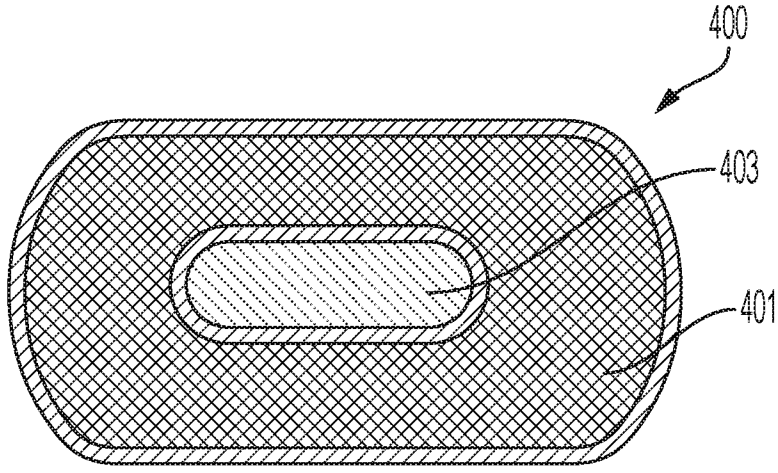

FIG. 4A

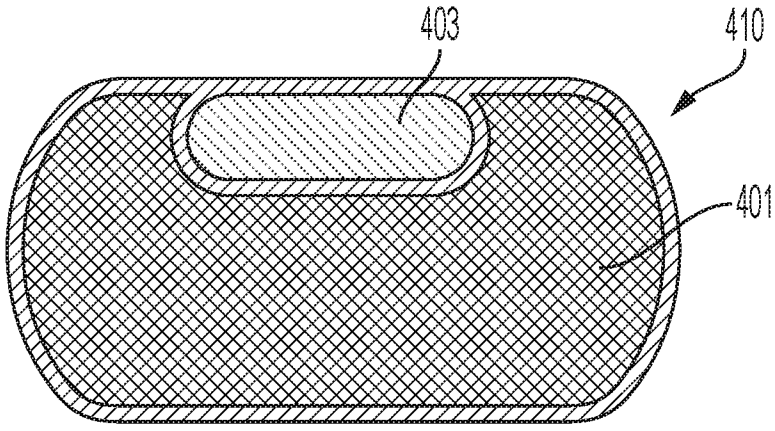

FIG. 4B

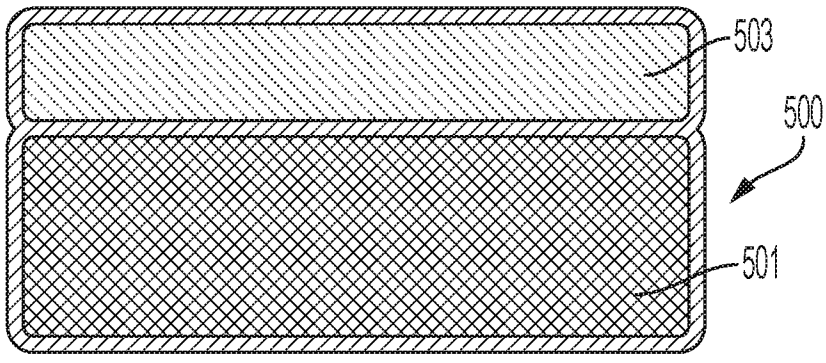

FIG. 5

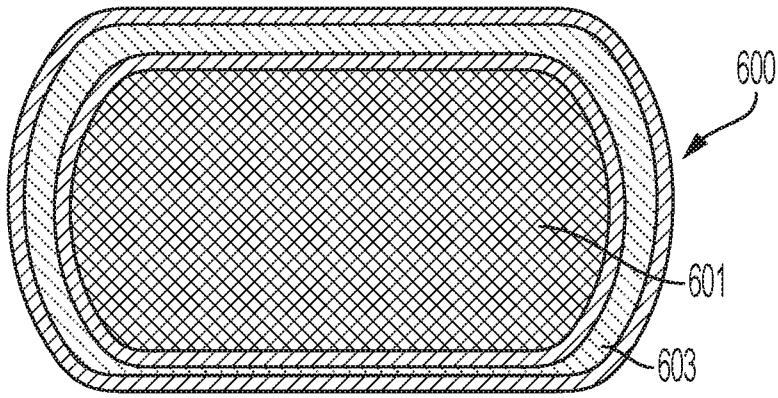

FIG. 6

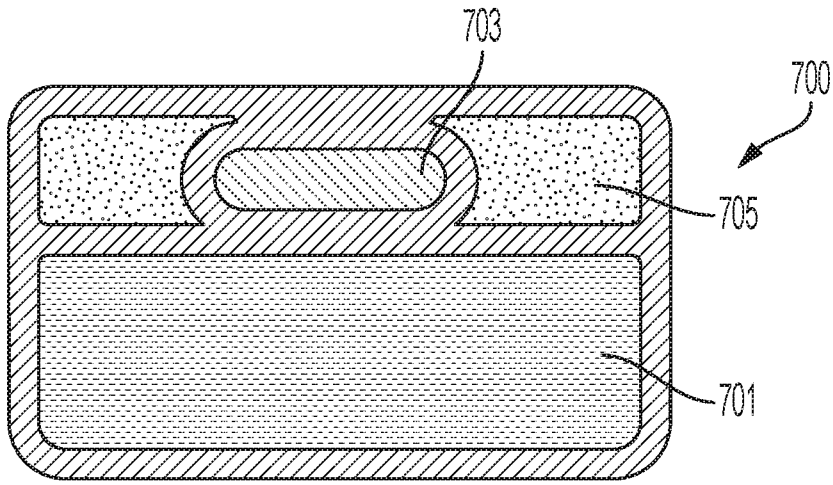

FIG. 7

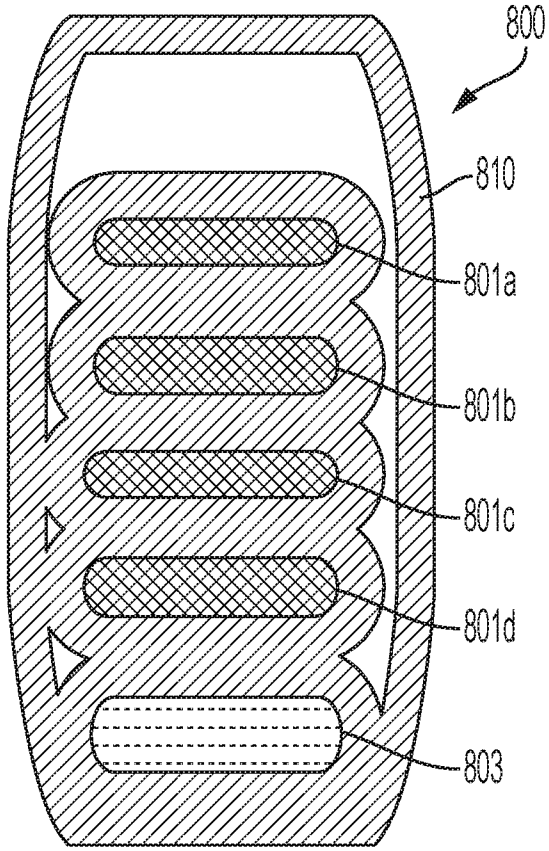

FIG. 8

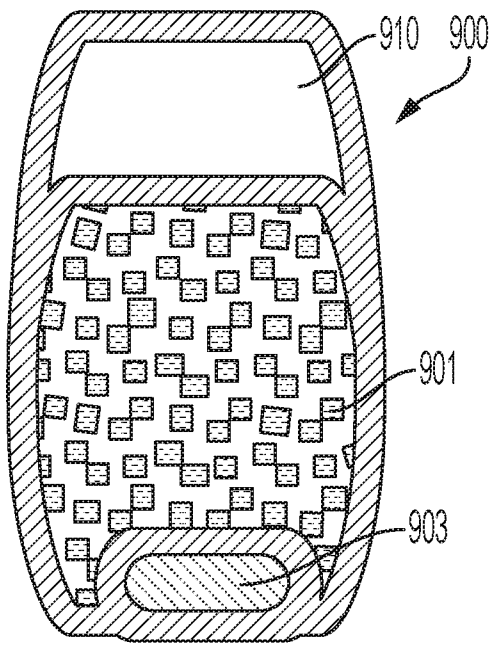

FIG. 9

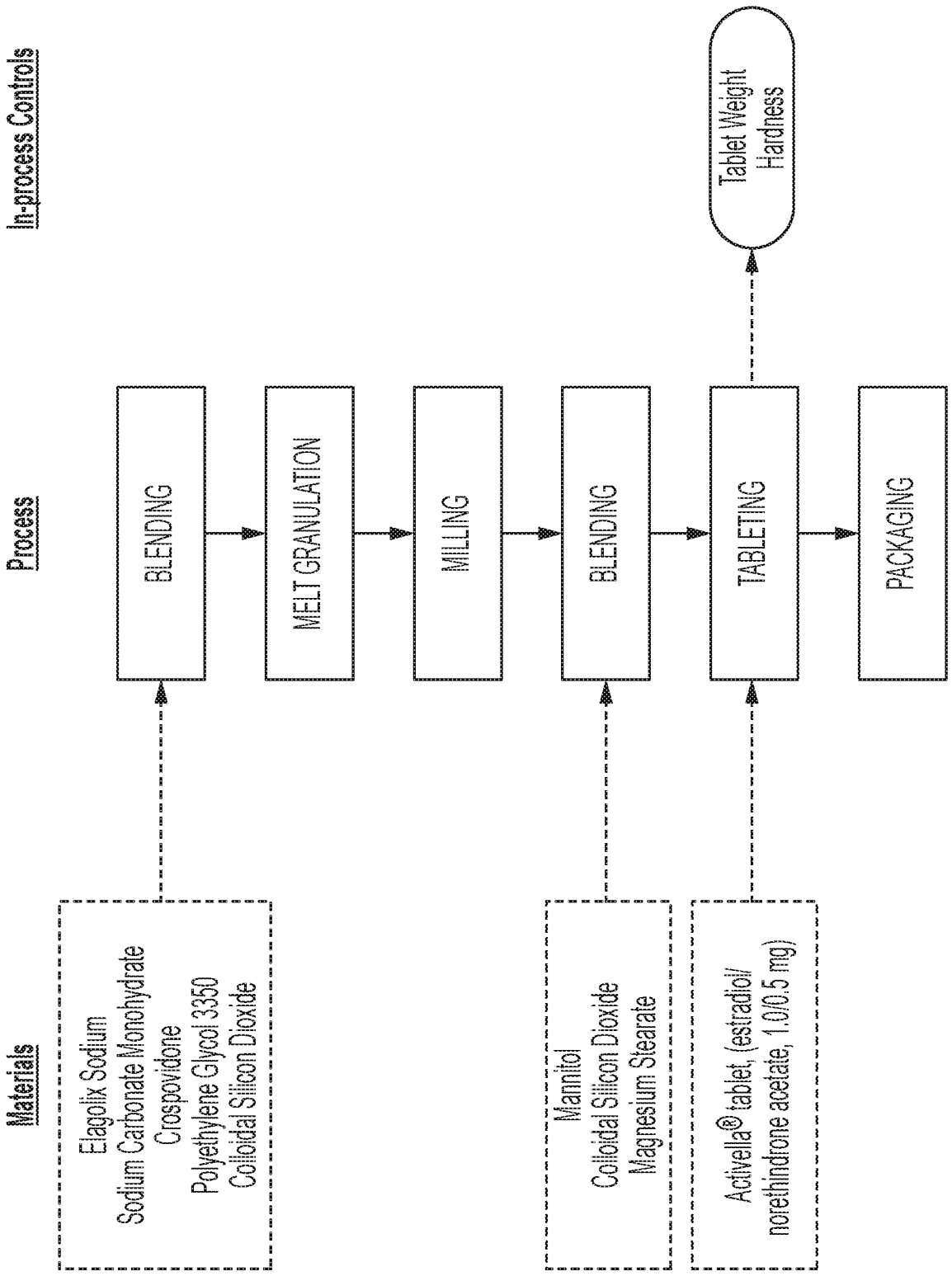
Materials
Process
In-process Controls
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
Mannitol
Colloidal Silicon Dioxide
Magnesium Stearate
BLENDING
Activella® tablet, (estradiol/
norethindrone acetate, 1.0/0.5 mg)
TABLETING
Tablet Weight
Hardness
PACKAGING

FIG. 10

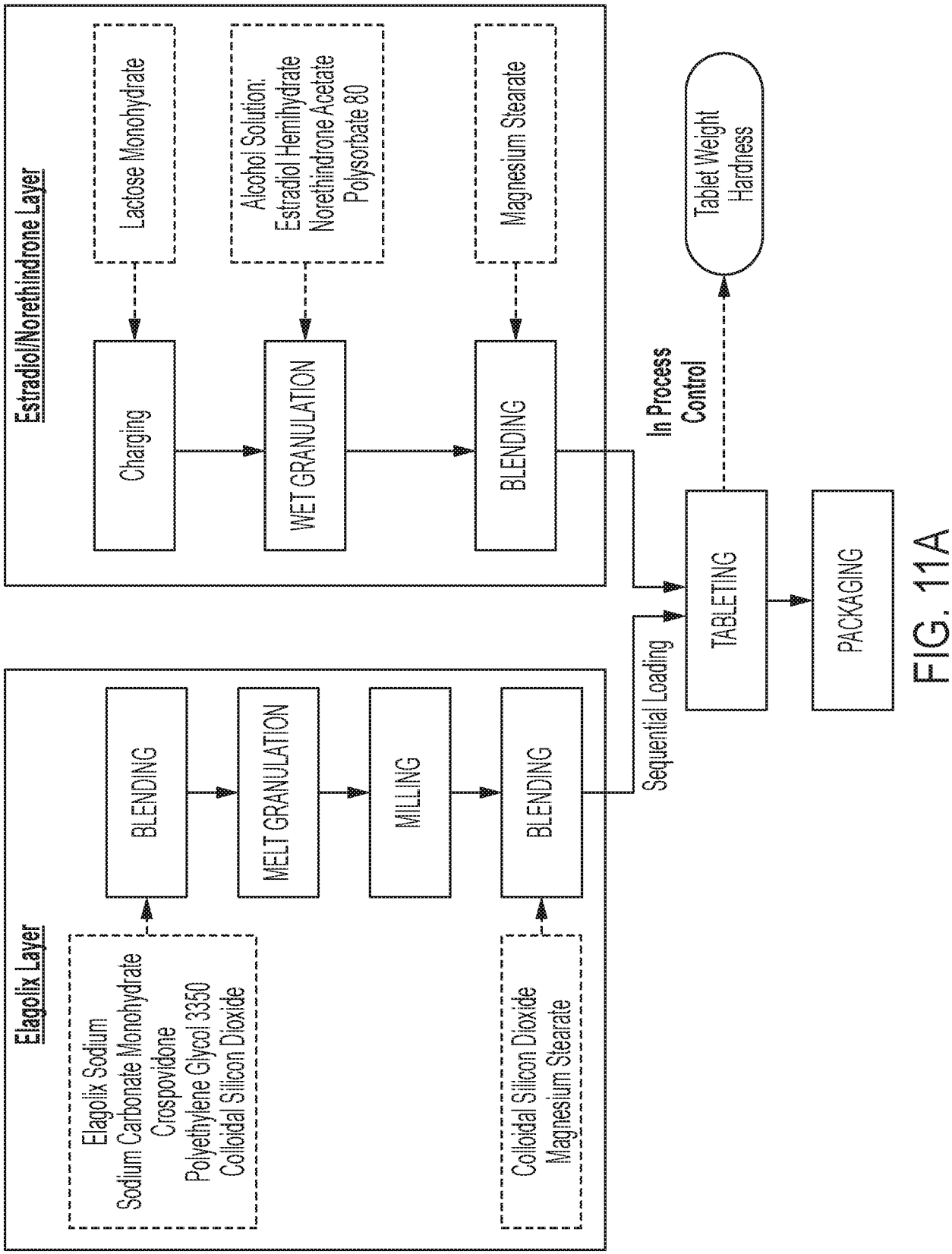
Estradiol/Norethindrone Layer
Charging
Lactose Monohydrate
WET GRANULATION
Alcohol Solution:
Estradiol Hemihydrate
Norethindrone Acetate
Polysorbate 80
BLENDING
Magnesium Stearate
Elagolix Layer
BLENDING
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
MELT GRANULATION
MILLING
BLENDING
Colloidal Silicon Dioxide
Magnesium Stearate
Sequential Loading
In Process Control
Tablet Weight
Hardness
TABLETING
PACKAGING

