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(54) Title: PROCESS FOR PREPARING ELAGOLIX FORMULATIONS AND DOSAGE FORMS COMPRISING THE SAME

Figure 1A

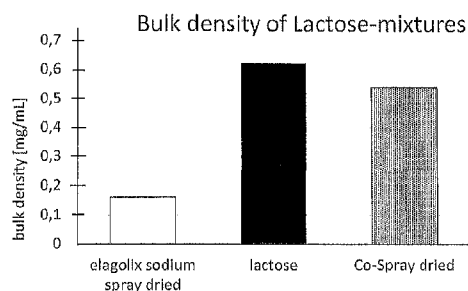
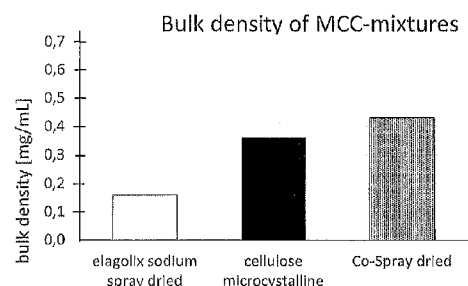


Figure 1B



(57) Abstract: The present invention relates to a process for the preparation of a powder comprising elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid) as pharmaceutically active ingredient (API) or its pharmaceutically acceptable salt, and a filler in its crystalline form. The process comprises a step of providing a solution containing the API, combining the solution with a filler in its crystalline form, and spray-drying the obtained suspension. The present invention also relates to a powder comprising a crystalline filler and elagolix or its pharmaceutically acceptable salt, to a dosage form comprising said powder, to a compressed tablet core consisting of said powder, and to the use of said pharmaceutical dosage form in the treatment of gonadotropin-releasing hormone (GnRH)-dependent diseases, such as endometriosis and uterine fibroids.

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- *with amended claims and statement (Art. 19(1))*

Process for preparing elagolix formulations and dosage forms comprising the same**Field of the invention**

The present invention relates to a process for the preparation of a powder comprising elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid) as pharmaceutically active ingredient (API) or its pharmaceutically acceptable salt, and a filler in its crystalline form. The process comprises a step of providing a solution containing the API, combining the solution with a filler in its crystalline form, and spray-drying the obtained suspension.

The present invention also relates to a powder comprising a crystalline filler and elagolix or its pharmaceutically acceptable salt, to a dosage form comprising said powder, to a compressed tablet core consisting of said powder, and to the use of said pharmaceutical dosage form in the treatment of gonadotropin-releasing hormone (GnRH)-dependent diseases, such as endometriosis and uterine fibroids.

Background of the invention

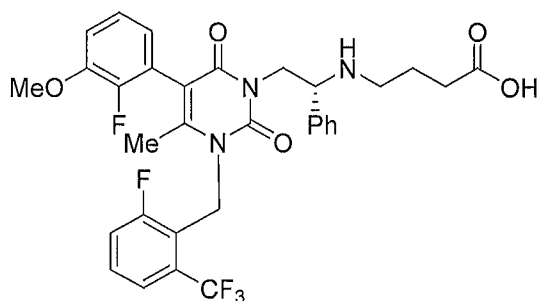
In the field of pharmacy, there exists a vast number of active pharmaceutical ingredients (API), with each API exhibiting its own specific, characteristic (material) properties. Such properties can influence on the one hand the bioavailability of the API, and on the other hand the handling, processing, and/or storing of said API. The processing of the API includes for instance the formulation process of said API into a pharmaceutical composition, and also into a (final) dosage form. When handling, storing, and/or processing an API, its specific (material) properties such as powder flow, hygroscopicity and electrostatic charge have to be accounted for, and respective measures have to be taken to allow for a proper handling of said API.

The improvement of the (material) properties of an API, such as the bulk density, can significantly contribute to enhance the processability of said API.

The API elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid and having the below structure (Formula I))

is a GnRH-antagonist that is hygroscopic. Thus, processability of elagolix is demanding.

Elagolix:



Formula I

In this context, in order to improve processability of elagolix, WO 2017/007895 discloses an acoustic mixing technology, where a bulk drug substance, for example elagolix, is acoustically granulated, that is, enlarged in size, thereby enhancing its flowability.

WO 2009/062087 refers to a process for preparing inter alia pure elagolix sodium.

However, there is still a need for a reliable formulation process that provides a powder exhibiting improved (material) properties such as increased bulk density and/or reduced electrostatic behavior and/or acceptable flowability. This improved (material) properties can e.g. not only enable an improved processing of said powder into a pharmaceutical composition, but also result in an improvement of the economic situation, such as a cost reduction due to reduced material consumption, and/or reduction of material loss as sticking of the powder to the equipment is reduced.

Summary of the invention

The present inventors have found that by applying the process of the present invention, certain properties of a powder comprising the API elagolix or a pharmaceutically acceptable salt thereof, can be improved. An example of such a property is an increased bulk density, and/or acceptable flowability and/or reduced electrostatic behavior, which, in turn, results amongst other also in reduced stickiness.

