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(54) Title: STABLE PHARMACEUTICAL COMPOSITION OF ELAGOLIX

(57) Abstract: The present invention provides a stable pharmaceutical composition comprising a therapeutically effective amount of elagolix or a pharmaceutically acceptable salt thereof. Further, the present invention specifically relates to a stable oral elagolix or pharmaceutically acceptable salt thereof in a tablet dosage form and the process of preparation thereof. Additionally, the present invention provides a stable elagolix or pharmaceutically acceptable salt thereof in a tablet dosage form for the effective treatment of endometriosis, uterine fibroids, polycystic ovary syndrome, or adenomyosis.

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STABLE PHARMACEUTICAL COMPOSITION OF ELAGOLIX

FIELD OF THE INVENTION

The present invention relates to a stable pharmaceutical composition comprising elagolix or a pharmaceutically acceptable salt thereof. This invention more particularly relates to elagolix tablet formulation, methods of preparation thereof, and their use in medical therapy.

BACKGROUND OF THE INVENTION

Elagolix sodium is a non-peptide small molecule, GnRH receptor antagonist. Chemically, Elagolix sodium is sodium 4-({(1R)-2-[5-(2-fluoro-3methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl) phenyl] methyl}-4-methyl-2,6-dioxo-3,6dihydropyrimidin-1(2H)-yl]-1-phenylethyl} amino) butanoate.

The molecular weight of Elagolix free acid is 631.60 g/mol, and Elagolix sodium has a molecular weight of 653.58 g/mol, the molecular formula is C32H29F5N3O5Na. Elagolix sodium is a white to off-white to light yellow powder and is freely soluble in water.

GnRH receptor antagonist inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland. Administration of ORILISSA® 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.

Elagolix is used in the treatment of endometriosis, uterine fibroids, PCOS, and adenomyosis and, in particular, management of pain associated with endometriosis, uterine fibroids, PCOS or adenomyosis, and heavy menstrual bleeding associated with endometriosis, uterine fibroids, PCOS, or adenomyosis.

Elagolix is available in the United States of America as ORILISSA® oral tablets and is indicated for the management of moderate to severe pain associated with endometriosis. It is available in various strengths i.e. eq 150 mg base and eq 200 mg base.

Elagolix is also available in the United States of America as a combination of elagolix sodium, estradiol, norethindrone acetate; elagolix ORIAHNN® (Co-packaged), and indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. It is available in strength eq 300mg base,1mg,0.5mg; eq 300mg base.

US 20190054027A1 discloses a solid pharmaceutical composition comprising Elagolix or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable

meltable binder. Further discloses compositions that achieve a high drug load of elagolix or a pharmaceutically acceptable salt thereof in such compositions which compositions are manufactured by melt-processing.

US 2019054088A1 discloses a pharmaceutical composition comprising about 150 mg, about 200 mg, or about 300 mg Elagolix or a pharmaceutically acceptable salt thereof; and an anti-gelling agent; wherein the pharmaceutical composition comprises at least 10% by weight of Elagolix or the pharmaceutically acceptable salt thereof. It identifies at least two challenges to developing pharmaceutical formulations comprising Elagolix or a pharmaceutically acceptable salt thereof. The main challenge was that Elagolix and, in particular, the monosodium salt of Elagolix tends to form a gel, particularly when present at an amount greater than about 10% by weight in the absence of an appropriate anti-gelling agent when administered orally in a solid dosage form. Such gel formation limits the dissolution of drug and, ultimately, can lead to highly variable inter and intrapatient bioavailability. Another challenge was that Elagolix can degrade to form a compound having a lactam moiety. Reducing the conversion of the drug substance into its lactam-containing degradation product is desirable, for example, to maintain safety and efficacy over the life of the product.

WO 2021180862A1 discloses the pharmaceutical compositions, in the form of immediate-release tablets, comprising elagolix sodium and pharmaceutically acceptable ingredients comprising a super disintegrant, wherein the super disintegrant is present in an amount of from 5% to 30%, more preferably 6.5 to 25%, even more preferably from 8 to 20% by weight based on the total weight of the composition. The super disintegrant can be selected from crospovidone, low-substituted hydroxypropyl cellulose (L-HPC), carboxymethylcellulose calcium, calcium silicate or it can be a mixture thereof.

US 10966979B2 discloses a solid dispersion comprising amorphous Elagolix sodium and at least one silicon-based inorganic compound. Further, it discloses that the solid dispersion of the composition requires an excess of excipients over elagolix to prevent elagolix sodium from deliquescence upon moisture contact. For example, a 1:1 weight ratio of elagolix sodium and a silica-based inorganic compound is sufficient to prevent the deliquescence of elagolix sodium. Hence, solid dispersion is advantageous for use in the pharmaceutical field, in particular for storage and/or for the preparation of a pharmaceutical composition.