FIG. 11A

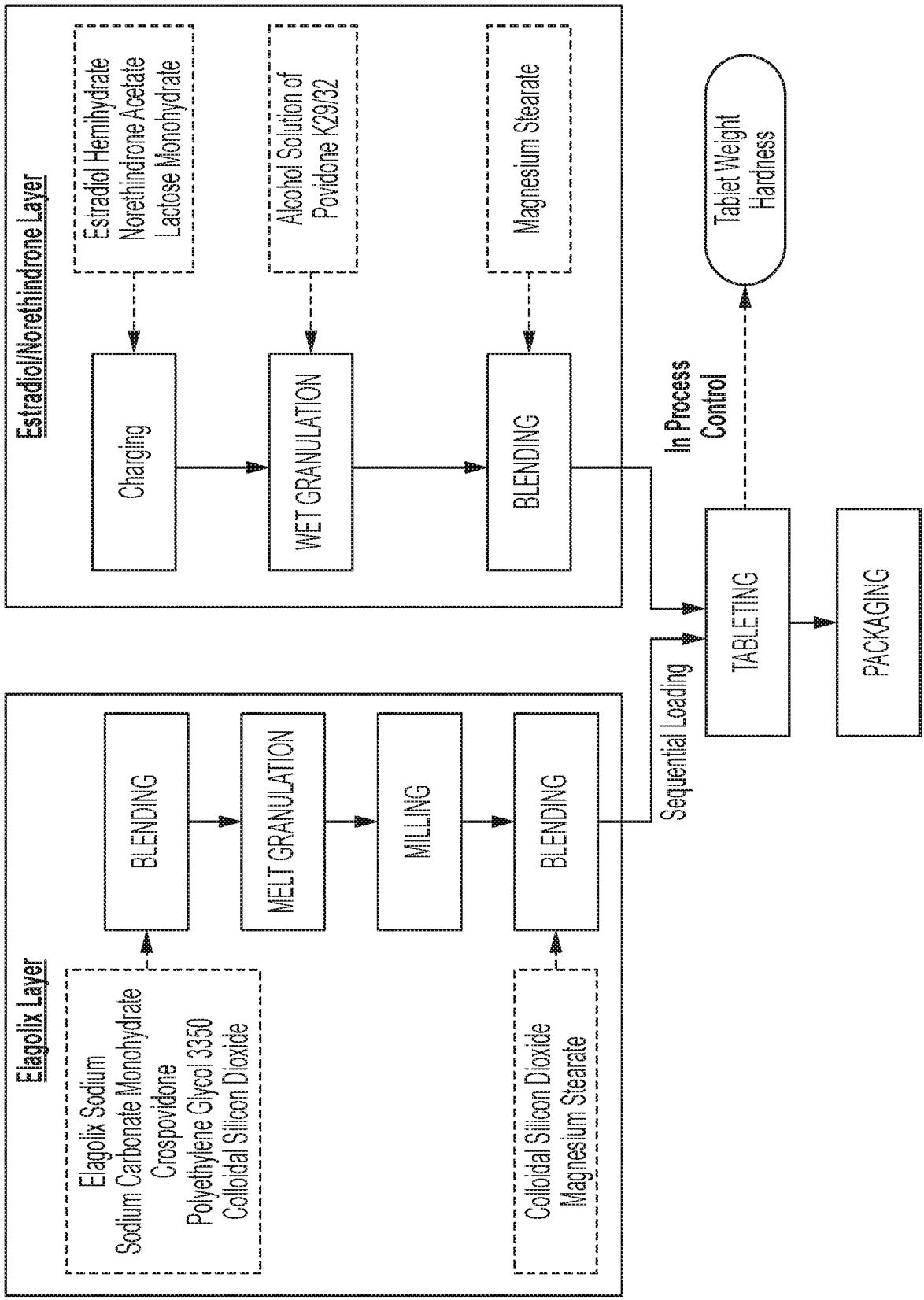
Estradiol/Norethindrone Layer
Estradiol Hemihydrate
Norethindrone Acetate
Lactose Monohydrate
Alcohol Solution of
Povidone K29/32
Magnesium Stearate
Charging
WET GRANULATION
BLENDING
Elagolix Layer
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
BLENDING
Colloidal Silicon Dioxide
Magnesium Stearate
Sequential Loading
In Process
Control
Tablet Weight
Hardness
TABLETING
PACKAGING

FIG. 11B

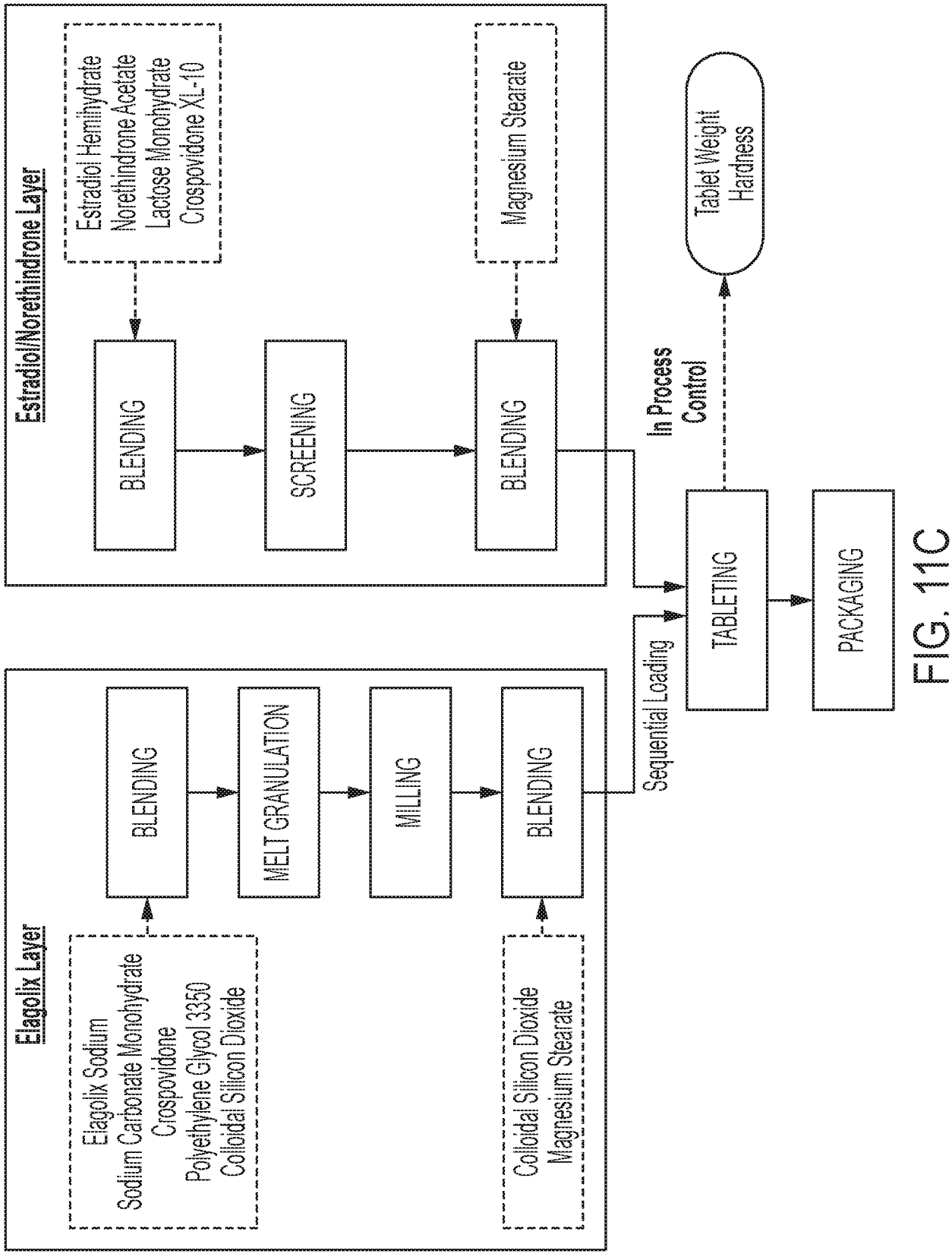
Estradiol/Norethindrone Layer
Estradiol Hemihydrate
Norethindrone Acetate
Lactose Monohydrate
Crospovidone XL-10
BLENDING
SCREENING
BLENDING
Magnesium Stearate
Elagolix Layer
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
BLENDING
Colloidal Silicon Dioxide
Magnesium Stearate
Sequential Loading
In Process Control
Tablet Weight
Hardness
TABLETING
PACKAGING

FIG. 11C

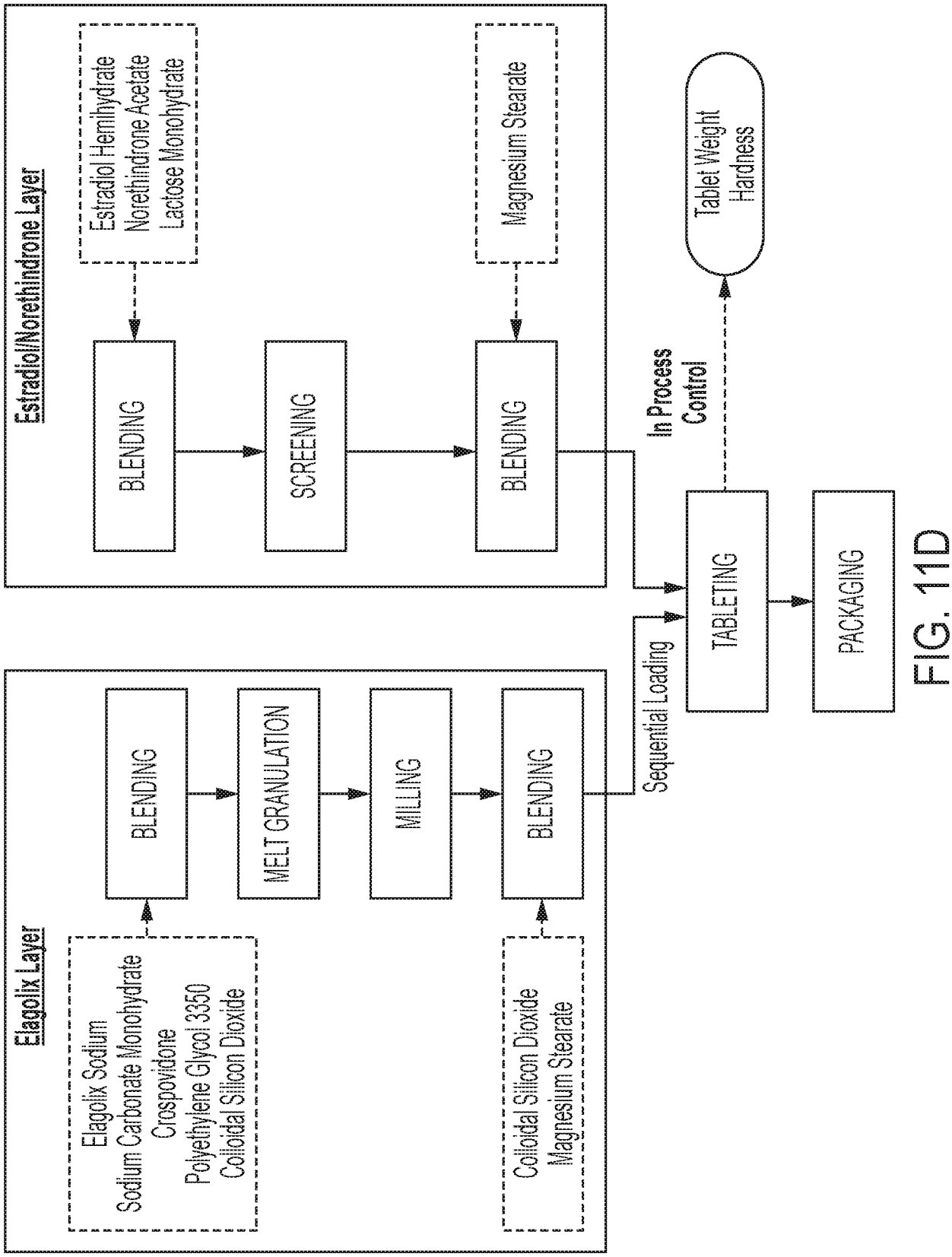
Estradiol/Norethindrone Layer
Estradiol Hemihydrate
Norethindrone Acetate
Lactose Monohydrate
BLENDING
SCREENING
BLENDING
Magnesium Stearate
Elagolix Layer
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
BLENDING
Colloidal Silicon Dioxide
Magnesium Stearate
Sequential Loading
In Process Control
Tablet Weight
Hardness
TABLETING
PACKAGING