Accordingly, the present invention provides the following aspects, subject-matters and preferred embodiments which, respectively taken alone or in combination, contribute to providing improved technical effects and to solving the afore-mentioned object of the invention:

1. Process for the preparation of a powder comprising as active pharmaceutical ingredient (API) elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-

phenylethyl)amino)butanoic acid) or a pharmaceutically acceptable salt thereof, wherein the process comprises the following steps:

- a) providing a solution comprising elagolix or a pharmaceutically acceptable salt thereof, and a suitable solvent or mixture of solvents;
- b) combining the solution of elagolix or a pharmaceutically acceptable salt thereof with one or more filler in its crystalline form, thereby obtaining a suspension;
- c) co spray-drying the suspension of step (b), and
- d) obtaining the powder.

2. Process according to any of the preceding items, wherein the elagolix or its pharmaceutically acceptable salt of step (a) is amorphous or crystalline.

3. Process according to any of the preceding items, wherein in step (a) the pharmaceutically acceptable salt of elagolix is selected from the group consisting of sodium elagolix, hydrochloric acid salt of elagolix, and sulfuric acid salt of elagolix; preferably the salt is sodium elagolix.

4. Process according to any of the preceding items, wherein the solvent or mixture of solvents is selected to the effect that the following conditions (i) to (iii) are met:

- (i) the elagolix or pharmaceutically acceptable salt used in step (a) is fully dissolved in the solvent or mixture of solvents;
- (ii) the one or more filler(s) used in step (b) is (are) at most only partially dissolved, or not dissolved at all in the solvent or mixture of solvents, thereby forming a suspension; and
- (iii) the solvent or mixture of solvents is suitable for spray drying.

5. Process according to any of the preceding items, wherein the solvent or mixture of solvents is selected from the group consisting of

water, alcohols, such as methanol, ethanol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol (n-butanol), 2-butanol, iso-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, cyclohexanol, glycerol, or C1-C6 alcohols and the like;

nitriles, such as acetonitrile or propionitrile;

amides, such as formamide, N,N- dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, or hexamethyl phosphoric triamide and the like;

sulfoxides, such as dimethylsulfoxide and the like;

or any mixtures of two or more solvents thereof;

preferably, alcohols or a mixture thereof are used.

6. Process according to the preceding item, wherein the solvent or mixture of solvents is a polar solvent or a polar mixture of solvents.
7. Process according to any of the preceding items, wherein the solvent or mixture of solvents is selected from the group consisting of methanol, ethanol, isopropyl alcohol, and n-butanol; preferably the solvent or mixture of solvents comprises ethanol.
8. Process according to any of the preceding items, wherein the solvent is a single solvent, preferably an alcohol, and most preferred, the solvent is ethanol.
9. Process according to any of the preceding items, wherein the ratio of the amount of elagolix or its pharmaceutically acceptable salt (or a mixture of different forms of elagolix) to the amount of the one or more filler(s) of step (b) is in a range of from about 1 : 0.5 to about 1 : 3.5; preferably in a range of from about 1 : 1 to about 1 : 3; more preferably in a range of from about 1 : 1 to about 1 : 2.5; and most preferred the ratio is about 1 : 2.
10. Process according to any of the preceding items, wherein the solution of step (a) consists of elagolix or its pharmaceutically acceptable salt, and the solvent or mixture of solvents.
11. Process according to any of the preceding items, wherein in step (b), at least a part of the amount of the one or more filler(s) is present in the suspension in its/their crystalline and suspended form.
12. Process according to any of the preceding items, wherein the one or more crystalline filler(s) of step (b) meets/meet the following conditions (i) and (ii):
 - (i) PSD (particle size distribution) characterized by a d(90) of at most 100 μ m, or at most 500 μ m, a d(50) of at most 400 μ m, or at most 300 μ m, and a d(10) of at most 100 μ m or at most 80 μ m; and preferably wherein the particle size distribution of said crystalline filler(s) is unimodal;
 - (ii) bulk density in a range of about between 0.30 g/ml and 0.80 g/ml.
13. Process according to any of the preceding items, wherein the one or more filler(s) of step (b) is/are selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol,

sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch;

preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;

more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

14. Process according to any of the preceding items, wherein the one or more filler(s) is selected from the group consisting of monohydrate lactose and microcrystalline cellulose.

15. Process according to any of the preceding items, wherein in step (b) a single filler is combined with the solution of step (a).

16. Process according to item 15, wherein the filler that is combined with the solution of step (a) is monohydrate lactose or microcrystalline cellulose.

17. Process according to any of the preceding items, wherein the step of combining the solution of step (a) with a filler is carried out by adding the filler to the solution of step (a).

18. Process according to any of the preceding items, wherein the co-spray-drying of step (c) is carried out by choosing the inlet temperature (T (inlet)) such that it is about 10°C or more above the boiling point of the solvent (or mixture of solvents) used.

19. Process according to any of the preceding items, wherein the co spray-drying of step (c) is carried out by applying the following co spray-drying parameters:

- | | | |
|-------|--|--|
| (i) | spraying rate (pump) [%] | 10-50, preferably 20-40, more preferable 25-35 |
| (ii) | N ₂ -Flow (pressure) [mmHg] | 10-100, preferably 20-80, more preferably 25-50 |
| (iii) | T (inlet) [$^{\circ}\text{C}$] | 40-200; preferably 50-150; more preferably 60-90 |

20. The process according to any of the preceding items, wherein at least 90% w/w of the elagolix or its pharmaceutically acceptable salt are characterized by a particle size distribution (PSD) as follows:

$d(0.1)$ is at most $15\mu\text{m}$, such as at most $10\mu\text{m}$, or at most $8\mu\text{m}$;

$d(0.5)$ is at most $30\mu\text{m}$, such as at most $25\mu\text{m}$, or at most $20\mu\text{m}$;

d(0.9) is at most 70µm, such as at most 60µm, or at most 55µm.