WO 2021041608A1 discloses a multi-drug delivery system that includes a first capsule including a first capsule body that includes a first interior, 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.

In spite of the above-mentioned prior art disclosing various pharmaceutical formulations of Elagolix or a pharmaceutically acceptable salt thereof, there still exists a need for a stable oral pharmaceutical composition of elagolix or pharmaceutical acceptable salt thereof which can overcome the problems associated with the existing formulations such as elagolix or pharmaceutical acceptable salt thereof has a tendency to form a gel in the presence of water while the most one difficult being the development of a stable oral formulation so it is necessary to add anti- gelling agent into to the formulation.

Thus, there is a need in the art for a new orally administered treatments for endometriosis, uterine fibroids, PCOS and adenomyosis and, in particular, management of pain associated with endometriosis, uterine fibroids, PCOS or adenomyosis, and heavy menstrual bleeding associated with endometriosis, uterine fibroids, PCOS or adenomyosis. Moreover, there remains a need in the art to develop orally bioavailable dosage forms comprising such treatments and, in particular, a nonpeptide GnRH antagonist.

It has now been found surprisingly, that a stable oral pharmaceutical composition of elagolix or pharmaceutical acceptable salt thereof, can be prepared in which the active ingredients do not convert into a gel in the absence of any anti-gelling agents and further this is achieved by using a suitable solubilizer in the composition.

OBJECT OF THE INVENTION

It is an object of the present invention to provide a stable pharmaceutical composition comprising Elagolix or a pharmaceutically acceptable salt thereof and processes for preparing thereof for the treatment of Endometriosis, Uterine Fibroids, Polycystic Ovary Syndrome, or Adenomyosis.

It is another object of the present invention to provide a stable pharmaceutical composition for oral administration comprising:

a) Elagolix or a pharmaceutically acceptable salt thereof, as an active ingredient;

b) One or more Solubilizers;

c) One or more pharmaceutically acceptable excipients.

It is also an object of the present invention to provide a process to prepare a stable pharmaceutical composition prepared by different processes such as direct compression, dry granulation like slugging-deslugging, or roller compaction process said composition comprising-

a) Elagolix or a pharmaceutically acceptable salt thereof, as an active ingredient;

b) One or more Solubilizers;

c) One or more pharmaceutically acceptable excipients.

It is yet another object of the present invention to provide a stable pharmaceutical composition comprising Elagolix or a pharmaceutically acceptable salt thereof for the treatment of Endometriosis, Uterine Fibroids, Polycystic Ovary Syndrome, or Adenomyosis.

It is yet another object of the present invention to provide a stable pharmaceutical composition of Elagolix or a pharmaceutically acceptable salt thereof, which is bioequivalent to the commercially available compositions in the United States of America i.e. **ORILISSA®** tablets.

SUMMARY OF THE INVENTION

The present invention provides a stable pharmaceutical composition comprising Elagolix or a pharmaceutically acceptable salt thereof and processes for preparing thereof wherein the pharmaceutical composition has an improved stability.

More particularly, the present invention relates to-

A) A Stable Pharmaceutical composition comprising:

   i. Elagolix or a pharmaceutically acceptable salt thereof as the active ingredient;

   ii. One or more Solubilizers;

   iii. One or more pharmaceutically acceptable excipients.

B) The Stable pharmaceutical composition as in A, wherein one or more Solubilizers are selected from Hydroxypropyl beta-cyclodextrin and Poloxamer P 188 micro.

C) The Stable pharmaceutical composition as in A, wherein the composition is a Tablet dosage form.

D) The Stable pharmaceutical composition as in A, wherein one or more pharmaceutically acceptable excipient(s) is selected from disintegrant, diluent, lubricant and the like.

E) The Stable pharmaceutical composition as in A, wherein the diluent is mannitol.

F) The Stable pharmaceutical composition as in A, wherein the disintegrant is pregelatinized starch.

G) The Stable pharmaceutical composition as in A, wherein the lubricant is magnesium stearate.

H) The Stable pharmaceutical composition as in A, wherein the composition is used for the treatment of Endometriosis, Uterine Fibroids, Polycystic Ovary Syndrome, or Adenomyosis.

I) A process for the preparation of a stable pharmaceutical composition comprising:

i. Elagolix or a pharmaceutically acceptable salt thereof as the active ingredient;

ii. One or more Solubilizer;

iii. One or more pharmaceutically acceptable excipients;

Wherein the process comprises a slugging-deslugging:

a) Preparation of compacted mass by using the active ingredient, Solubilizer and one or more pharmaceutically acceptable excipients;

b) Milling the compacted mass obtained in step (a);

c) Blending the milled composition obtained in step (b) with a Solubilizer,

d) Lubricating the blended material obtained in step (c) with a suitable lubricating agent/s,

e) Compressing the lubricated material obtained step (d) to obtain a tablet; Coating the tablet obtained in step (e) by using a suitable coating composition.