FIG. 11D

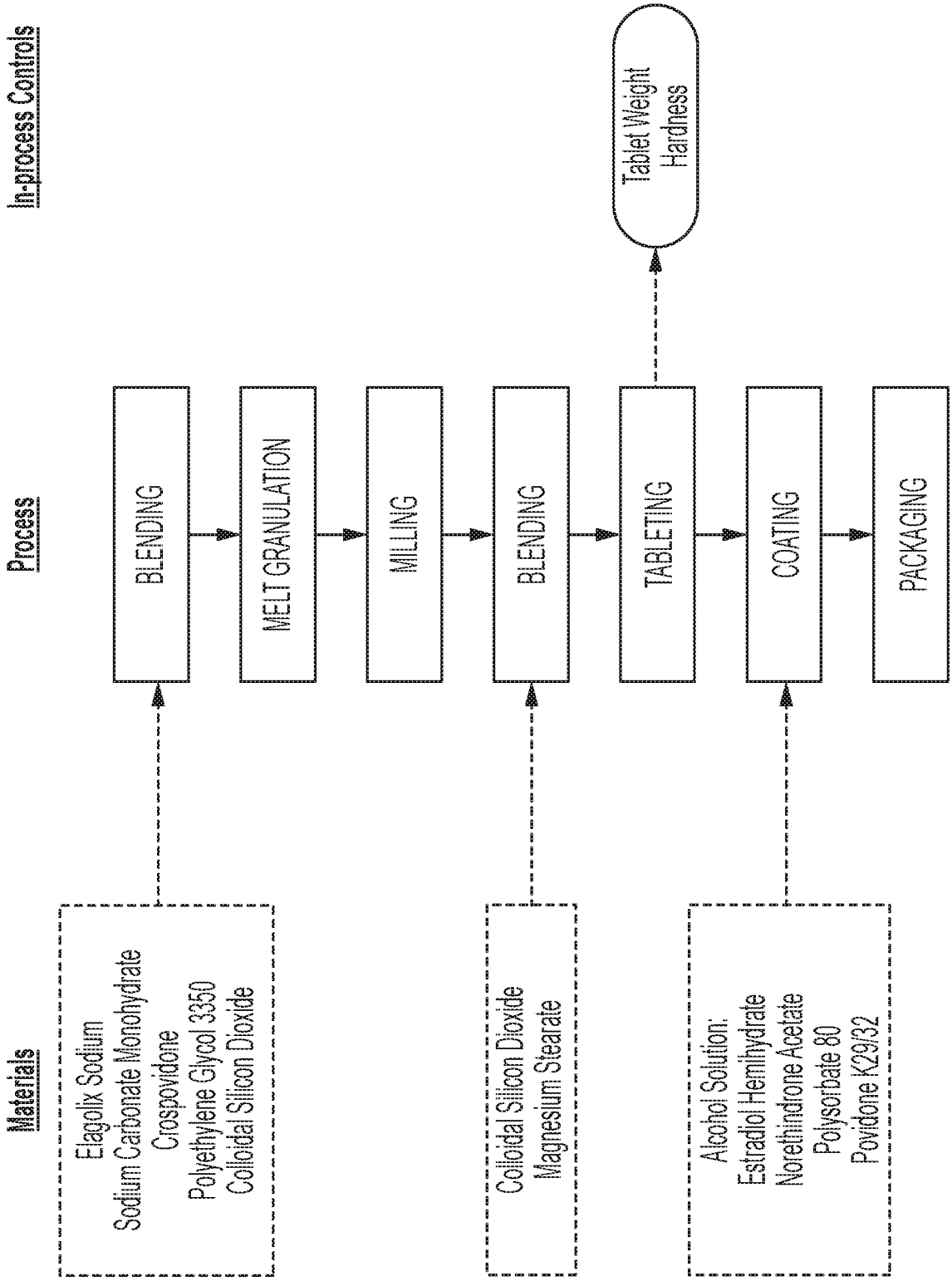
Materials
Process
In-process Controls
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
Colloidal Silicon Dioxide
Magnesium Stearate
BLENDING
TABLETING
Tablet Weight
Hardness
Alcohol Solution:
Estradiol Hemihydrate
Norethindrone Acetate
Polysorbate 80
Povidone K29/32
COATING
PACKAGING

FIG. 12

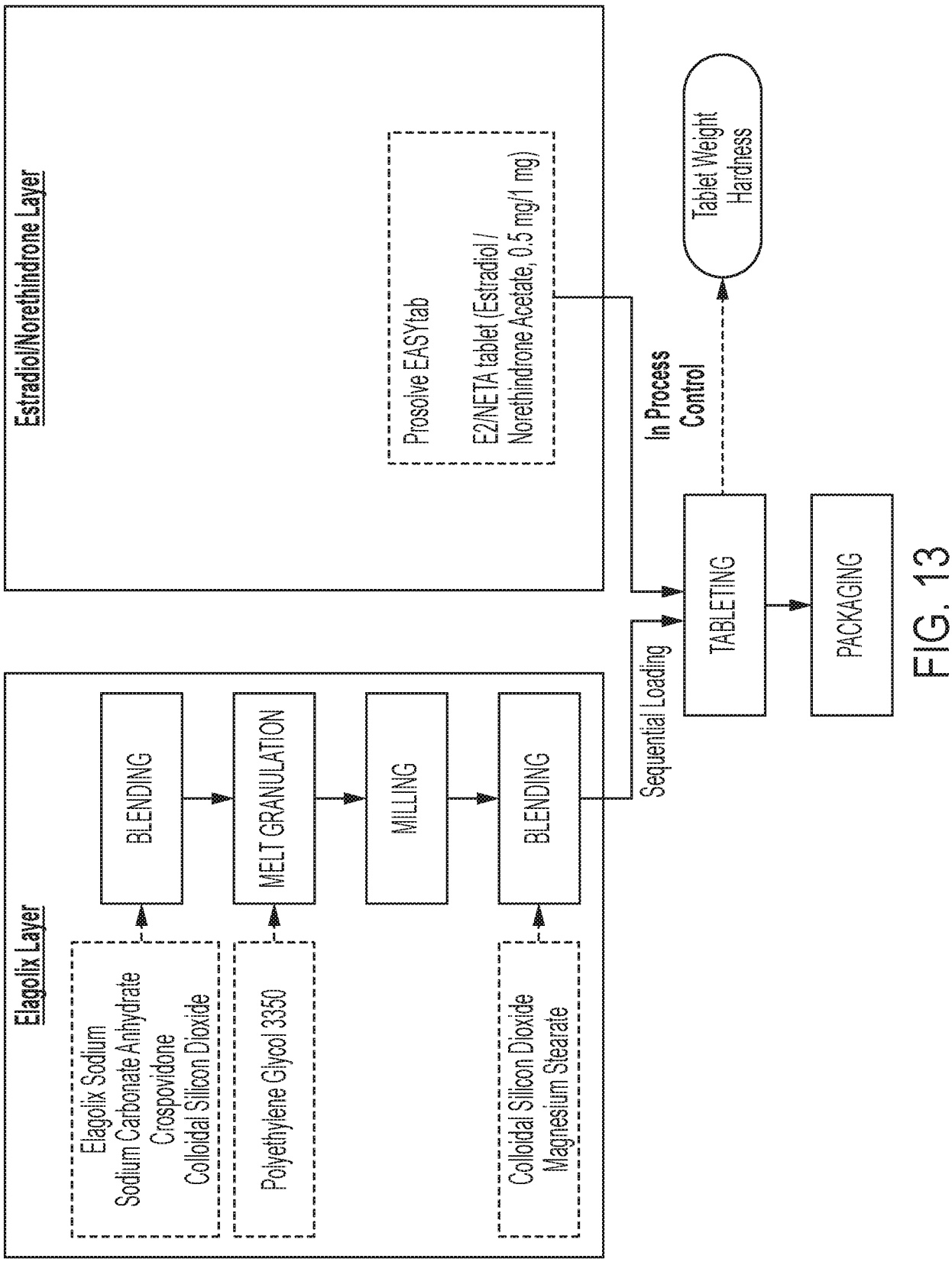
Elagolix Layer
Elagolix Sodium
Sodium Carbonate Anhydrate
Crospovidone
Colloidal Silicon Dioxide
BLENDING
Polyethylene Glycol 3350
MELT GRANULATION
MILLING
Colloidal Silicon Dioxide
Magnesium Stearate
BLENDING
Sequential Loading
Estradiol/Norethindrone Layer
Prosolve EASYtab
E2/NETA tablet (Estradiol / Norethindrone Acetate, 0.5 mg/1 mg)
In Process Control
Tablet Weight
Hardness
TABLETING
PACKAGING

FIG. 13

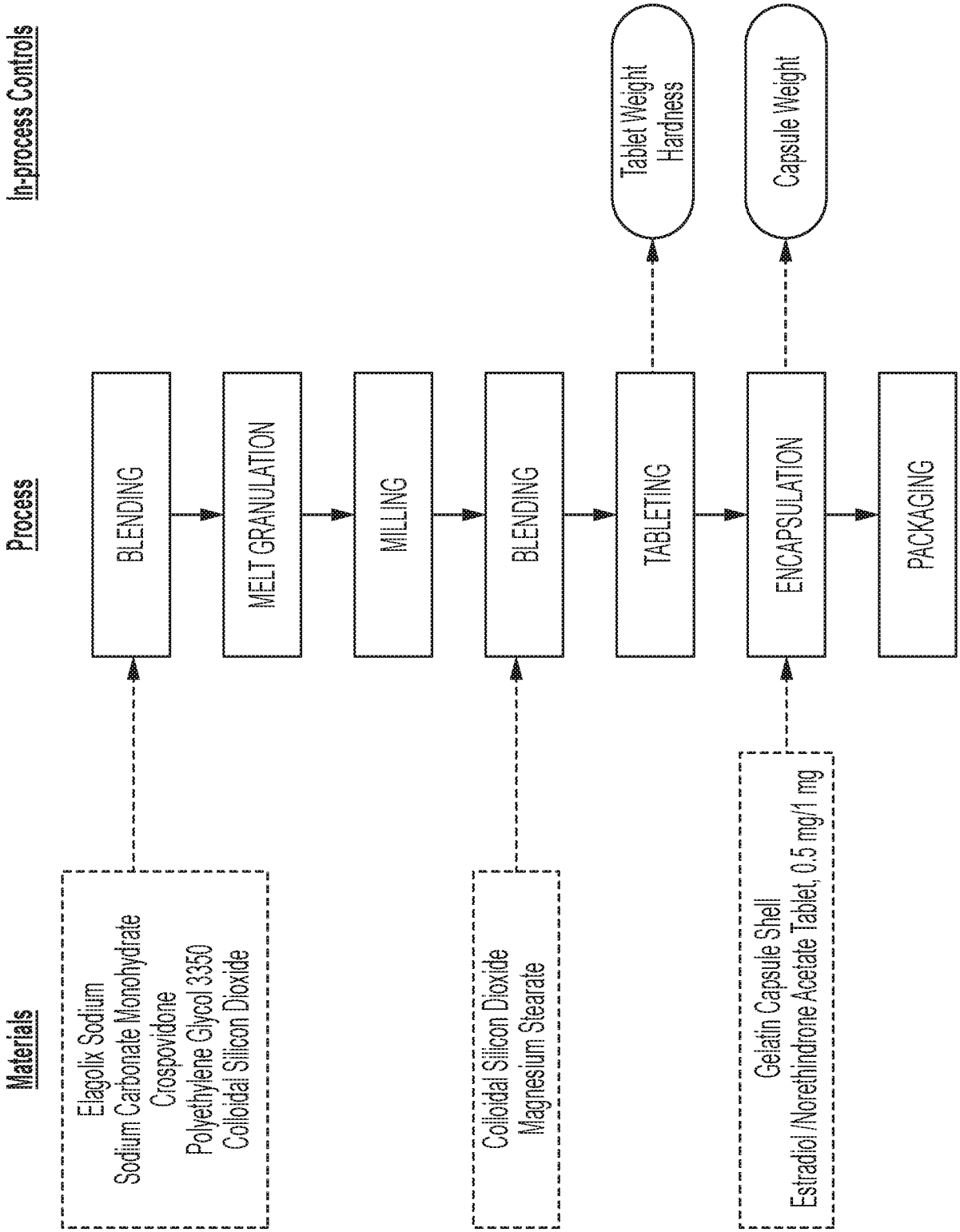
Materials
Process
In-process Controls
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
Colloidal Silicon Dioxide
Magnesium Stearate
BLENDING
TABLETING
Tablet Weight
Hardness
Gelatin Capsule Shell
Estradiol /Norethindrone Acetate Tablet, 0.5 mg/1 mg
ENCAPSULATION
Capsule Weight
PACKAGING

FIG. 14

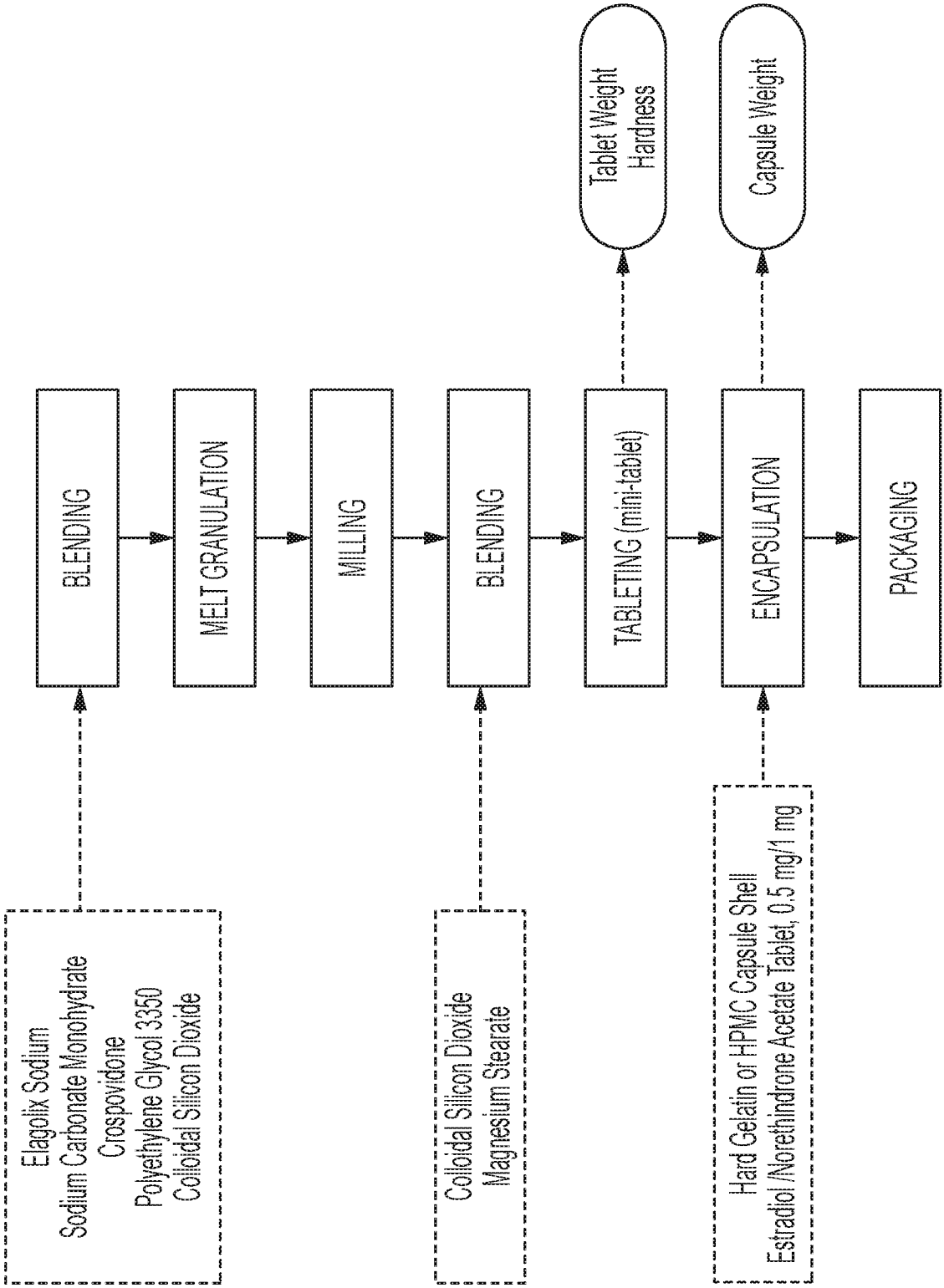
Materials
Process
In-process Controls
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
Colloidal Silicon Dioxide
Magnesium Stearate
BLENDING
TABLETING (mini-tablet)
Tablet Weight
Hardness
Hard Gelatin or HPMC Capsule Shell
Estradiol /Norethindrone Acetate Tablet, 0.5 mg/1 mg
ENCAPSULATION
Capsule Weight
PACKAGING