21. Process according to any of the preceding claims, wherein the powder density, preferably bulk density, of the co-spray dried mixture is improved (that is, higher), compared to the powder density, preferably bulk density, of a physically mixed powder or pharmaceutical composition.

The powder density can be determined by measuring the bulk density of the respective powder or pharmaceutical composition.

22. Process according to any of the preceding items, further comprising a step of dry granulating, preferably slugging of the powder of step (d).

23. Process for the preparation of a pharmaceutical composition comprising elagolix or a pharmaceutically acceptable salt thereof, the process comprising carrying out a process according to any one of items 1 to 22, and a further step of formulating the powder into a pharmaceutical composition.

24. Process according to item 23, wherein the pharmaceutical composition is a dosage form, preferably the dosage form is a solid oral dosage form, more preferably a capsule or a tablet, and even more preferably the solid oral dosage form is a tablet.

25. Process according to item 23 or 24, wherein the step of formulating the powder into a pharmaceutical composition comprises the addition of one or more further excipient(s), preferably selected from the group consisting of diluents, binders, fillers, disintegrants, lubricants, sweeteners, glidants, flavourings and colouring agents.

26. Process according to item 25, wherein the fillers are selected from the group consisting of different grades of starches, such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch; cellulose, such as microcrystalline cellulose or silicified microcrystalline cellulose; mannitol, erythritol; lactose, such as lactose monohydrate, lactose anhydrous, spray dried lactose or milled lactose; calcium salts, such as calcium hydrogenphosphate; sorbitol, and xylitol; particularly preferably the fillers are selected from the group consisting of pregelatinized starch, microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, spray dried lactose, and milled lactose;

the disintegrants are selected from the group consisting of agar, alginic acid, bentonite, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, carboxymethylcellulose, cellulose, a cation exchange resin, gums, colloidal silicon dioxide, corn starch, croscarmellose sodium, crospovidone, guar gum, hydrous aluminum silicate, an ion exchange resin such as polacrillin potassium, magnesium aluminum silicate, microcrystalline cellulose, modified cellulose gum, modified corn starch, montmorillonite clay, natural sponge, polacrillin potassium, potato starch, powdered cellulose, povidone, pregelatinized starch, sodium alginate, sodium bicarbonate, optionally in admixture with one or more acidulants, sodium starch glycolate, starch, silicates;

the lubricants are selected from the group consisting calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycerol behenate, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate;

the binders are selected from the group consisting of polyvinyl pyrrolidone (Povidone), copolymers of vinylpyrrolidone with other vinyl derivatives (Copovidone), hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, powdered acacia, gelatin, guar gum, carbomer such as carbopol, polymethacrylates and pregelatinized starch;

the diluents are selected from the group consisting of calcium carbonate, dicalcium phosphate, dry starch, calcium sulfate, cellulose, compressible sugars, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, glyceryl palmitostearate, hydrogenated vegetable oil, inositol, kaolin, lactose, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, powdered sugar, pregelatinized starch, sodium chloride, sorbitol, starch, sugar spheres, talc, tribasic calcium phosphate;

the glidants are selected from the group consisting of colloidal silica, hydrophobic colloidal silica and magnesium trisilicate, such as talc, starch, starch derivatives; particularly preferably the glidants are selected from the group consisting of colloidal silica and hydrophobic colloidal silica;

and/or

the sweeteners are selected from the group consisting of aspartame, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, and the like; preferably the excipients are microcrystalline cellulose, silicified microcrystalline cellulose, milled lactose, spray dried lactose, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropylcellulose, crospovidone, magnesium stearate, and sodium stearyl fumarate.

27. Process for the preparation of a pharmaceutical composition according to item 25 or 26, wherein the step of formulating the powder into a pharmaceutical composition comprises,

preferably consists of, a direct compression step, wherein this direct compression step preferably comprises a step of mixing the powder with a filler.

28. Process according to any one of items 22 to 27, further comprising a step of coating the pharmaceutical composition.

29. The process according to item 28, wherein the coating is a gastroresistant coat or a non-gastroresistant coat.

30. Powder obtained by or obtainable by the process defined in any of items 1 to 22.

31. Powder obtained by or obtainable by the process defined in any of items 1 to 22, wherein the powder is characterized in that it exhibits the following characteristics:

- (i) bulk density of at least 0.42 g/ml, preferably of at least 0.43 g/ml; and/or
- (ii) tapped density of at least 0.63 g/ml, preferably of at least 0.64 g/ml.

32. Powder according to the preceding item, wherein, if the filler is lactose monohydrate and preferably the API is elagolix sodium, the powder is characterized by the following characteristics:

- (i) bulk density of at least 0.50 g/ml, preferably of at least 0.53 or 0.54 g/ml; and/or
- (ii) tapped density of at least 0.75 g/ml, preferably of at least 0.80 g/ml.

33. Powder according to the preceding item, wherein, if the filler is microcrystalline cellulose and preferably the API is elagolix sodium, the powder is characterized by the following characteristics:

- (i) bulk density of at least 0.42 g/ml, preferably of at least 0.43 g/ml; and/or
- (ii) tapped density of at least 0.63 g/ml, preferably of at least 0.64 g/ml.

34. Powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein at least 80%, or at least 90%, or at least 95%, or even all, of the one or more filler(s) is/are present in its crystalline form (that means, is crystalline), and the elagolix or a pharmaceutically acceptable salt is present in amorphous form.

In other words, in one embodiment, a part of the one or more filler(s) that is/are present in the powder is/are amorphous. Hence, a part of the one or more filler(s) in the powder is amorphous, and a part of the one or more filler(s) is/are crystalline.

It is also possible that all of the one or more filler(s) that is/are present in the powder is/are crystalline.

35. Powder according to item 34, wherein the powder essentially consists of the elagolix or its pharmaceutically acceptable salt and the one or more filler(s). In one embodiment, "essentially" means that the powder consists of at least 90% or 95% by weight of elagolix or its pharmaceutically acceptable salt and the one or more filler(s). In another embodiment, the powder consists of at least 90% or 95% by weight of elagolix or its pharmaceutically acceptable salt and the one or more filler(s).

36. Powder according to any of the preceding two items, wherein at most 25% of the elagolix or its pharmaceutically acceptable salt are adhered to the one or more filler(s), preferably at most 20%, more preferably at most 15%, and most preferred at most 10% or 5%.

37. Powder according to any one of items 30 to 36, wherein the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol, sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch;
preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;
more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

38. Powder according to any preceding item, wherein the one or more filler(s) is selected from the group consisting of monohydrate lactose and microcrystalline cellulose.

39. Powder according to any of items 30 to 38, wherein the filler is monohydrate lactose or microcrystalline cellulose.

40. Pharmaceutical composition comprising the powder as defined in any one of items 30 to 39.

41. Dosage form comprising the powder as defined in any one of items 30 to 39.
42. Dosage form according to item 41, being an oral dosage form, preferably a solid oral dosage form, more preferably being a tablet.
43. Compressed tablet core comprising or consisting of the powder according to any of items 30 to 39 and 5-15 wt% of one or more disintegrants(s) and optionally 0.1-5 wt% of glidant(s) and/or other excipients.
44. Powder as defined in any one of items 30 to 39, pharmaceutical composition as defined in item 40, dosage form as defined in item 41 or 42, or compressed tablet core as defined in item 43, for use in the treatment of GnRH-dependent diseases, such as endometriosis and uterine fibroids.
45. Powder comprising elagolix or a pharmaceutically acceptable salt thereof, wherein the bulk density of said powder is at least 0.38 g/ml, preferably at least 0.39, at least 0.40, at least 0.41 or at least 0.42 g/ml; and/or the tapped density of said powder is at least 0.63 g/ml.
- The bulk density and the tapped density can be determined by applying suitable methods that are known to a person skilled in the art. In a preferred embodiment, the bulk density and the tapped density are determined as described in the methods part by using the Tapped Density Tester SVM 121 from ERWEKA, equipped with a 10 mL glass cylinder.
46. Powder according to item 45, additionally comprising one or more filler(s) as defined in any one of items 37 to 39.
47. Powder according to item 46, wherein the one or more filler(s) is/are at least partially crystalline, and the elagolix or a pharmaceutically acceptable salt is present in amorphous form.
48. Use of the powder as defined in any one of items 30 to 39, or as defined in items 45 - 47, for the preparation of a pharmaceutical composition, preferably a tablet.
49. Use according to item 48, wherein the pharmaceutical composition is as defined in item 24.

50. Use according to item 48 or 49, wherein the pharmaceutical composition comprises one or more further excipient(s) preferably selected from the group consisting of diluents, binders, fillers, disintegrants, lubricants, sweeteners, glidants, flavourings and colouring agents, more preferably the one or more further excipient(s) is (are) as defined in item 26.

51. Process for the preparation of a pharmaceutical dosage form, preferably a tablet, comprising elagolix or a pharmaceutically acceptable salt thereof, wherein the process comprises a step of providing a powder as defined in any of items 45 - 47, and a further step of formulating the powder into a pharmaceutical dosage form.

52. Process according to item 51, wherein the pharmaceutical dosage form is as defined in item 42.

53. Process for the preparation of a pharmaceutical dosage form, preferably a tablet, comprising elagolix or a pharmaceutically acceptable salt thereof, wherein the process comprises a step of formulating a powder as defined in any of items 45 - 47 into a pharmaceutical dosage form.

54. Pharmaceutical composition comprising the powder as defined in any one of items 44 - 47.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the description and the following specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the description and the other parts of the present disclosure.

Definitions

In the context of the present invention the following abbreviations have the indicated meaning, unless explicitly stated otherwise:

The term "crystalline" refers to materials which have crystal lattice structure and show peaks in an X-ray powder diffraction measurement (e.g., when using a copper anode). For example, it is possible that a crystalline filler shows peaks when being subjected to X-ray powder diffraction (XRD) using a PANalytical X'Pert PRO diffractometer equipped with a theta/theta

coupled goniometer in transmission geometry, Cu-K α 1,2 radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. The patterns can for instance be recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a 2-theta step size of 0.013° with 40 s per step (255 channels) in the 2-theta angular range of 2° to 40° at ambient conditions.