J) The process for the preparation of a stable pharmaceutical composition as in I, wherein the one or more Solubilizer is selected from Hydroxypropyl beta-cyclodextrin and Poloxamer P 188 micro.

K) The process for the preparation of a stable pharmaceutical composition as in I, wherein the composition is a Tablet dosage form.

L) The process for the preparation of a stable pharmaceutical composition as in I, wherein one or more pharmaceutically acceptable excipient(s) is selected from disintegrant, diluent, lubricant and alike.

M) The process for the preparation of a stable pharmaceutical composition as in L, wherein the diluent is mannitol.

N) The process for the preparation of a stable pharmaceutical composition as in L, wherein the disintegrant is pregelatinized starch.

O) The process for the preparation of a stable pharmaceutical composition as in L, wherein the lubricant is magnesium stearate.

P) The process for the preparation of a stable pharmaceutical composition according as in I, wherein the composition is used for the treatment of Endometriosis, Uterine Fibroids, Polycystic Ovary Syndrome, or Adenomyosis.

DETAILED DESCRIPTION OF THE INVENTION

Before the present process and methods are described, it is to be understood that this invention is not limited to particular compounds, formulas, or steps described, as such may, of course, vary. It is also to be understood that the terminology used herein is to describe particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of such compounds, and reference to "the step" includes reference to one or more steps and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their availability to the applicant before the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by the prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

The present invention provides a stable pharmaceutical composition for oral administration comprising:

A. Elagolix or a pharmaceutically acceptable salt thereof, as an active ingredient;
B. One or more Solubilizer;
C. One or more pharmaceutically acceptable excipients.

In an embodiment, the present invention provides that the stable pharmaceutical composition is in a Tablet dosage form.

The term "stable" as used herein refers to Elagolix in a solid dosage form wherein there is no change in assay values and dissolution and/or the total impurity remains less than 1.5%, when the dosage form is kept at 40°C/75% RH for 6 months.

The term "composition" "formulation" or "dosage form" as used herein synonymously include solid dosage forms such as granules, multiunit particulate systems (MUPS), pellets, spheres, tablets, capsules, mini-tablets, layered tablets (e.g. bilayer or trilayer), beads, particles, granules and the like; and liquid dosage forms such as solutions, suspensions, emulsions, colloids and the like, meant for oral administration.

The compositions in accordance with the present invention can be prepared either by simple conventional process for examples- direct compression, dry granulation like slugging-deslugging, or roller compaction.

As term “active ingredient” as used herein means an ingredient or compound having an intended biological effect. “Active ingredient” may be broadly construed to include an active compound and vice versa. Such active ingredients or active compounds are thus considered to be “biologically active”.

Elagolix or its pharmaceutically acceptable salt(s) may be present in crystalline or amorphous forms and may include salts with inorganic bases and organic bases. Inorganic bases may include, but are not limited to, salts with alkali metals such as sodium, potassium, lithium, or alkaline earth metals such as calcium, barium or magnesium. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Suitable organic bases may include but not limited to dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, and the like. Preferably Elagolix is in the form of a sodium salt of Elagolix in an amorphous form.

As term “intra-granular” (part/phase/portion) refers to the components of formulation of the present invention that are within the granules. As used herein, the term “extra-granular” (part/phase/portion) refers to those components of formulation of the present invention that are outside the granules.

The term "excipient" as used herein means a pharmacologically inactive component such as, but not limited to, a diluent or filler, binder, disintegrant, lubricant, glidant, surfactant, colorants, or the like. The excipients that are useful in preparing a pharmaceutical composition are generally safe, non-toxic, and acceptable for human use. Reference to an excipient includes both one and more than one such excipient and the said excipients may be added intragranular or extra granularly.

The term "solubilizer" as used herein means any substance or mixture of substances that can be used to improve solubility. In a further embodiment, one or more Solubilizers used in the composition of the present invention are selected from Hydroxypropyl beta-cyclodextrin, Poloxamer P 188 micro, Dibasic calcium phosphate, Syloid 244FP and Magnesium Aluminium silicate combinations thereof and the like. Preferably, the Solubilizer is Hydroxypropyl beta-cyclodextrin, Poloxamer P 188 micro or a combination thereof.

As used herein, the term "compaction" refers to the general process of dry granulating to form a tablet (for example, by chopping or roller compaction). Therapeutic agents and pharmaceutically acceptable excipients are formed into pieces (as in the formation of pieces) or slats (as in roller compaction). The roller compaction process densifies the dust by removing the air. The dosed material is then reduced to a uniform

granule size and subsequently compressed. Useful excipients in a roller compaction process include, but are not limited to, fillers, binders, lubricants and disintegrants. Roller compaction is particularly suitable for a solid oral dosage form having a concentration of 50 to 800 mg of the therapeutic agent.