FIG. 15

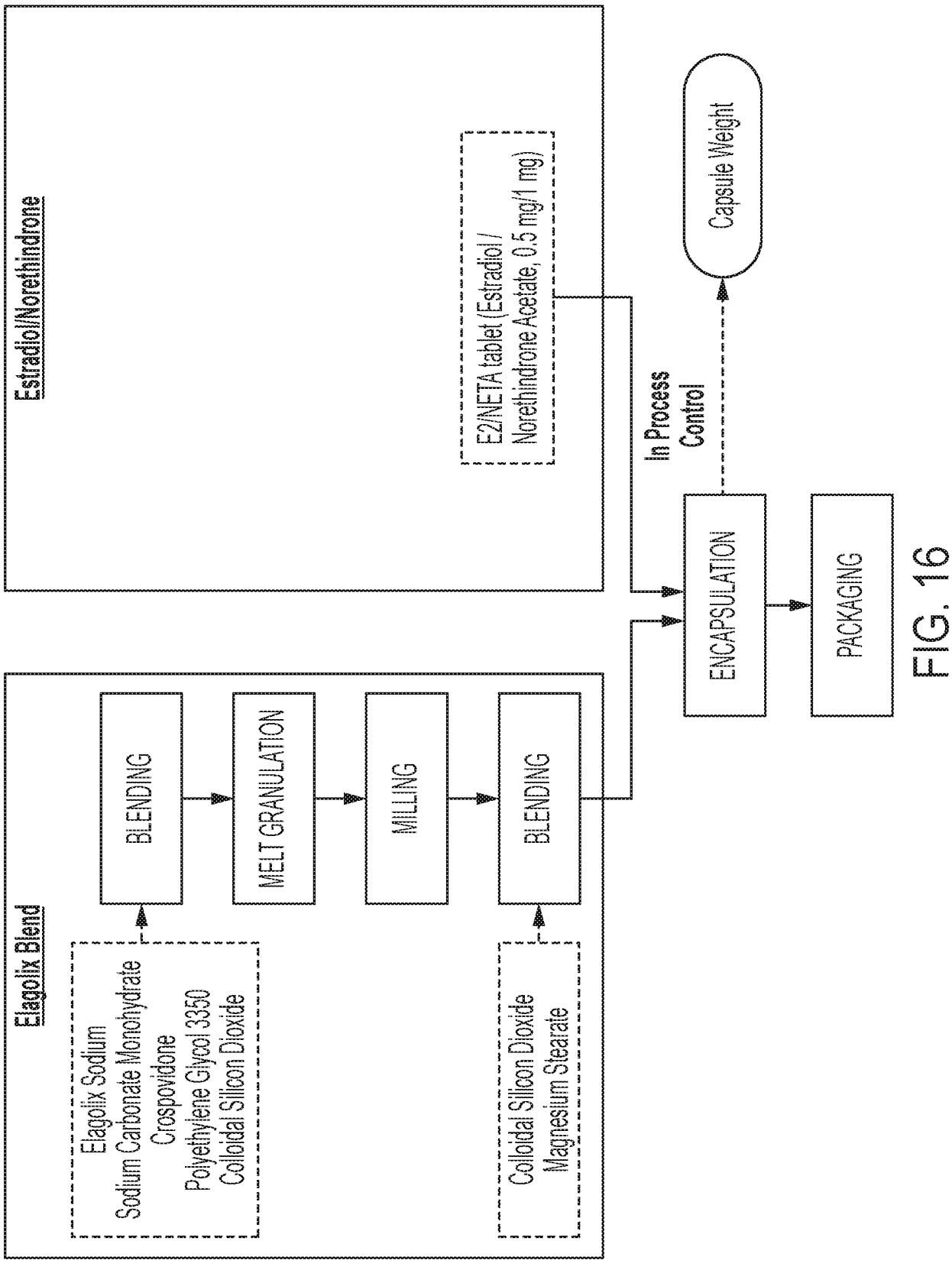
Estradiol/Norethindrone
E2/NETA tablet (Estradiol / Norethindrone Acetate, 0.5 mg/1 mg)
In Process Control
Capsule Weight
Elagolix Blend
Elagolix Sodium
Sodium Carbonate Monohydrate
Crospovidone
Polyethylene Glycol 3350
Colloidal Silicon Dioxide
BLENDING
MELT GRANULATION
MILLING
BLENDING
Colloidal Silicon Dioxide
Magnesium Stearate
ENCAPSULATION
PACKAGING

FIG. 16

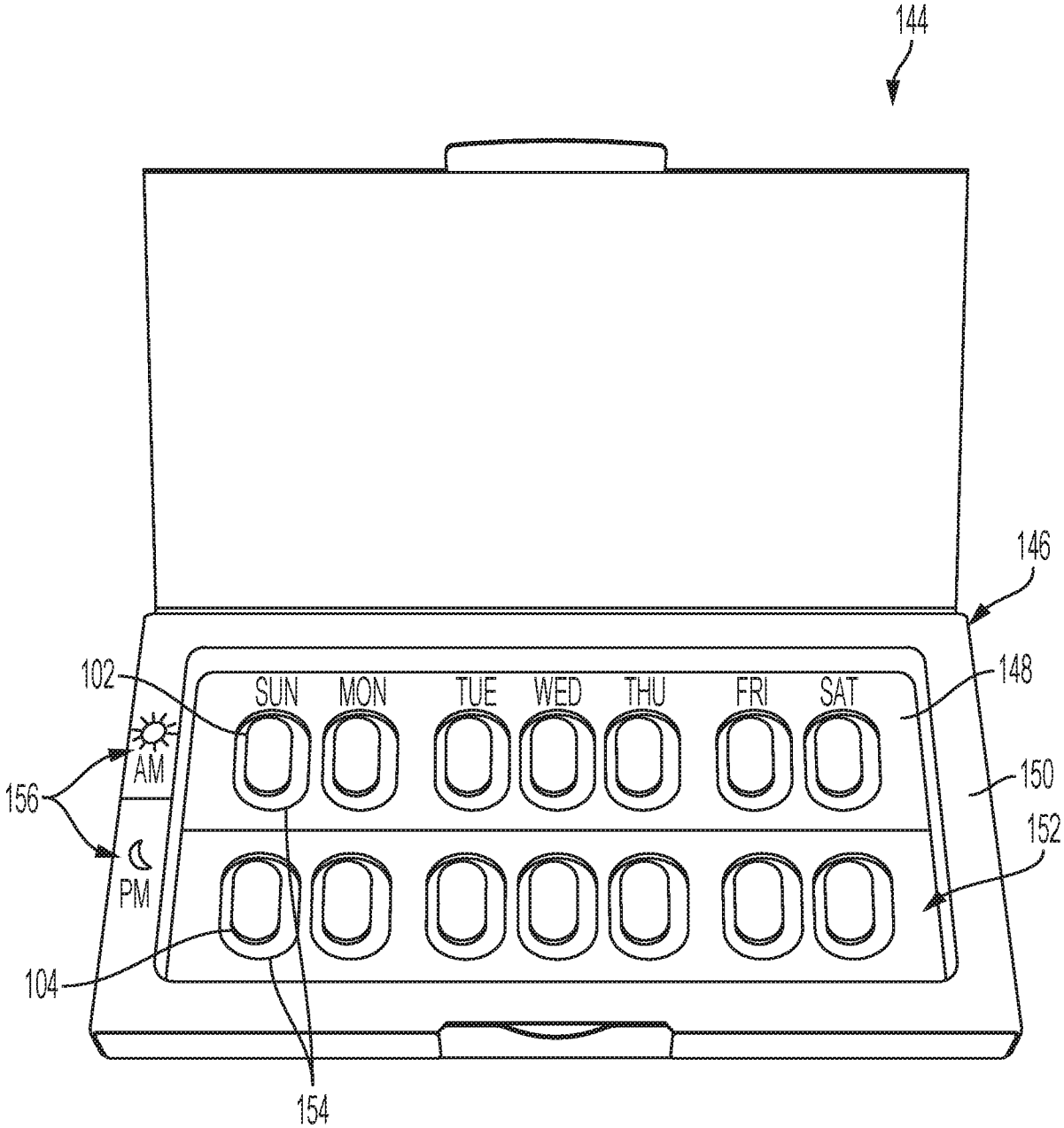
144
146
102
148
SUN
MON
TUE
WED
THU
FRI
SAT
AM
156
150
PM
152
104
154

FIG. 17

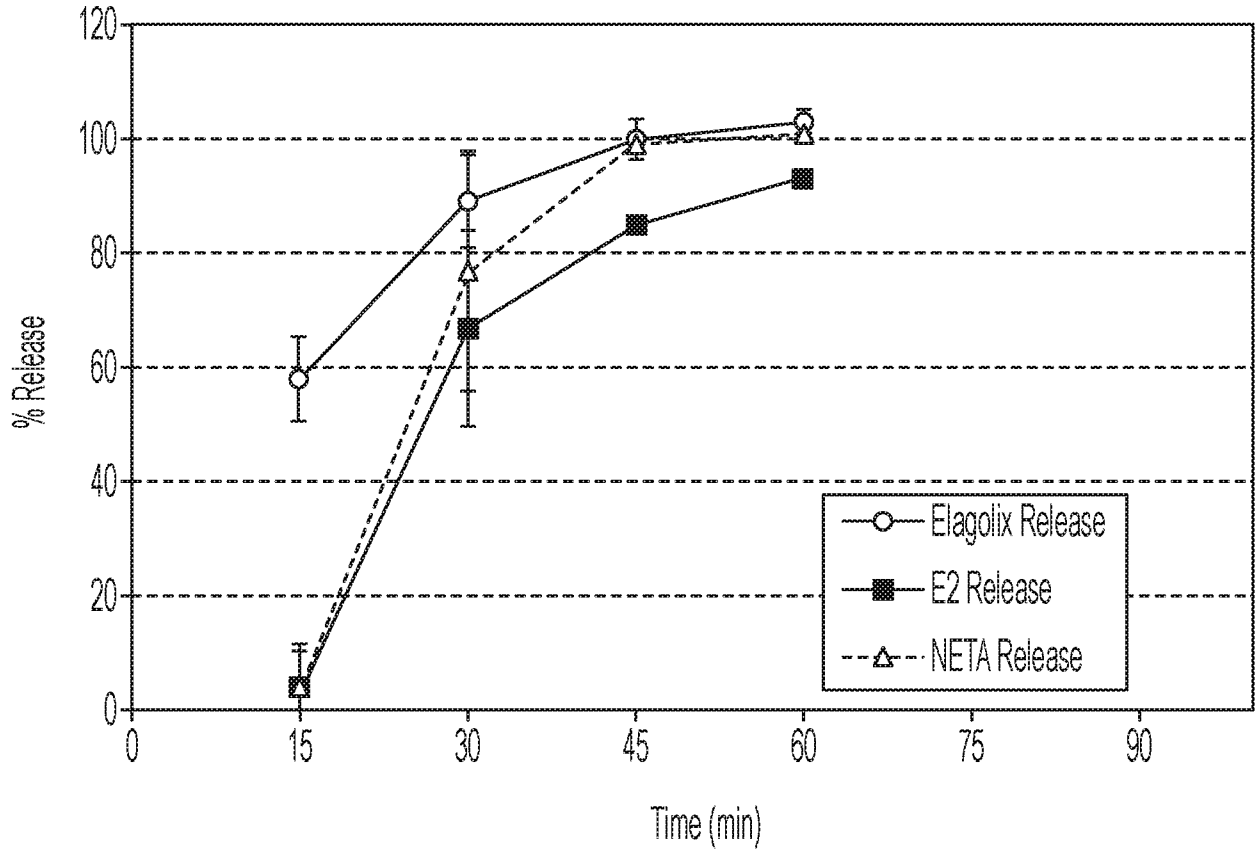
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 18

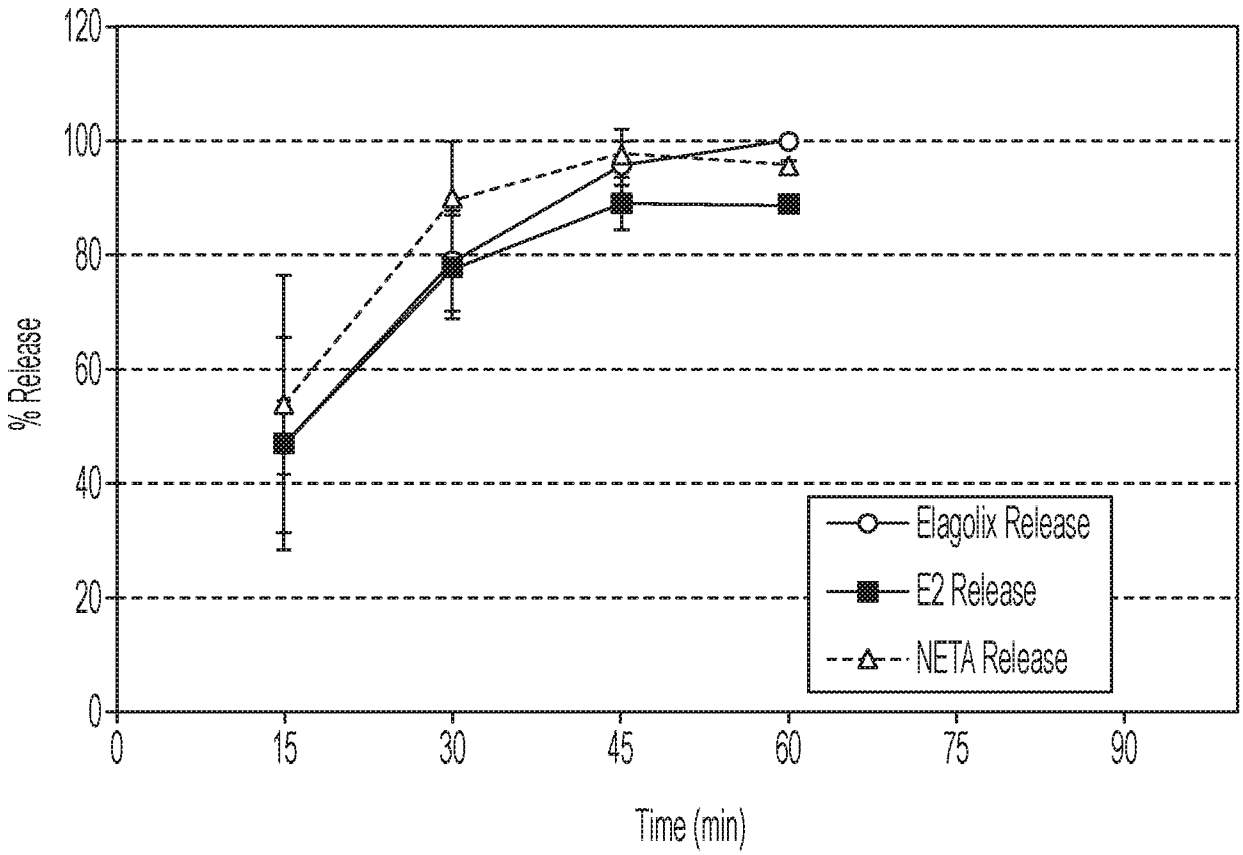
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 19