Within the meaning of the present invention, the term "elagolix" refers to the active pharmaceutical ingredient (API) (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid (also referred to as "elagolix") and having the structure depicted in Formula I, or a pharmaceutically acceptable salt thereof. "Pharmaceutically acceptable salts" can be all pharmaceutically acceptable salts that are suitable and known to a person skilled in the art. In a preferred embodiment, the pharmaceutically acceptable salt of elagolix is elagolix sodium.

In general, "spray-drying" is a commonly known method used in pharmaceutical industry for producing a dry powder from a liquid phase. The term "spray drying" in general thus refers to a method of drying liquids, solutions, and liquid suspensions.

In the process of the present invention, a solution containing elagolix or its pharmaceutically acceptable salt is combined with a filler in its crystalline form, thereby resulting in a suspension. This suspension, comprising elagolix or its pharmaceutically acceptable salt, and filler in its crystalline form, is then subjected to a spray-drying process. This spray-drying process, where a suspension is subjected to spray-drying, and not a solution, can be referred to as "co spray-drying". Thus, the term "co spray-drying" as used herein denotes the process of spray drying a suspension, that is, in the present invention, the suspension comprising elagolix and filler in its crystalline form.

The terms "essentially" or "about" used herein means at least 90%, preferably at least 95% and more preferably at least 98% of the indicated reference (in wt.% if a material is referred to) or subject-matter.

In general, the type of coating depends e.g. on the intended release site of the API, such as elagolix or its pharmaceutically acceptable salt.

If it is desired that the API is released in the stomach, then a non-gastroresistant coating can be applied. Such a non-gastroresistant coating allows for the release of the API in the stomach.

If it is desired to release the API after the stomach passage, a gastroresistant coating can be applied. Such a gastroresistant coating prevents the release of the API in the stomach and thus e.g. allows for the release of the API after the stomach passage.

Thus, the term "gastro-resistant coating" as used herein is interchangeable with the term "enteric coating" and it refers to a coating that does not allow acidic gastric juice to penetrate through but it allows the penetration of water to the dosage form, such as the tablet at the essentially neutral pH of the intestines. In particular, a pH- dependent gastro-resistant polymer suitable for purposes of the present invention is a polymer which dissolves, swells or degrades at a pH of 4.5 or higher, preferably pH 5.0 or higher. In a typical embodiment, the polymer dissolves, swells or degrades at a pH in the range of from 4.5 to 7.0, preferably from 5.0 to 6.5. Non-limiting examples of suitable pH-dependent entero-resistant polymers useful as the coating material for purpose of the present invention can include, alone or in combination, cellulose esters such as cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate or cellulose acetate succinate; and/or methacrylic acid copolymers such as those sold as Eudragit(R) L, Eudragit(R) S by Evonik or Acryleze(R) by Colorcon. The polymer can be hydroxypropyl methylcellulose acetate succinate and/or methacrylic acid - ethyl acrylate copolymer. Most preferably, the polymer in the gastro- resistant coating is methacrylic acid - ethyl acrylate copolymer (1:1). Gastro-resistant coating can comprise at least one polymer being insoluble in aqueous solutions having pH value of less than 4.5, such as the polymers mentioned above, and at least one further excipient selected from plasticizers, antitacking agents, pigments, colorants and/or surface active substances. The thickness of the gastro-resistant coating can for instance be in the range of 40 to 250 μm , such as 45 μm to 200 μm or 50 μm to 180 μm .

For the purpose of this invention, particle size distribution (PSD) is determined as the percent volume at each particle size and measured by a laser diffraction method.

The particle size distribution $d(50)$ is the median diameter or the medium value of the particle size distribution. It is an indication that 50% of the particles in a sample are smaller than the given $d(50)$ value.

The particle size distribution $d(10)$ is the particle diameter corresponding to 10% cumulative undersized particle size distribution. It is an indication that 10% of the particles in a sample are smaller than the given $d(10)$ value.

The particle size distribution $d(90)$ is the particle diameter corresponding to 90% cumulative undersized particle size distribution. It is an indication that 90% of the particles in a sample are smaller than the given $d(90)$ value.

The particle size distribution $d(0.1)$, $d(0.5)$ and $d(0.9)$ likewise indicate that 90% of the particles in a sample are smaller than the respectively given $d(0.1)$, $d(0.5)$ and $d(0.9)$ value.

The expression "unimodal particle size distribution" as used herein refers to a particle size distribution with one clear peak. A particle size distribution exhibiting two clear peaks is bimodal.

Whenever within this description a ratio of substances is given in the form of 1:2, etc. this ratio means "weight/weight" unless otherwise specified in the description or unless a weight/weight ratio technically does not make sense.

Brief description of the drawings

Figure 1 A: This figure shows the bulk densities of lactose (filler)-mixtures (ratio API : filler = 1:2)

Spray dried elagolix sodium ("elagolix sodium spray dried"); lactose monohydrate ("lactose"); and co-spray dried elagolix sodium and lactose monohydrate (spray-drying a mixture prepared according to the present invention, that is, spray-drying a suspension comprising lactose (filler), suspended in a solution comprising elagolix sodium; "Co-Spray dried").