In a further embodiment, the lubricants used in the composition of the present invention are selected from metallic stearates such as magnesium stearate, calcium stearate, zinc stearate; stearic acid, hydrogenated vegetable oil, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyethylene glycols, corn starch, sodium stearyl fumarate, sodium benzoate, mineral oil, talc, and the like and mixtures thereof. The glidant used in the composition of the present invention is selected from talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, tribasic calcium phosphate; and the like and mixtures thereof.

In a further embodiment, the fillers or diluents used in the composition of the present invention are selected from sugars such as lactose, dextrose, glucose, sucrose, cellulose, starches, carbohydrate derivatives, polysaccharides (including dextrose and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins, calcium carbonates, magnesium carbonates, microcrystalline cellulose, combinations thereof, and the like. In certain preferred embodiments, the filler or diluent is lactose, microcrystalline cellulose, or a combination thereof. Several types of microcrystalline cellulose are suitable for use in the formulations described herein, for example, microcrystalline cellulose selected from the group consisting of Avicel® types: PH101, PH102, PH103, PH105, PH112, PH113, PH200, PH301, and other types of microcrystalline cellulose, such as silicified microcrystalline cellulose. Several types of lactose are suitable for use in the formulations described herein, for example, lactose is selected from the group consisting of anhydrous lactose, lactose monohydrate, lactose fast flow, directly compressible anhydrous lactose, and modified lactose monohydrate. In one embodiment of the invention, the filler or diluent is a combination of microcrystalline cellulose and lactose.

In a further embodiment, the binders used in the composition of the present invention are selected from cellulose derivatives (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, ethylcellulose and sodium carboxymethyl cellulose), sugar (including sucrose, glucose, dextrose, molasses, lactose, dextrin, xylitol, sorbitol), glycol, corn syrup, polysaccharides (including acacia, tragacanth, guar, alginates, and starch), corn starch, pregelatinized starch, modified corn

starch, gelatin, polyvinylpyrrolidone, polyethylene, polyethylene glycol, combinations thereof and the like. Preferably, the binding agent, if present, is hydroxypropyl cellulose.

In a further embodiment, the disintegrants used in the composition of the present invention are selected starches, clays, celluloses, alginates, gums, crosslinked starches, celluloses, polymers, combinations thereof, and the like. Representative disintegrants include microcrystalline cellulose, croscarmellose sodium, alginic acid, sodium alginate, crospovidone, cellulose, agar, and related gums, sodium starch glycolate, corn starch, potato starch, sodium starch glycolate, Veegum HV, methylcellulose, agar, bentonite, carboxymethylcellulose, alginic acid, guar gum combinations thereof, and the like. Preferably, the disintegrant, if present, is cross-linked cellulose, more preferably cross-linked sodium carboxymethylcellulose or croscarmellose sodium.

In a further embodiment, the glidants used in the composition of the present invention are selected silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide, silicon hydrogel, or mixtures thereof. Glidant may be used in the range of 0.01 - 4 % w/w of the total weight of the stable oral pharmaceutical composition.

"Colorants" may be selected from, but are not limited to, iron oxide yellow, iron oxide red, titanium dioxide, or mixtures thereof. Colourants may be used in the range of 0.01 - 1.5 % w/w of the total weight of the stable oral pharmaceutical composition.

The pharmaceutical compositions of the present invention may be further coated with a functional or non-functional coating. The coating composition may be comprised of pharmaceutically acceptable excipients such as coating agents, binders, plasticizers, coloring agents, and opacifiers. The total weight gain after coating may be about 1% w/w to 10% w/w of the uncoated pharmaceutical composition.

"Coating agents" which are useful in the coating process, may be selected from, but not limited to, water-soluble polymers such as, but not limited to, polyvinylpyrrolidone or water-soluble cellulose such as, but not limited to, hydroxypropyl methylcellulose or hydroxypropyl cellulose. It may be selected from, but not limited to, soluble agents such as polysorbate 80, polysaccharides such as maltodextrin, acacia, corn starch, sucrose, gelatin, shellac, cellulose acetate phthalate, lipids, synthetic resins, acrylic polymers, opadry, polyvinyl alcohol, copolymers of vinylpyrrolidone, vinyl acetate or combinations thereof. These may be applied from aqueous or non-aqueous systems or combinations of the aqueous and non-aqueous systems as appropriate.