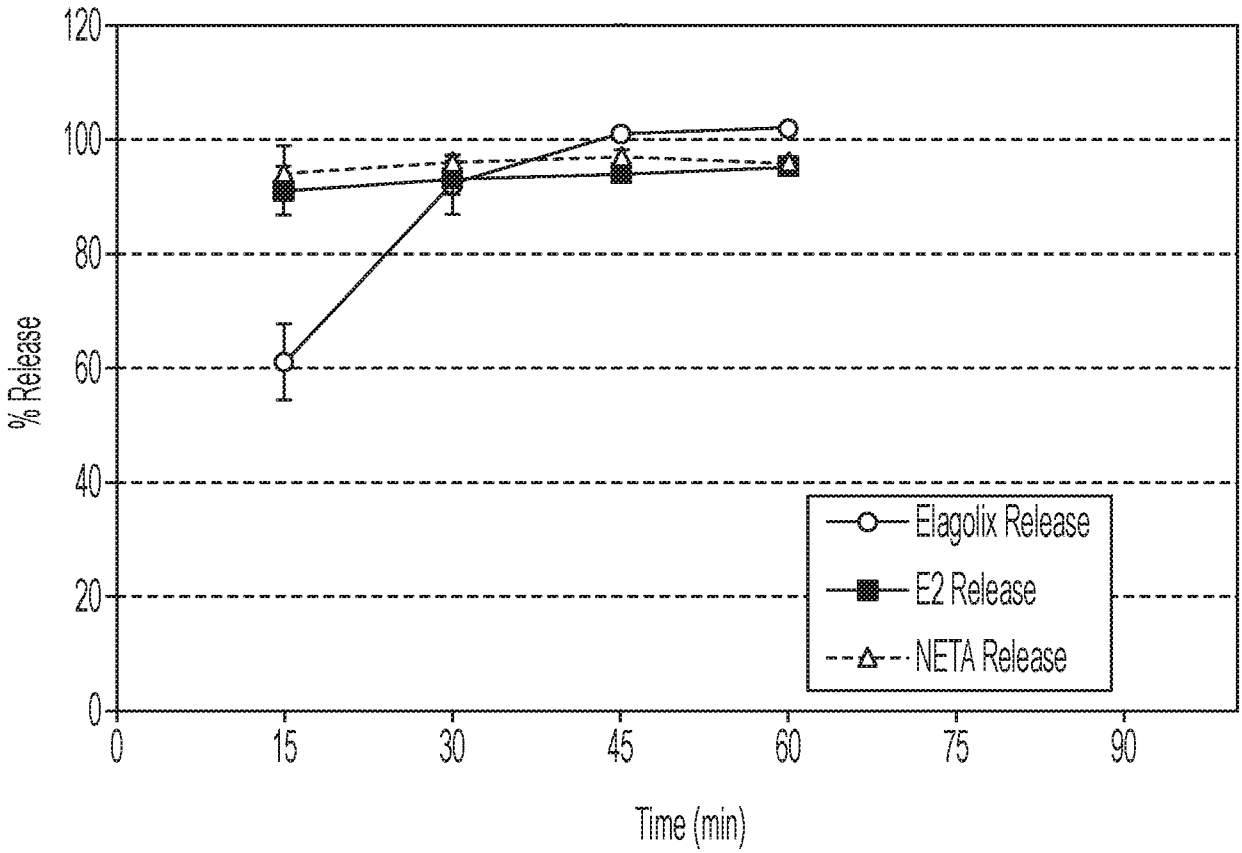
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 20A

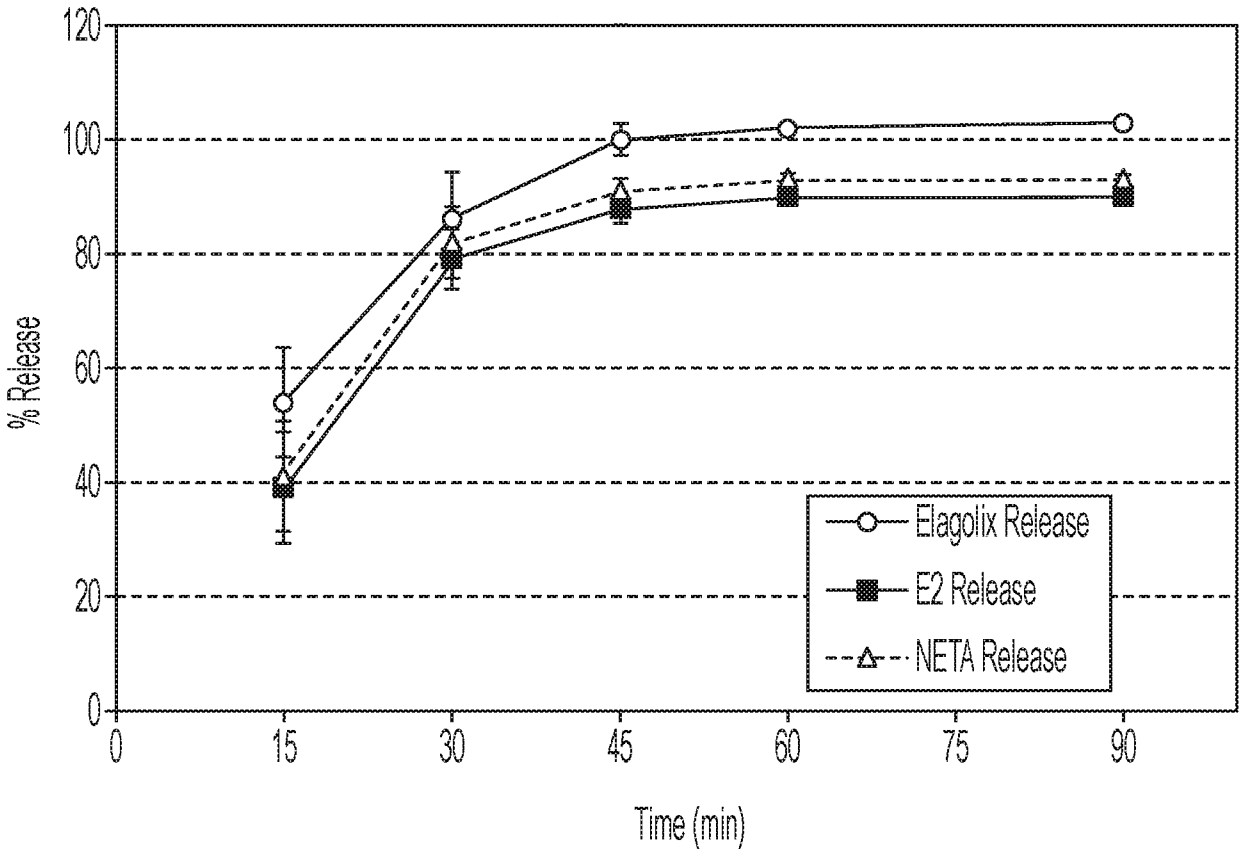
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 20B

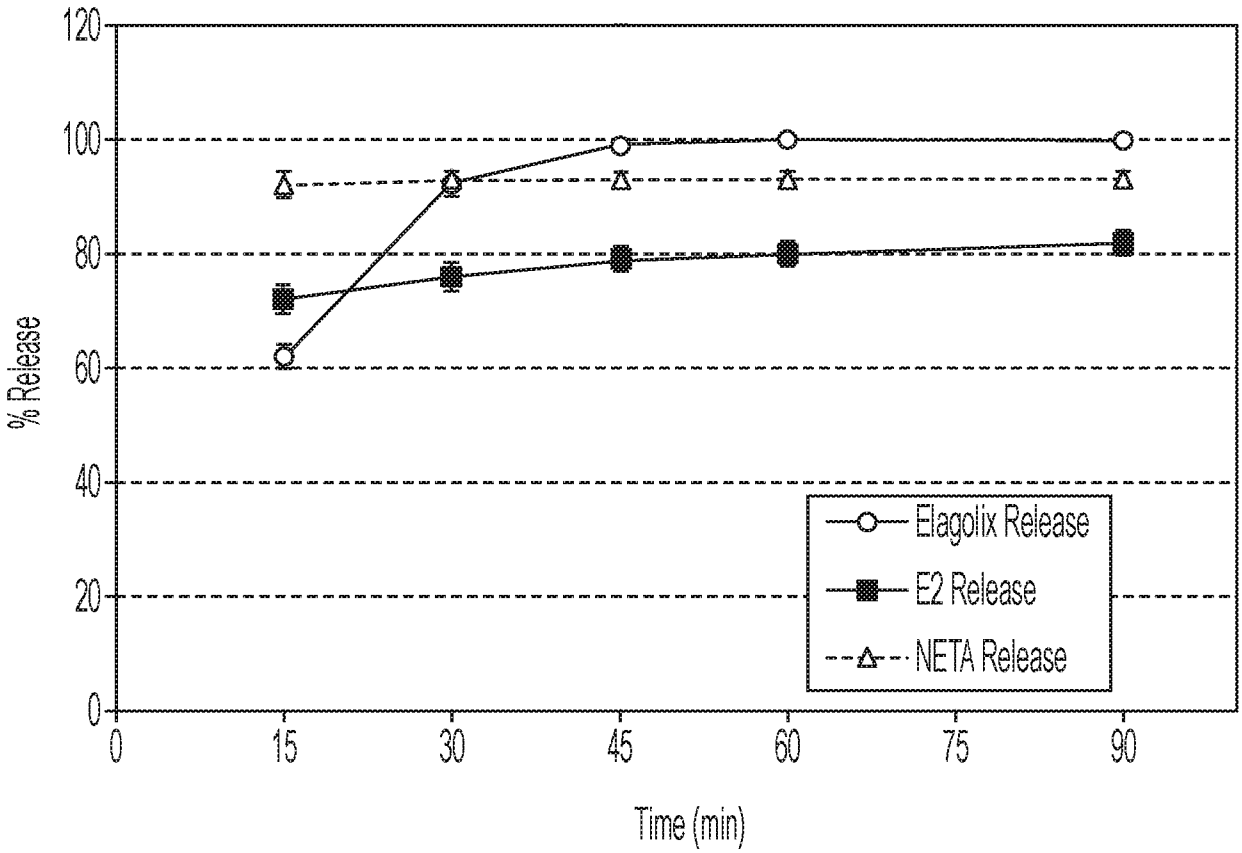
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 20C

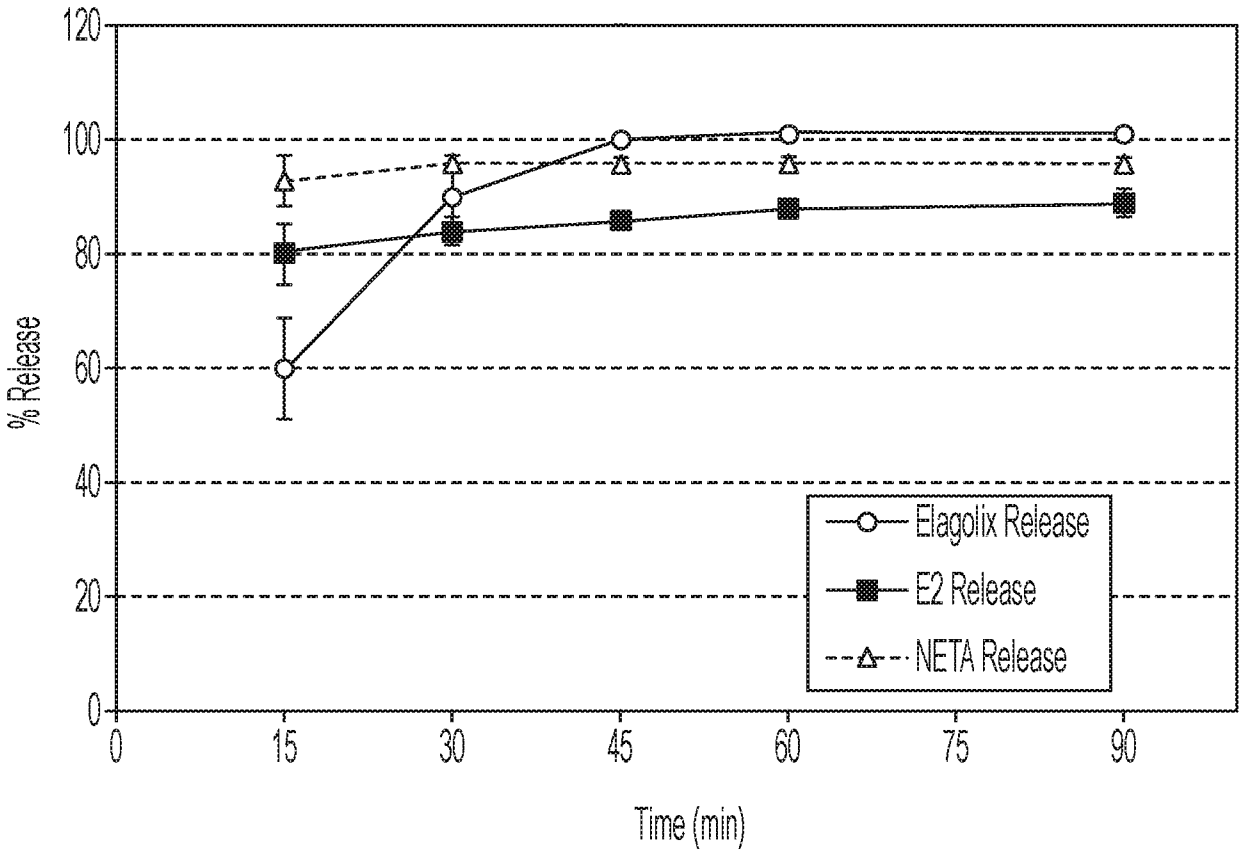
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 20D

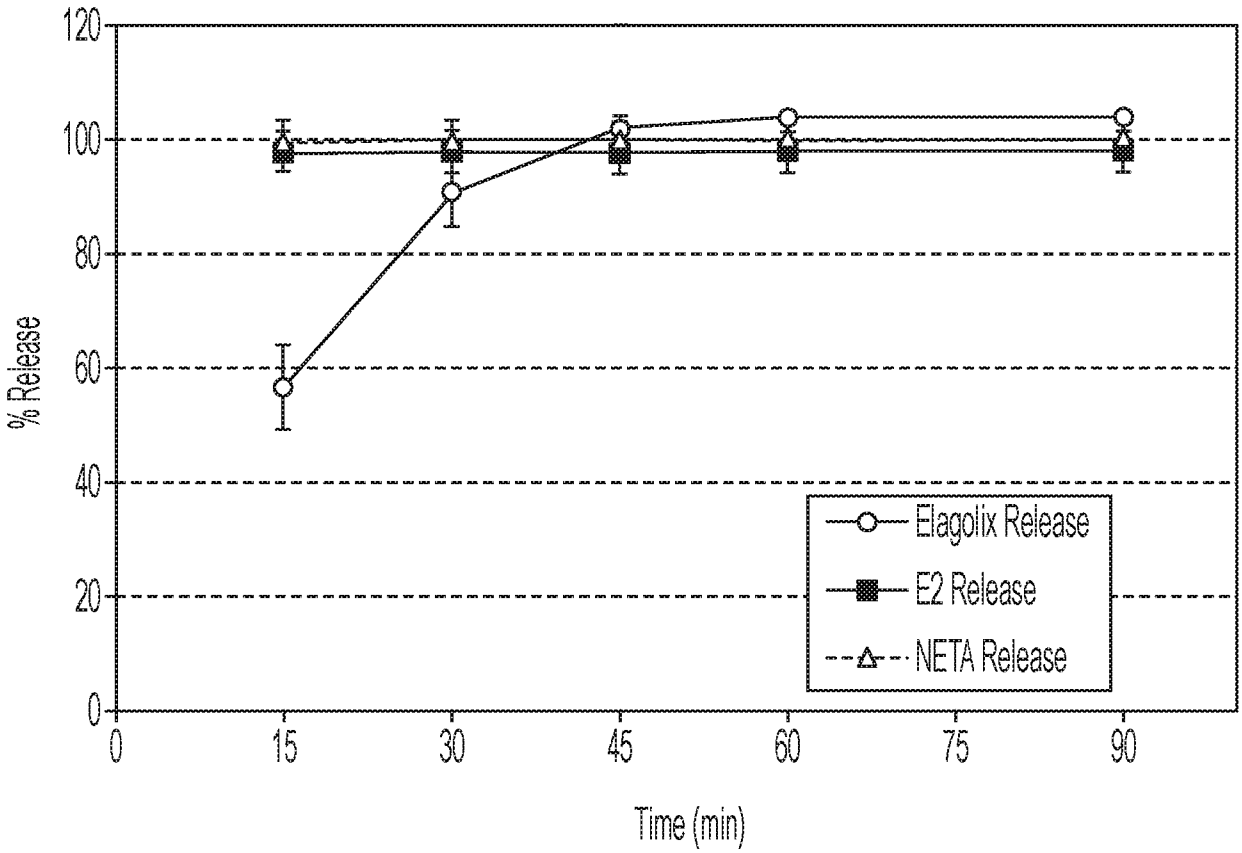
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 21