Figure 1 B: This figure shows the bulk densities microcrystalline cellulose (MCC) (filler)-mixtures (ratio 1:2):

Spray dried elagolix sodium ("elagolix sodium spray dried"); MCC ("cellulose microcrystalline"); and co-spray dried elagolix sodium and MCC (spray-drying a mixture prepared according to the present invention, that is, spray-drying a suspension comprising MCC (filler), suspended in a solution comprising elagolix sodium; "Co-Spray dried").

Figure 2: This figure shows SEM images of co-spray dried elagolix sodium and the filler lactose monohydrate (Fig. 2 A, C), and elagolix sodium and the filler microcrystalline cellulose (Fig. 2 B, D). Fig. A and B represent a 100-fold magnification, Fig. C represents a 600-fold magnification, and Fig. D represents a 1500-fold magnification of a certain section of Fig. A and B. SEM-images show clearly that most parts of filler and elagolix are separated within the powder and only very few elagolix sodium particles were sticking on the filler.

Figure 3: This figure shows an SEM image (x1500) of spray-dried pure elagolix sodium, wherein the elagolix sodium was dissolved in ethanol.

Figure 4: This figure shows the dissolution profile of elagolix sodium co-spraydried tablets (200 mg) with lactose and cellulose microcrystalline (USP II, HCl, 0.1N, 900mL, 37°C, 75 rpm). The x-axis shows the time in minutes, the y-axis shows the drug release of elagolix in percent (%).

Detailed description of the invention

The invention is described below in further detail by embodiments, without being limited thereto.

The present inventors have surprisingly found that by applying the process of the present invention, certain properties of a powder comprising the API elagolix or a pharmaceutically acceptable salt thereof, can be improved. An example of such a property is an increased bulk density, and/or acceptable flowability and/or reduced electrostatic behavior, which, in turn, results amongst other also in reduced stickiness. The reduced electrostatic behavior, preferably in combination with the at least acceptable flow properties, can additionally lead to a reduced material loss during processing. This is inter alia due to a significant reduction of material sticking for example to walls or equipment used. Additionally, by applying the process of the present invention, the powder density (preferably the bulk density) of the powder is improved compared to a physically mixed powder or pharmaceutical composition, and the number of overall production steps can be reduced.

The process of the present invention is based on a spray-drying technique, wherein a suspension is used for co-spray drying instead of spraying an API solution onto filler particles. Surprisingly, the process of the invention does not provide a coating of API on the filler particles. Rather, the use of a suspension allows maintaining the crystalline structure and particle size of the filler. This leads to reduced electrostatic properties of the API (that is, elagolix or its pharmaceutically acceptable salts) and to improved powder characteristics such as bulk density of the powder.

When analyzed by scanning electron microscopy (SEM), the powder may consist of discrete particles of elagolix or a pharmaceutically acceptable salt thereof and filler particles. Neither the filler nor the API forms a coating on the respective other type of particles. Furthermore, while the different types of particles may adhere to each other (preferably only a minor amount) to a certain degree, they do not form a composite material wherein e.g., one type of particles forms a matrix which incorporates the respective other type of particles. The particles also do not form granules consisting of several or a multitude of single particles. It was found that the co-spray drying process of the invention provides a higher bulk density as compared with elagolix spray-dried in neat form, or elagolix mixed with filler (see Figure 1A and 1B).

The bulk density can be further increased by dry-granulating the co-spray-dried powder.

Therefore, in one aspect, the present invention refers to a process for the preparation of a powder comprising as active pharmaceutical ingredient (API) elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid) or a pharmaceutically acceptable salt thereof, wherein the process comprises the following steps:

- a) providing a solution comprising elagolix or a pharmaceutically acceptable salt thereof, and a suitable solvent or mixture of solvents;
- b) combining the solution of elagolix or a pharmaceutically acceptable salt thereof with one or more filler in its crystalline form, thereby obtaining a suspension;
- c) co spray-drying the suspension of step (b), and
- d) obtaining the powder.

According to the invention, is possible to have more than one type of API or more than one type/form of elagolix. That is, the powder may contain elagolix free acid and one or more pharmaceutically acceptable salts thereof or may contain a mixture of pharmaceutically acceptable salts of elagolix.

The solution of elagolix in step (a) and the suspension in step (b) can be prepared at room temperature, i.e. 20-25°C. Preferably, the temperature of the suspension for the spray-drying process is also between 20 and 25°C.

In one embodiment, the powder obtained in step (d) comprises elagolix in its amorphous form, and most of the one or more filler in its crystalline form (that is, most of the one or more filler is/are crystalline). In this case, a small part of the one or more filler(s) is dissolved in the solvent/mixture of solvents, such as at most 20%, or at most 10%, or at most 5%, in preceding step (b).

In a further embodiment, the powder obtained in step (d) comprises elagolix in its amorphous form (that is, elagolix is amorphous), and the one or more filler in its crystalline form. In this case, the one or more filler(s) is/are not dissolved in the solvent/mixture of solvents in preceding step (b).

The elagolix or its pharmaceutically acceptable salt of step (a) can be amorphous or crystalline when preparing the solution. In a preferred embodiment, the powder of the invention comprises only amorphous elagolix. Therefore, if crystalline elagolix is used for preparing the solution, it should be ensured that elagolix is completely dissolved without leaving seeding crystals.

Whether the salt of elagolix is amorphous or crystalline in step (a) may depend on the respective salt that is used. For instance, sodium salt and hydrochloric acid salt of elagolix in general is amorphous, and the sulfuric acid salt of elagolix is crystalline.