Examples of binders for coating include cellulose or cellulose derivatives such as, but not limited to, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, and microcrystalline cellulose, alginic acid, sodium alginate and gelatin, polyvinyl pyrrolidone, crospovidone, starch, pregelatinized starch, or mixtures thereof. Examples of plasticizers for coating include, but are not limited to, propylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin, polyethylene glycol, diethyl phthalate, acetylated monoglycerides, or mixtures thereof. Examples of opacifiers for coating include, but are not limited to, titanium dioxide, talc, calcium carbonate, behenic acid, cetyl alcohol, or mixtures thereof. Anti-tacking agents such as, but are not limited to, talc, stearic acid, magnesium stearate, colloidal silicon dioxide, or the like. Examples of coloring agents for coating include but are not limited to, FDA-approved colorants such as iron oxide, the lake of tartrazine, Allura red, the lake of quinoline yellow, the lake of erythrosine, titanium dioxide, or mixtures thereof. Suitable solvents for the coating include but are not limited to, ethanol, methanol, isopropyl alcohol, methylene chloride, acetone, or mixtures thereof.

Further, the present invention provides a process for the preparation of a stable pharmaceutical composition comprising;

i. Elagolix or pharmaceutically acceptable salt as an active ingredient;
ii. One or more Solubilizer
iii. One or more than one pharmaceutically acceptable excipient.

Wherein the process comprises a Slugging-deslugging process.

In an embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form.

In an embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form comprising 100 mg to 300 mg of elagolix or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form comprising 150 mg to 200 mg of elagolix or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form comprising 20 % to 50 % of elagolix or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form comprising 25 % to 40 % of elagolix or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to a stable solid pharmaceutical composition for oral administration comprising:

(i) Elagolix or a pharmaceutically acceptable salt thereof,

(ii) Solubilizer,

(iii) diluent,

(iv) disintegrant,

(v) binder,

(vi) glidant, and

(vii) lubricant.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form wherein the tablet comprises:

about 20-50% elagolix or a pharmaceutically acceptable salt thereof,

about 10-40% Mannitol 200 SD,

about 02-20% pregelatinized starch,

about 02-30% Hydroxypropyl beta cyclodextrin,

about 0.1-10% Magnesium stearate,

about 01-15% Poloxamer P 188 micro, and

about 01-20% Opadry II 85F540583,

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form wherein the tablet comprises:

about 25-40% elagolix or a pharmaceutically acceptable salt thereof,

about 21-37% Mannitol 200 SD,

about 05-14% pregelatinized starch,

about 11-19% Hydroxypropyl beta cyclodextrin,

about 0.5-03% Magnesium stearate,

about 02-07% Poloxamer P 188 micro, and

about 02-05% Opadry II 85F540583.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form wherein the tablet comprises of:

155.25 mg Elagolix sodium,

139.75 mg Mannitol 200 SD,

50 mg pregelatinized starch,

80 mg Hydroxypropyl beta cyclodextrin,

3.75 mg Magnesium stearate,

25 mg Poloxamer P 188 micro, and

20 mg Opadry II 85F540583.

In another embodiment, the present invention provides a stable pharmaceutical composition in a tablet dosage form wherein the tablet comprises of:

207 mg Elagolix sodium,

179 mg Mannitol 200 SD,

65 mg pregelatinized starch,

110 mg Hydroxypropyl beta cyclodextrin,

14 mg Magnesium stearate,

39 mg Poloxamer P 188 micro, and

28 mg Opadry II 85F540583.

In certain embodiments the pharmaceutical composition is prepared by dry processing methods, such as, but not limited to, direct compression or dry granulation methods. An example of dry granulation is roller compaction. The pharmaceutical composition obtained by the dry processing method is preferably compressed into tablets or encapsulated.

In further embodiments, the disclosed pharmaceutical compositions are prepared using a roller compaction process. The roller compaction process may include any suitable steps. Roller compaction may include steps such as blending the active agent with one or more intragranular excipients sized for blending; feeding the blend into a roller compactor to densify loose powder into ribbons; milling the resultant ribbons into granules; optionally blending the granules with extragranular excipients such as lubricants; compressing the granules into tablets, and optionally coating the tablets with a film-coating.

In further embodiments, the disclosed pharmaceutical compositions are prepared using “direct compression” refers to the general process of directly compressing the ingredients in the pharmaceutical formulation (i.e., therapeutic agent and excipients) without changing the physical and chemical properties of the therapeutic agent. The therapeutic agent, along with pharmaceutically acceptable excipients, in the form of powders, are blended in a low-shear apparatus, for example, a twin-shell blender. The blended

composition is then filled into a die and directly compressed into a punch. A tablet press, for example, can accomplish this compression step. Useful excipients in a direct compression process include, but are not limited to fillers, binders, lubricants and glidants.

In another embodiment, the stable pharmaceutical compositions of the present invention are bioequivalent to the existing Elagolix pharmaceutical compositions marketed under the trade name, ORILISSA® in USA.

An aspect of the present invention provides a tablet formulation of Elagolix or pharmaceutically acceptable salt for the treatment of Endometriosis, Uterine Fibroids, Polycystic Ovary Syndrome, or Adenomyosis. Another aspect of the present invention further provides a process of preparation of tablet formulation of Elagolix or pharmaceutically acceptable salt.