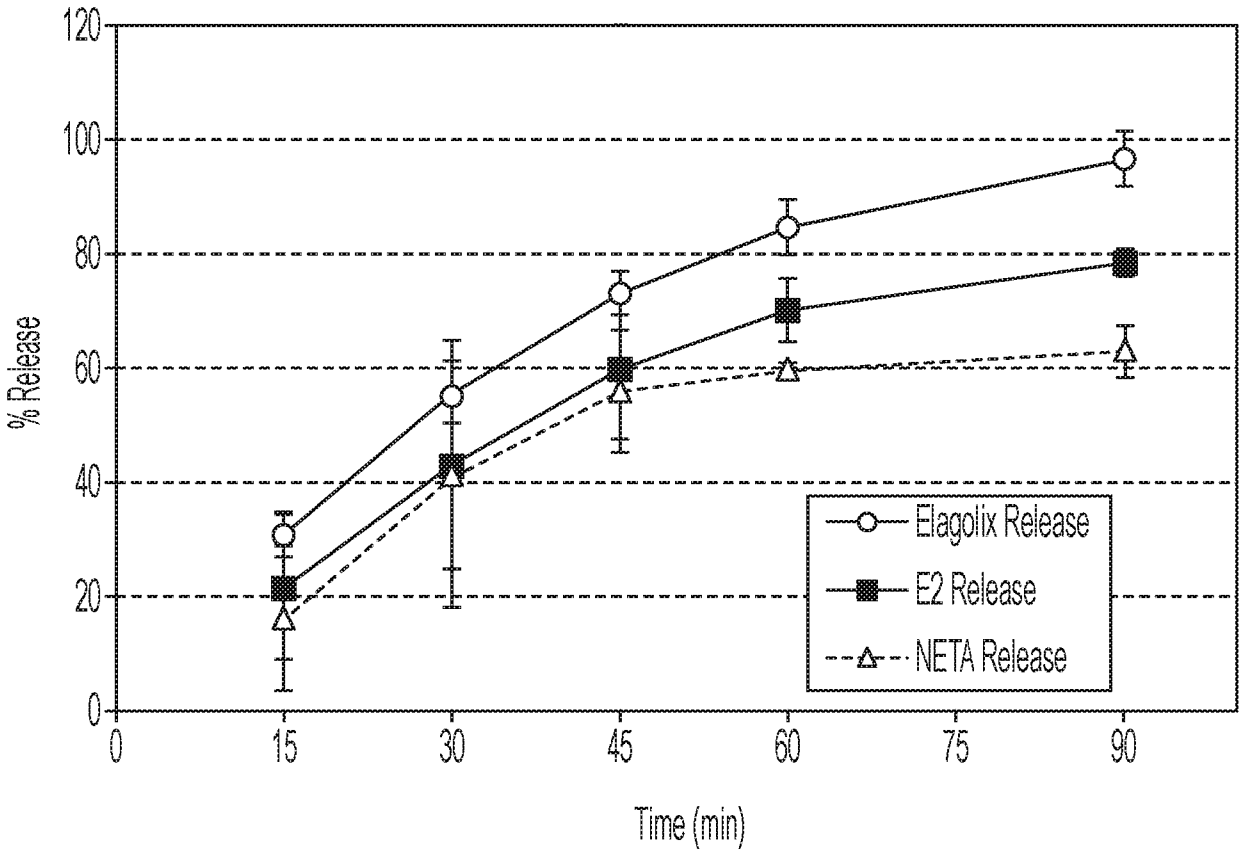
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 22

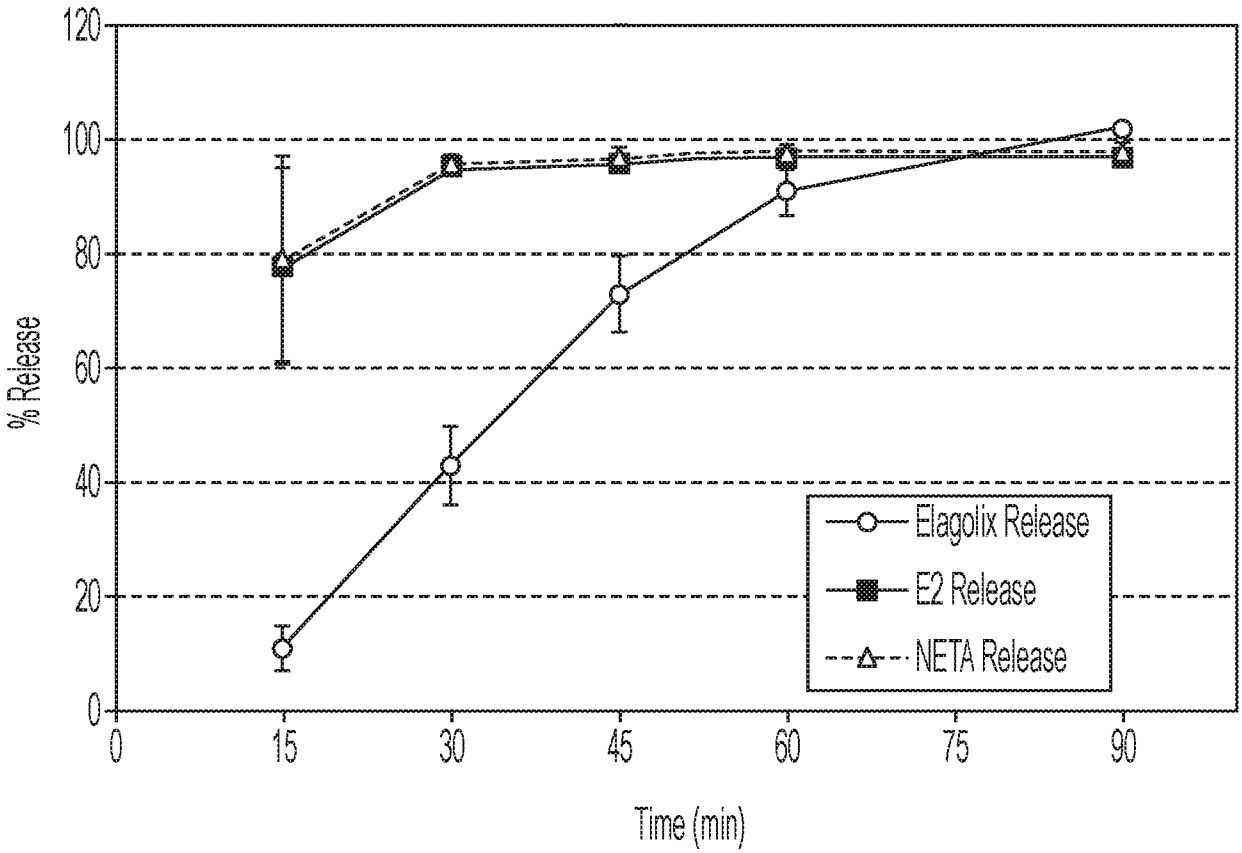
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 23

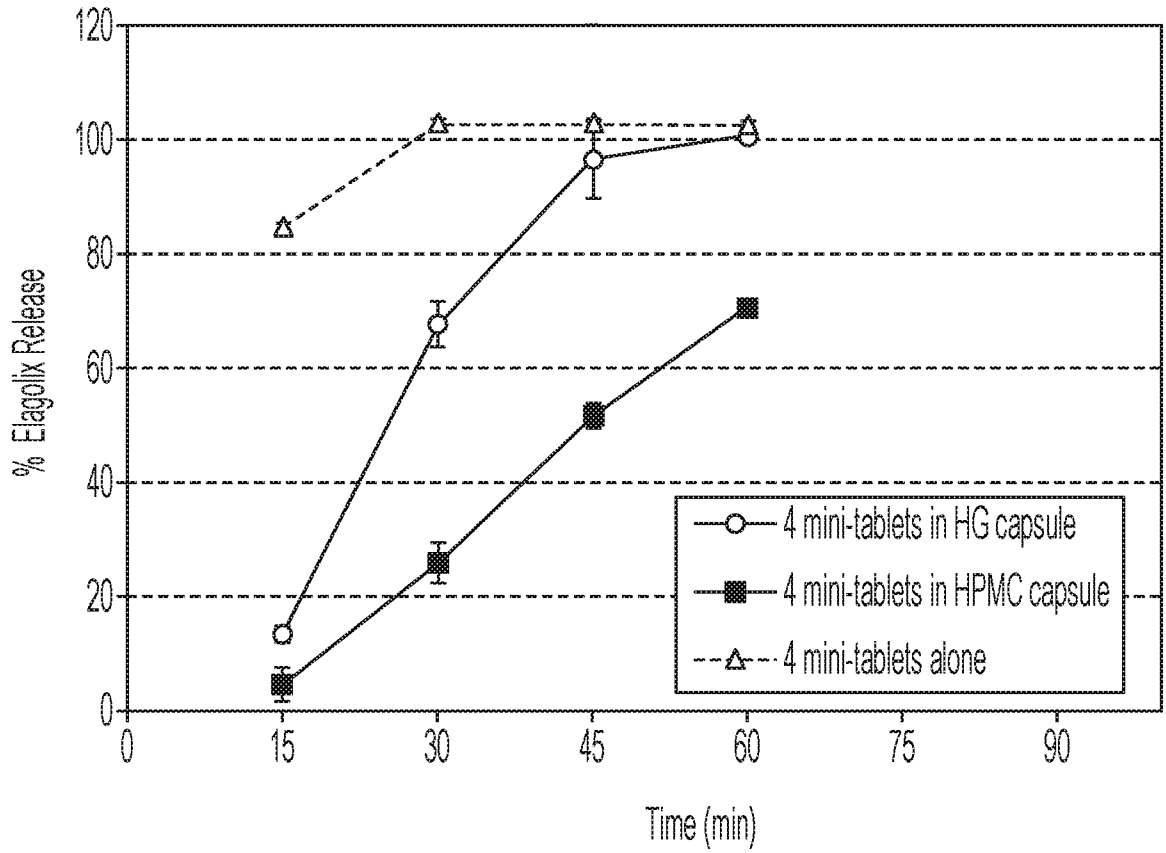
120
100
80
60
40
20
0
% Elagolix Release
0
15
30
45
60
75
90
Time (min)
4 mini-tablets in HG capsule
4 mini-tablets in HPMC capsule
4 mini-tablets alone

FIG. 24

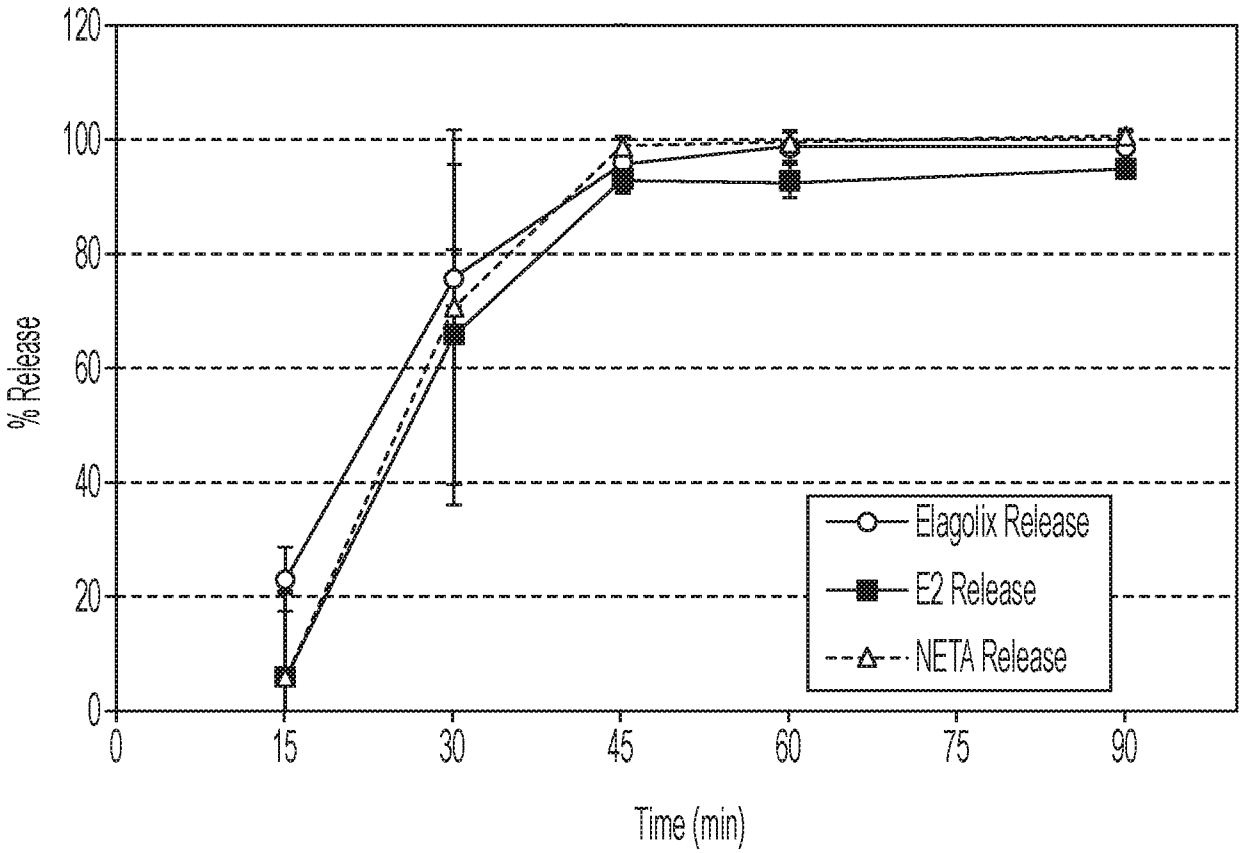
120
100
80
60
40
20
0
% Release
0
15
30
45
60
75
90
Time (min)
Elagolix Release
E2 Release
NETA Release