In step (a), the pharmaceutically acceptable salt(s) of elagolix can be selected from the group consisting of sodium elagolix, hydrochloric acid salt of elagolix, and sulfuric acid salt of elagolix; preferably the salt is sodium elagolix.

The solvent or mixture of solvents may be selected to the effect that the following conditions (i) to (iii) are met:

- (i) the elagolix or pharmaceutically acceptable salt used in step (a) is fully dissolved in the solvent or mixture of solvents;
- (ii) the one or more filler(s) used in step (b) is (are) at most only partially dissolved, or not dissolved at all in the solvent or mixture of solvents, thereby forming a suspension; and
- (iii) the solvent or mixture of solvents is suitable for spray drying.

With regard to condition (ii), a solvent or mixture of solvents is suitable for spray drying if safety aspects are fulfilled, such as no explosive gas or mixtures are formed. In order to make this sure, the respective appropriate measures that have to be taken are known to a skilled person; such measures are for instance the flash and ignition point of the respective solvent(s) that have to be checked, as well as the decomposition temperature of the API (elagolix or pharmaceutically acceptable salt thereof) have to be checked.

The solvent or mixture of solvents is preferably a polar solvent or a mixture of polar solvents.

For example, the solvent or mixture of solvents can be selected from the group consisting of

water, alcohols, such as methanol, ethanol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol (n-butanol), 2-butanol, iso-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, cyclohexanol, glycerol, or C1-C6 alcohols and the like;

nitriles, such as acetonitrile or propionitrile;

amides, such as formamide, N,N- dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, or hexamethyl phosphoric triamide and the like;

sulfoxides, such as dimethylsulfoxide and the like;

or any mixtures of two or more solvents thereof;

preferably, alcohols or a mixture thereof are used. Although water can be used as a solvent, it is preferable to avoid water in order to allow for an easier drying process/reduced final water content.

The solvent or mixture of solvents is preferably selected from the group consisting of methanol, ethanol, isopropyl alcohol, and n-butanol; further preferred, the solvent or mixture of solvents comprises ethanol. The solvent can be a single solvent, preferably an alcohol, and most preferred, the solvent is ethanol.

The quantity of solvent used for preparing the solution of step (a) depends on various parameters such as the solvent, the amount of elagolix or pharmaceutically acceptable salt thereof, and the dissolution temperature adopted.

The ratio of the amount of elagolix or its pharmaceutically acceptable salt (or a mixture of different forms of elagolix) to the amount of the one or more filler(s) of step (b) is in a range of from about 1 : 0.5 to about 1 : 3.5; preferably in a range of from about 1 : 1 to about 1 : 3; more preferably in a range of from about 1 : 1 to about 1 : 2.5; and most preferred the ratio of the amount of elagolix or its pharmaceutically acceptable salt to the amount of filler is in a range of about 1 : 2.

The solution of step (a) preferably consists of elagolix or its pharmaceutically acceptable salt, and the solvent or mixture of solvents.

In the suspension of step (b), at least a part of the amount, or the complete amount of the one or more filler(s) in its/their crystalline form is present in suspended form. In other words, according to the invention, not all (i.e. not the complete amount) of the one or more filler(s) is present in the suspension in dissolved form.

This means that it can happen that a part of the one or more filler(s) is/are dissolved in the solvent, e.g. at most 20%, at most 10%, or at most 5%. As a result, the part of the filler(s) that is/are not dissolved will be present in its amorphous form after (co-)spray drying. This can be checked by any suitable means that is known to a person skilled in the art, such as by DSC (differential scanning calorimetry), and/or by quantitative DSC.

Advantageously, the part of the one or more filler(s) that is dissolved can then, being present in the powder in amorphous form, additionally contribute to improving properties of the pharmaceutical dosage form comprising said powder: For instance, the hardness of a tablet comprising this powder can be improved, and therefore, during formulation, lower compaction pressure can be applied.

The part of the one or more filler(s) that is/are dissolved in the solvent can be determined for instance by HPLC (high pressure liquid chromatography), a method that is well-known to a person skilled in the art. Then, the part can be calculated that is not dissolved.

A further possible method for determining the part of filler(s) that is not dissolved would be filtering the solids (that is, the part that is not dissolved in the solvent), followed by drying and weighing.

The part of the one or more filler(s) that is/are dissolved will then be amorphous after the (co-) spray drying process. This can for instance be checked by applying DSC (differential scanning calorimetry) methods.

The one or more crystalline filler(s) of step (b) preferably meets/meet the following conditions (i) and (ii):

- (i) PSD (particle size distribution) characterized by a d(90) of at most 1000µm, a d(50) of at most 400µm, and a d(10) of at most 80µm, and wherein the particle size distribution of said crystalline filler(s) is unimodal;
- (ii) bulk density in a range of about between 0.30 g/ml and 0.80 g/ml.

The PSD can be determined by any suitable mean that is known to a person skilled in the art, such as by laser diffraction, e.g., as described herein.

The one or more filler(s) of step (b) may be selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol, sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch;

preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;

more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

The one or more filler(s) may preferably be selected from the group consisting of monohydrate lactose and microcrystalline cellulose.

In one embodiment, in step (b) a single filler is combined with the solution of step (a). The filler that is combined with the solution of step (a) may be monohydrate lactose or microcrystalline cellulose.