A stability study carried out for Elagolix or pharmaceutically acceptable salt tablet provided satisfactory data for all the physical and chemical parameters, wherein initial, 1 months', 3 months' and 6 months' stability studies were performed at 40^0C /75 %RH and 25^0C /60 %RH.

It should be appreciated that the invention can be embodied / aspects in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will convey the scope of the invention to those skilled in the art. Other features and embodiments of the invention will become apparent from the following examples, which are given for illustration of the invention rather than for limiting its intended scope.

The pharmaceutical compositions of the present invention are prepared by the Slugging-desludging process.

The following examples are intended to illustrate the scope of the present invention in all its aspects but not to limit it thereto.

Example 1

Table -1

Percentage Range in Formulation

Sr. No.	Ingredient	% Range (w/w)
1	Elagolix Sodium	25- 40
2	Mannitol 200 SD	21-37
3	Pregelatinized Starch	05-14
4	Hydroxypropyl beta cyclodextrin	11-19

5	Magnesium stearate	0.5-03
6	Poloxamer P 188 micro	02-07
7	Opadry II 85F540583	02-05
8	Purified Water	Q.S.

Q.S.- Quantity sufficient

Manufacturing Process:

Elagolix Sodium, Mannitol (200 SD), Pregelatinized Starch, and Hydroxy Propyl Betacylodextrin material were loaded into a blender and blended for 05 minutes at appropriate rpm. Blended material was milled through a Quadro mill fitted with a 1.5 mm S.S. screen at the appropriate speed and milled material was collected in double Polythene lined labelled containers. Screen integrity before and after milling operation checked. Further milled material was blended in a blender for 20 minutes at appropriate rpm. Magnesium stearate was sifted through #60 S.S. Sieve which was fitted to a Mechanical Sifter and collected separately in double Polythene lined labelled container. The above-blended material was lubricated with sifted magnesium stearate for 5 minutes at appropriate rpm.

The compression machine was set with dies and punches for slugging as per the optimum parameters. The above-mixed materials were transferred to the compression. The appropriate slugging parameter was adjusted.

The Slugg material was milled through a Quadro mill fitted with a 2.5 mm S.S. screen at the appropriate speed and milled material was collected in double Polythene lined labelled containers. Screen integrity before and after milling operation checked. Milled material passed through #16 S.S. sieve fitted to a sifter and #16 passed and oversized if any material was collected in separate double polythene lined labelled containers. The #16 oversized material was milled through a Quadro mill fitted with a 1.5 mm S.S. screen at the appropriate speed and collected the milled material in double Polythene lined labelled containers.

The Milled material passed through #16 S.S. sieve fitted to a sifter and #16 passed and oversized if any material was collected in separate double polythene lined labelled containers. The #16 oversized milled material was milled through a Quadro mill fitted with a 1.0 mm S.S. screen at the appropriate speed and collected the milled material in double Polythene lined labelled containers. The operation was done till there was no retention on

the #16 S.S. sieve. The 16# passed above material was sifted through Sieve No 60 S (60#) which fitted to the sifter. Collect the 60# retained (granules) and 60# passed material (fines) collected in separate double Polythene lined labelled containers. The slugging-deslugging cycle was repeated by using the 60# passed material (fines) to get 50%±10% of 60# retained material (granules).

The #60 S.S. retained (granules) and #60 S.S. passed material (fines) were mixed in Blender and blended for 5 minutes at appropriate rpm. Poloxamer USP was sifted through #30 S.S. Sieve which fitted to a Mechanical Sifter and collected separately in double Polythene lined labelled container. The above-blended material was lubricated with sifted Poloxamer USP for 10 minutes at appropriate rpm. Magnesium stearate was sifted through #60 S.S. Sieve which was fitted to a Mechanical Sifter and collected separately in double Polythene lined labelled container.

The above-Lubricated material was lubricated with sifted magnesium stearate for 5 minutes at an appropriate rpm. The lubricated blend is compressed by using a suitable die and punches. The compressed tablet was coated using non-aqueous dispersion of Opadry.

Example 2

Table -2

Sr. No.	Ingredient(s)	200 mg Tablets*	150mg Tablets**
1	Elagolix Sodium	207	155.25
2	Mannitol 200 SD	179	139.75
3	Pregelatinized Starch	65	50.0
4	Hydroxypropyl beta cyclodextrin	110	80.0
5	Magnesium stearate	14	3.75
6	Poloxamer P 188 micro	39	25.00
7	Opadry II 85F540583	28	20.00
8	Purified Water	Q.S.	Q.S.

*207 mg equivalent to 200 mg of Elagolix

**155.25 mg equivalent to 150 mg of Elagolix

Q.S.- Quantity sufficient

Manufacturing procedure: Same as in Example 1.