FIG. 25

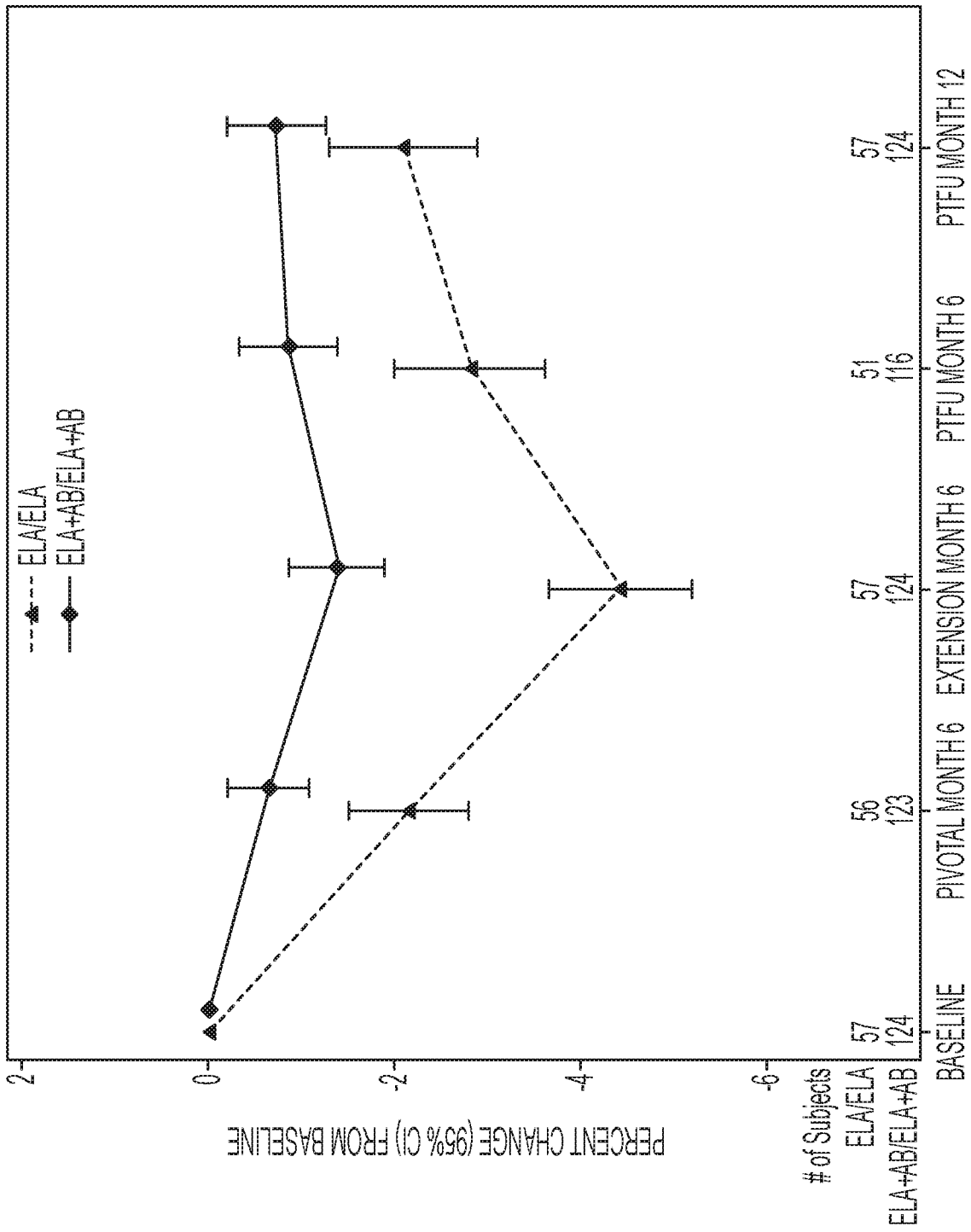
ELA/ELA
ELA+AB/ELA+AB
PERCENT CHANGE (95% CI) FROM BASELINE
2
0
-2
-4
-6
# of Subjects
ELA/ELA 57
ELA+AB/ELA+AB 124
BASELINE
56
123
PIVOTAL MONTH 6
57
124
EXTENSION MONTH 6
51
116
PTFU MONTH 6
57
124
PTFU MONTH 12
TIME

FIG. 26

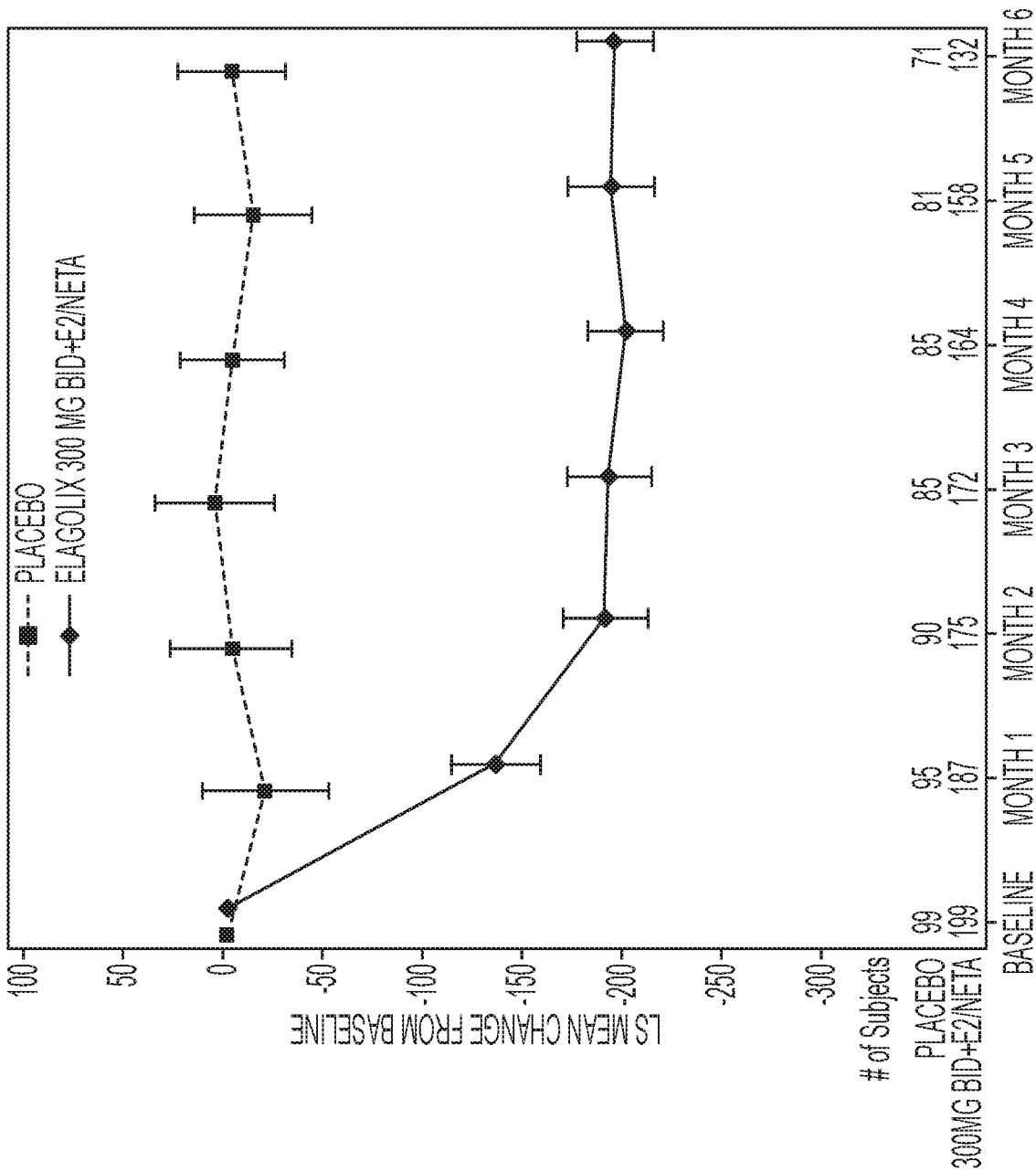
PLACEBO
ELAGOLIX 300 MG BID+E2/NETA
LS MEAN CHANGE FROM BASELINE
100
50
0
-50
-100
-150
-200
-250
-300
# of Subjects
PLACEBO 99 95 90 85 85 81 71
300MG BID+E2/NETA 199 187 175 172 164 158 132
BASELINE MONTH 1 MONTH 2 MONTH 3 MONTH 4 MONTH 5 MONTH 6
TIME

FIG. 27

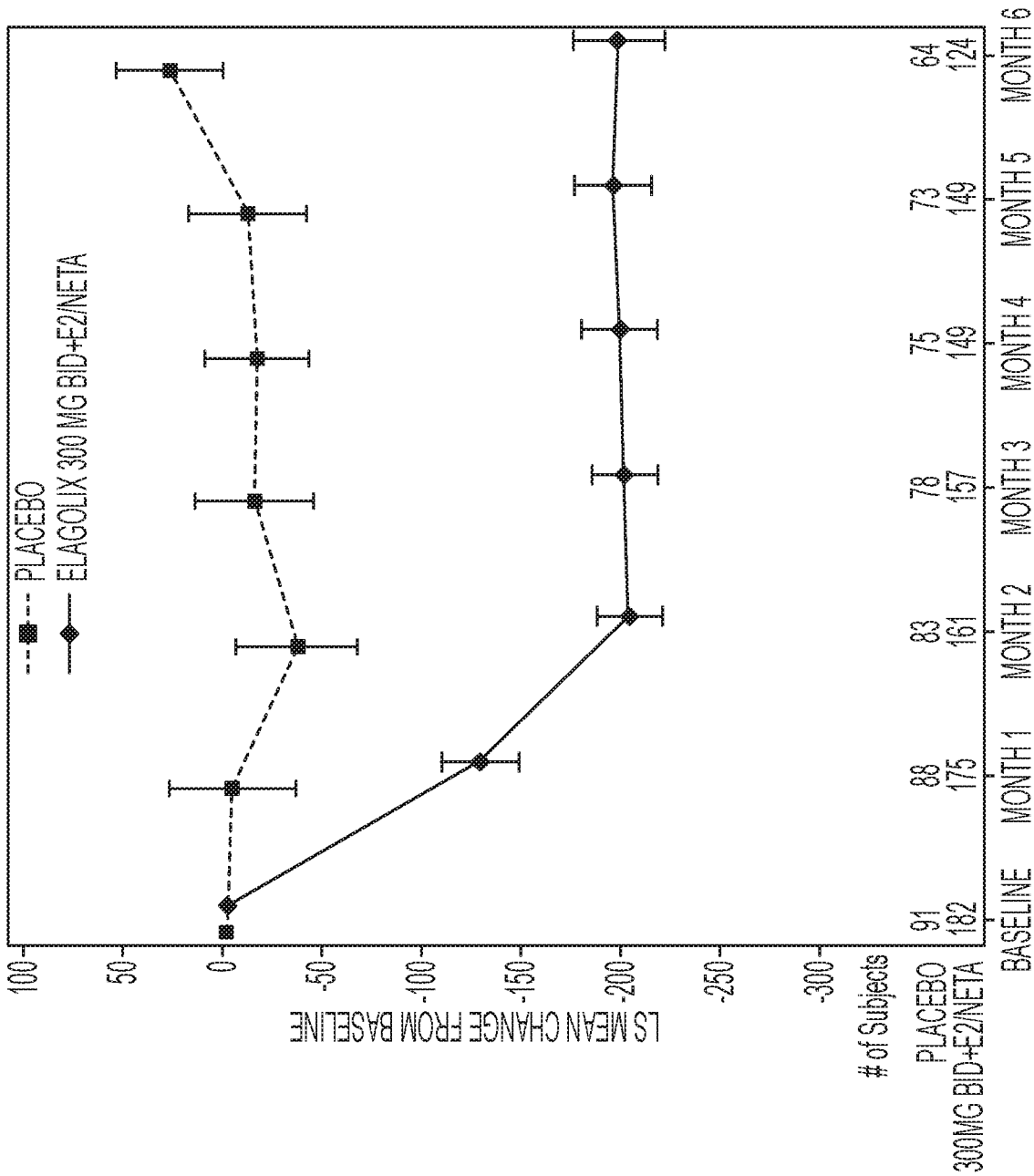
PLACEBO
ELAGOLIX 300 MG BID+E2/NETA
LS MEAN CHANGE FROM BASELINE
100
50
0
-50
-100
-150
-200
-250
-300
# of Subjects
PLACEBO 91 88 83 78 75 73 64
300MG BID+E2/NETA 182 175 161 157 149 149 124
BASELINE MONTH 1 MONTH 2 MONTH 3 MONTH 4 MONTH 5 MONTH 6
TIME

FIG. 28

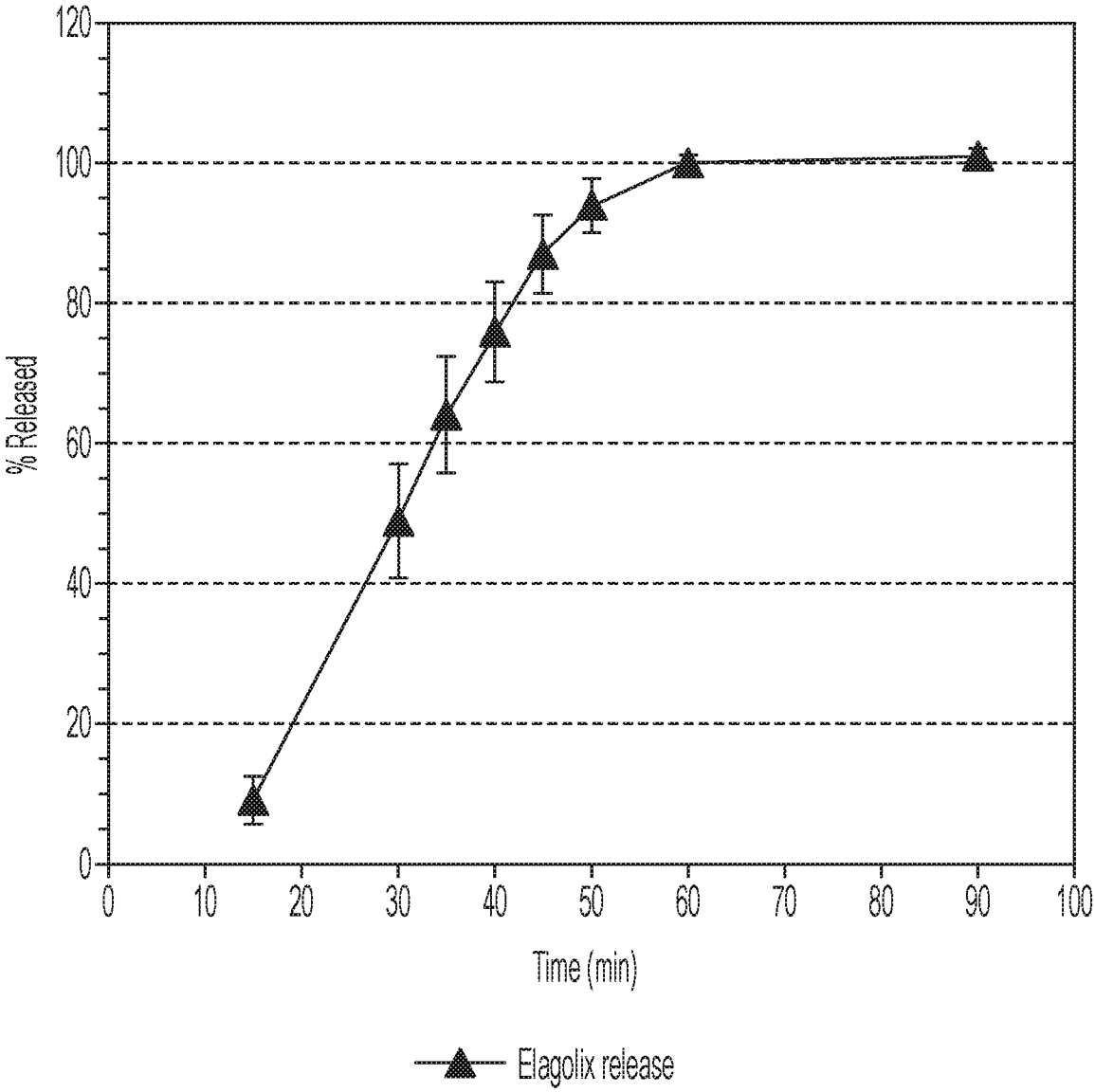
120
100
80
60
40
20
0
% Released
0
10
20
30
40
50
60
70
80
90
100
Time (min)
Elagolix release

FIG. 29A

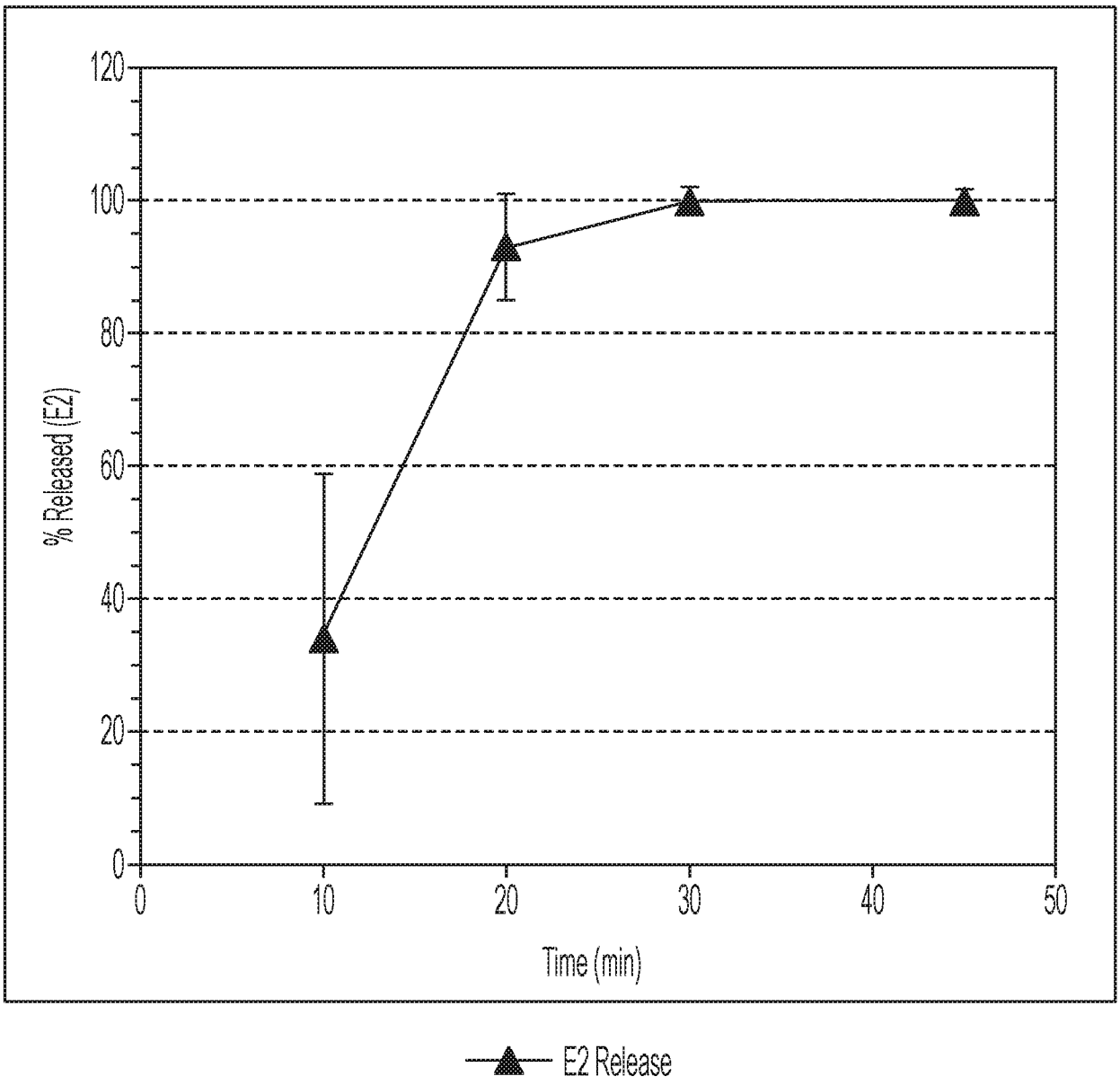
120
100
80
60
40
20
0
% Released (E2)
0
10
20
30
40
50
Time (min)
E2 Release

FIG. 29B

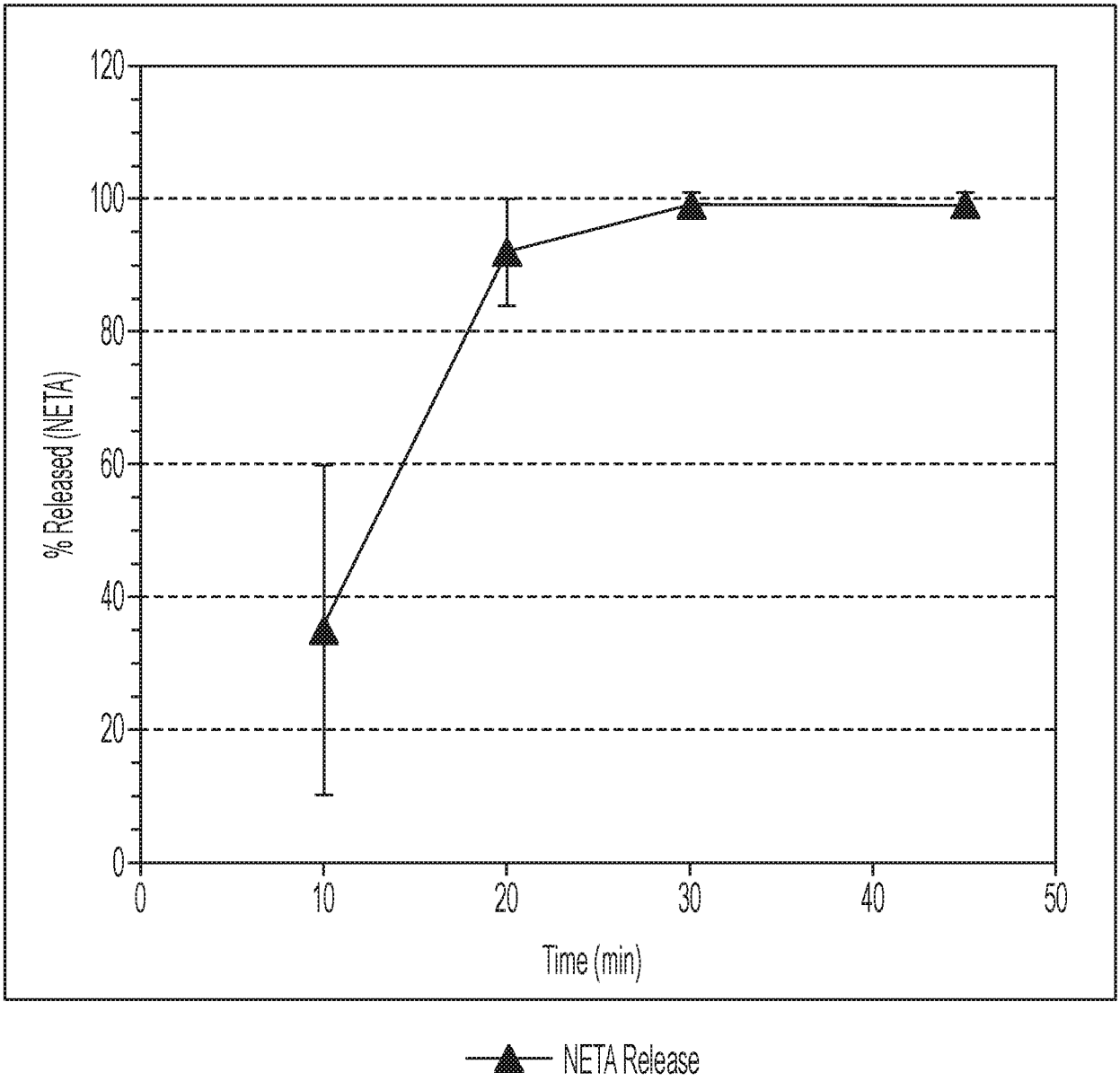
120
100
80
60
40
20
0
% Released (NETA)
0
10
20
30
40
50
Time (min)
NETA Release

FIG. 29C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/48107

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 9/48, 9/20; A61J 3/07 (2020.01)

CPC - A61K 9/4808, 9/4883; A61J 3/007, 3/005, 3/071, 3/07; A61K 9/48, 9/2072, 9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2010/0255082 A1 (CHAUHAN, I et al.) 07 October 2010; figure 3; paragraphs [0008], [0011]-[0012], [0017], [0021], [0031]	1, 14, 18, 22, 24, 34-35, 45, 47 -- 2-9, 15-17, 19-21, 23, 25-30, 36-37
A	(U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research) Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances	1, 14, 18, 22, 24, 34-35, 45, 47
Y	(ABBIVIE) AbbVie Presents Positive Phase 3 Data Demonstrating Investigational Elagolix Reduces Heavy Menstrual Bleeding in Women with Uterine Fibroids at 2018 AAGL Global Congress. https://news.abbvie.com/news/press-releases/therapeutic-area/womens-health/abbvie-presents-positive-phase-3-data-demonstrating-investigational-elagolix-reduces-heavy-menstrual-bleeding-in-women-with-uterine-fibroids-at-2018-aagl-global-congress.htm. 14 November 2018; title; page 1, second paragraph; page 1, first paragraph	2-5, 15-17, 25, 36-37
Y	US 2008/0075772 A1 (SOLOMON, L et al.) 27 March 2008; abstract; paragraphs [0066]-[0067], [0125], [0128]; claim 66	6-9, 27-28
Y	US 2014/0227356 A1 (HANMI PHARM CO., LTD.) 14 August 2014; paragraphs [0007], [0024], [0042]-[0043]	19, 21
Y	US 9,456,987 B2 (BINTURA INC.) 04 October 2016; abstract; column 4, lines 1-14; claim 9	20, 23

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2020 (30.10.2020)	08 JAN 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,022,053 B2 (MUELLER, K et al.) 20 September 2011; column 2, lines 53-59; column 3, lines 26-31; column 6, lines 52-58	5, 17, 26
Y	US 2019/0201285 A1 (MYLAN INC.) 04 July 2019; abstract; figures 6, 14; paragraphs [0040], [0044]	29-30

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10-13, 46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-9, 14-30, 34-37, 45, and 47 are directed toward multi-drug tablet capsule comprising multiple tablets within a first capsule configured for simultaneous release and a second capsule co-packaged with the first capsule.
Group II: Claims 31-33 are directed toward multi-drug tablet having a first tablet and a second tablet coated on the first tablet.
Group III: Claims 38-44 are directed toward oral multi-drug capsule composition comprising elagolix, estradiol, and norethindrone acetate.

-***-Continued Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9, 14-30, 34-37, 45, and 47

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued from Box No. III Observations where unity of invention is lacking-***-
The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
the special technical features of Group I include a multi-drug delivery system comprising a first capsule comprising: a first capsule body comprising a first interior; a first tablet within the first interior, the first tablet comprising a first drug; and a second tablet within the first interior, the second tablet comprising at least a second drug different from the first drug, and a third drug different from the first and second drug, wherein the first tablet and the second tablet are configured for simultaneous release upon dissolution of the first capsule body within a patient; and a second capsule, co-packaged with the first capsule, comprising: a second capsule body comprising a second interior; and a third tablet within the second interior, the third tablet comprising the first drug; and a method of delivering drugs to a patient, which are not present in Groups II-III;
the special technical features of Group II include multi-drug tablet having a first tablet and a second tablet coated on the first tablet, which are not present in Groups I and III; and
the special technical features of Group III include an oral multi-drug capsule composition comprising: (a) 300 mg of free acid equivalent of elagolix; (b) 1 mg of estradiol; and (c) 0.5 mg of norethindrone acetate; wherein, following administration of a single dose of the composition to healthy adult subjects results in a mean peak concentration (Cmax) for said elagolix of about 1218.4 ng/mL to about 2185 ng/mL; a mean peak concentration (Cmax) for said estradiol of about 0.0424 ng/mL to about 0.0775 ng/mL; a mean peak concentration (Cmax) for said norethindrone acetate of about 4.56 ng/mL to about 8.0 ng/mL; a mean Area Under the Curve (AUC(t)) for said elagolix of about 3293.6 ng.hr/mL to about 5892.5 ng.hr/mL; a mean Area Under the Curve (AUC(t)) for said estradiol of about 0.688 ng.hr/mL to about 1.1375 ng.hr/mL; and a mean Area Under the Curve (AUC(t)) for said norethindrone acetate of about 17.6 ng.hr/mL to about 33.125 ng.hr/mL, which are not present in Groups I-II.

The common technical features of Groups I-III are an oral multi-drug capsule composition comprising a first tablet and a second tablet; a first drug, second drug, and a third drug; wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes.

The common technical features are Groups I-III are disclosed by US 2010/0255082 A1 to Chauhan, et al. (hereinafter 'Chauhan') as evidenced by the publication "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (hereinafter 'FDA'). Chauhan discloses an oral multi-drug capsule composition (oral tablet and capsule formulations with at least two drug containing units; paragraphs [0002], [0008]) comprising a first tablet and a second tablet (one or more core tablets can be encapsulated in a capsule; paragraph [0011]); a first drug, second drug, and a third drug (wherein the drug containing units comprise two or more drugs; figures 1-3; paragraphs [0008], [0029]-[0030]; claims 3-4); wherein using USP apparatus 2 at 50 rpm, pH 6.8, and 37.5±0.5°C, at least 75% of the first drug in the first tablet dissolves after 60 minutes and at least 70% of the second and third drugs in the second tablet dissolve after 30 minutes (the drug containing unit may comprise more than one drug designated as an immediate release layer "IR", where dosage forms designated as immediate release have a dissolution criteria of 80% in 30 minutes under the USP conditions; paragraph [0031]) (as evidenced by FDA where immediate release solid oral drug products tested with USP apparatus 2, have a dissolution criterion of Q=80% in 30 minutes; page 4, paragraph IV to page 5, paragraph V).

Since the common technical features are previously disclosed by Chauhan, as evidenced by FDA, these common features are not special and so Groups I-III lack unity.