The distinct formulations of the invention exemplified in Example 2 were evaluated for stability at conditions of 25°C ± 2°C and 60% RH ± 5% RH, 40°C ± 2°C and 75%RH ± 5% RH for initial, 3 months' and 6 months' in different pack conditions i.e. (Alu-Alu Blister, PVC-PVDC Blister and HDPE container).

A. Stability study of Example 2: 200mg Tablets at 40^0C /75 %RH and 25^0C /60% RH at 3 Months:

Table -3

Pack Condition	**Specification Shelf life**	**Initial**	**Alu-Alu Blister**		**PVC-PVDC Blister**		**HDPE**	
			25^0C /60%RH	40^0C /75 %RH	25^0C /60%RH	40^0C /75 %RH	25^0C /60%RH	40^0C /75 %RH
Dissolution (45 Min.)	80% (Q)	101	101.9	101.8	104	103	106	104
Assay	90-110%	101.3	106`	106	104.7	104.6	101.6	100.7
Organic impurities (%)								
N-Oxide Impurity	NMT 0.4%	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ
M2b Impurity	NMT 0.3%	0.06	0.05	0.08	0.06	0.08	0.06	0.09
Any unspecified degradation product	NMT 0.2%	0.03	0.03	0.16	0.03	0.18	0.03	0.16
Total degradation product	NMT 1.5%	0.1	0.2	0.5	0.2	0.5	0.2	0.5
Water content (% w/w)	NMT 7.0%	2.8	2.4	2.6	4.6	2.7	2.4	2.3

B. Stability study of Example 2: 200mg Tablets at 40^0C /75 %RH and 25^0C /60% RH at 6 Months:

Table 4:

Pack Condition	**Specification Shelf life**	**Initial**	**Alu-Alu Blister**		**PVC-PVDC Blister**		**HDPE**	
			25^0C /60%RH	40^0C /75 %RH	25^0C /60%RH	40^0C /75 %RH	25^0C /60%RH	40^0C /75 %RH
Dissolution (45 Min.)	80% (Q)	101	101	100	101	99	100	99
Assay	90-110%	101.3	101	99.6	101.1	100.3	99.8	99.8
Organic impurities (%)								

N-Oxide Impurity	NMT 0.4%	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ
M2b Impurity	NMT 0.3%	0.06	0.06	0.12	0.06	0.11	0.07	0.13
Any unspecified degradation product	NMT 0.2%	0.03	0.01	0.02	0.01	0.03	0.01	0.02
Total degradation product	NMT 1.5%	0.1	0.3	0.9	0.2	1.0	0.3	0.9
Water content (% w/w)	NMT 7.0%	2.8	2.2	2.5	3.0	5.4	2.3	2.4

C. Stability study of Example 2: 150mg Tablets at 40^{0}C /75 %RH and 25^{0}C /60% RH at 3 Months:

Table -5

Pack Condition	**Specification Shelf life**	**Initial**	**Alu-Alu Blister**		**PVC-PVDC Blister**		**HDPE**	
			25^{0}C /60%RH	40^{0}C /75 %RH	25^{0}C /60%RH	40^{0}C /75 %RH	25^{0}C /60%RH	40^{0}C /75 %RH
Dissolution (45 Min.)	80% (Q)	101	107	106	107	105	103	103
Assay	90-110%	103.1	101.7	101.1	101.6	101.5	101.7	101.8
Organic impurities (%)								
N-Oxide Impurity	NMT 0.4%	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ	Below LOQ
M2b Impurity	NMT 0.3%	0.06	0.05	0.08	0.05	0.07	0.06	0.11
Any unspecified degradation product	NMT 0.2%	0.01	0.03	0.16	0.03	0.17	0.02	0.18
Total degradation product	NMT 1.5%	0.1	0.2	0.5	0.2	0.5	0.2	0.6
Water content (% w/w)	NMT 7.0%	2.5	2.4	2.5	2.8	5.0	2.2	2.3

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D. Stability study of Example 2: 150mg Tablets at 40^{0}C /75 %RH and 25^{0}C /60% RH at 6 Months:

Table -6

Pack Condition	**Specification Shelf life**	**Initial**	**Alu-Alu Blister**		**PVC-PVDC Blister**		**HDPE**	
			25^{0}C /60%RH	40^{0}C /75 %RH	25^{0}C /60%RH	40^{0}C /75 %RH	25^{0}C /60%RH	40^{0}C /75 %RH

Dissolution (45 Min.)	80% (Q)	101	102	100	105	98	103	102
Assay	90-110%	103.1	102.6	102.4	100.6	100.2	102.3	102
Organic impurities (%)								
N-Oxide Impurity	NMT 0.4%	Below LOQ	Below LOQ	0.1	Below LOQ	Below LOQ	Below LOQ	0.1
M2b Impurity	NMT 0.3%	0.06	0.07	0.15	0.07	0.11	0.07	0.15
Any unspecified degradation product	NMT 0.2%	0.01	0.01	0.02	0.01	0.04	0.01	0.02
Total degradation product	NMT 1.5%	0.1	0.2	1.1	0.3	1.0	0.2	1.0
Water content (% w/w)	NMT 7.0%	2.5	2.6	2.4	2.9	5.7	2.2	2.4

All the physical and chemical parameters were found satisfactory and the initial, 3 months' and 6 months' stability data at 40^0C /75 % RH and 25^0C /60 % RH were also found to be satisfactory.

E. Bioequivalence Study:

The Elagolix tablet compositions in Example 2 (200mg) were compared with ORILISSA® tablets under fasting and fed conditions in 28 healthy subjects. Values for various pharmacokinetic parameters, including observed $C_{max,}$, AUC_{0-t} and $AUC_{0-\infty}$ were calculated and are provided in Tables 7 and 8 below:

Reference (R): ORILISSA® Tablets, 200mg

Test Product (T): Elagolix Sodium Tablets, 200mg (Example 2):

Table 7:

Comparative Pharmacokinetic data for Elagolix Tablets of Example 2 (T) and Orilissa®			
Test (T) Vs Reference (R) Under fasting conditions			
	Ln $C_{max,}$	Ln AUC_{0-t}	AUC_{0-inf}
Ratio (T/R)	98.80	99.61	99.68
90% Confidence Interval	89.17 – 109.02	95.33 – 104.09	95.43 – 104.11

Table 8:

Comparative Pharmacokinetic data for Elagolix Tablets of Example 2 (T) and Orilissa®			
Test (T) Vs Reference (R) Under fed conditions			
	Ln $C_{max,}$	Ln AUC_{0-t}	AUC_{0-inf}
Ratio (T/R)	88.57	97.29	97.42
90% Confidence Interval	76.87 – 102.05	90.23 – 104.91	90.77 – 104.55

Conclusion-

Based on the statistical analysis of Elagolix Tablets it is concluded that the Test Product (T) Elagolix Sodium Tablets, 200mg (Example 2) manufactured by Alkem Laboratories Ltd., India is bioequivalent to the Reference Product (R): Orilissa® 200 mg manufactured by ABBVIE INC, North Chicago, USA, in terms of rate and extent of absorption under fasting conditions.

We Claim:

1. A stable pharmaceutical composition comprising elagolix or a pharmaceutically acceptable salt thereof, one or more Solubilizers and one or more pharmaceutically acceptable excipients.

2. The stable pharmaceutical composition as in claim 1, wherein one or more Solubilizers are selected from Hydroxypropyl beta-cyclodextrin and Poloxamer P 188 micro or a combination thereof.

3. The stable pharmaceutical composition as in claim 1, wherein one or more pharmaceutically acceptable excipient(s) is selected from disintegrant, diluent, and lubricant.

4. The stable pharmaceutical composition as in claim 3, wherein the diluent is mannitol.

5. The stable pharmaceutical composition as in claim 3, wherein the disintegrant is pregelatinized starch.

6. The stable pharmaceutical composition as in claim 3, wherein the lubricant is magnesium stearate.

7. The stable pharmaceutical composition as in claim 1, wherein the composition is tablet dosage form.

8. A process for the preparation of a stable pharmaceutical composition comprising; elagolix or a pharmaceutically acceptable salt thereof, one or more Solubilizers and one or more pharmaceutically acceptable excipients.

9. The process for the preparation of a stable pharmaceutical composition as in claim 8, wherein the process is aa slugging-deslugging process which comprises:

(a) preparation of a compacted mass by using the active ingredient, solubilizer and one or more pharmaceutically acceptable excipients;
(b) Milling the compacted mass obtained in step (a);
(c) Blending the milled material obtained in step (b) with a solubilizer;
(d) Lubricating the blended material obtained in step (c) with a suitable lubricating agent;
(e) Compressing the lubricated materials obtained in step (d) to form a tablet;
(f) Coating the tablet obtained step (e) by using a suitable coating composition.

10. The process for the preparation of a stable pharmaceutical composition as in claim 8, wherein the composition is a tablet dosage form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2022/051140

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/00,A61K47/40,A61K47/10 Version=2023.01

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)

A61K

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2021180862A1 (SYNTHON B.V., 16 SEPTEMBER 2021) Example 1, Table 1, page 8, claims 1-10	1-10
X	US20190054027A1 (ABBVIE INC, 21 FEBRUARY, 2019) Claims 63-74, Table 5, para 0136, 0156, 0202	1-8
A	WO2020043763A1 (SANDOZ AG, 05 MARCH, 2020) Claims 1-15	1-10

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

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06-03-2023	06-03-2023

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2022/051140

Citation	Pub.Date	Family	Pub.Date
US 20190054027 A1	21-02-2019	WO 2019036713 A1	21-02-2019
		TW 201912157 A	01-04-2019