The step of combining the solution of step (a) with a filler may be carried out by adding the filler to the solution of step (a).

Combining the solution of step (a) with a filler can be carried out by any suitable method that is known to a person skilled in the art. For instance, the filler can be added to the solution of step (a): In a first step, the elagolix is dissolved in the solvent or mixture of solvents, until the elagolix or its pharmaceutically active salt is completely dissolved. This procedure can be carried out e.g. by using a stirring speed of about 100 to 200 rpm, and a conventional magnetic stirrer and stirring bar. Then the one or more filler was (were) added, and the resulting solution was stirred for another 10 to 15 minutes with a higher stirring rate (about 500 to 600 rpm).

The spray-drying of step (c) can be carried out by choosing the inlet temperature (T (inlet)) such that it is about 10°C or more above the boiling point of the solvent (or mixture of solvents) used.

For example, the spray-drying of step (c) is carried out by applying the following spray-drying parameters:

- | | | |
|-------|--|--|
| (i) | spraying rate (pump) [%] | 10-50, preferably 20-40, more preferably 25-35 |
| (ii) | N ₂ -Flow (pressure) [mmHg] | 10-100, preferably 20-80, more preferably 25-50 |
| (iii) | T (inlet) [$^{\circ}\text{C}$] | 40-200; preferably 50-150; more preferably 60-90 |

In one embodiment, at least 90% w/w of the elagolix or its pharmaceutically acceptable salt are characterized by a particle size distribution as follows:

- $d(0.1)$ is at most $15\mu\text{m}$, such as at most $10\mu\text{m}$, or at most $8\mu\text{m}$;
- $d(0.5)$ is at most $30\mu\text{m}$, such as at most $25\mu\text{m}$, or at most $20\mu\text{m}$;
- $d(0.9)$ is at most $70\mu\text{m}$, such as at most $60\mu\text{m}$, or at most $55\mu\text{m}$.

It is however possible to tailor the desired particle size distribution (PSD) by accordingly adapting different process parameters within the spray drying parameters.

By applying the process of the present invention, the powder density (preferably, the bulk density), of the co-spray dried mixture is improved (e.g. higher), when compared to a physically

mixed powder or pharmaceutical composition. The powder density can be determined by measuring the bulk density of the respective powder or pharmaceutical composition.

The process may further comprise a step of dry granulating, preferably slugging of the powder of step (d) in order to further increase the bulk density.

The invention also refers to a process for the preparation of a pharmaceutical composition comprising elagolix or a pharmaceutically acceptable salt thereof, the process comprising carrying out a process according to any one of items 1 to 21, and a further step of formulating the powder into a pharmaceutical composition.

The pharmaceutical composition can be a dosage form, preferably the dosage form is a solid oral dosage form, more preferably a capsule or a tablet, and even more preferably the solid oral dosage form is a tablet. In the process for preparing a pharmaceutical composition, the step of formulating the powder into a pharmaceutical composition may comprise the addition of one or more further excipient(s), preferably selected from the group consisting of diluents, binders, fillers, disintegrants, lubricants, sweeteners, glidants, flavourings and colouring agents.

Within the meaning of the present invention, the term "further excipient(s)" denotes the excipient or excipients that is/are present in addition to the one or more filler(s) that is combined in step (b) with the solution of step (a).

The fillers may be selected from the group consisting of different grades of starches, such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch; cellulose, such as microcrystalline cellulose or silicified microcrystalline cellulose; mannitol, erythritol; lactose, such as lactose monohydrate, lactose anhydrous, spray dried lactose or milled lactose; calcium salts, such as calcium hydrogenphosphate; sorbitol, and xylitol; particularly preferably the fillers are selected from the group consisting of pregelatinized starch, microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, spray dried lactose, and milled lactose; the disintegrants are selected from the group consisting of agar, alginic acid, bentonite, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, carboxymethylcellulose, cellulose, a cation exchange resin, gums, colloidal silicon dioxide, corn starch, croscarmellose sodium, crospovidone, guar gum, hydrous aluminum silicate, an ion exchange resin such as polacrilin potassium, magnesium aluminum silicate, microcrystalline cellulose, modified cellulose gum, modified corn starch, montmorillonite clay, natural sponge, polacrilin potassium,

potato starch, powdered cellulose, povidone, pregelatinized starch, sodium alginate, sodium bicarbonate, optionally in admixture with one or more acidulants, sodium starch glycolate, starch, silicates;

the lubricants are selected from the group consisting calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycerol behenate, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate;

the binders are selected from the group consisting of polyvinyl pyrrolidone (Povidone), copolymers of vinylpyrrolidone with other vinyl derivatives (Copovidone), hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, powdered acacia, gelatin, guar gum, carbomer such as carbopol, polymethacrylates and pregelatinized starch;

the diluents are selected from the group consisting of calcium carbonate, dicalcium phosphate, dry starch, calcium sulfate, cellulose, compressible sugars, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, glyceryl palmitostearate, hydrogenated vegetable oil, inositol, kaolin, lactose, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, powdered sugar, pregelatinized starch, sodium chloride, sorbitol, starch, sugar spheres, talc, tribasic calcium phosphate;

the glidants are selected from the group consisting of colloidal silica, hydrophobic colloidal silica and magnesium trisilicate, such as talc, starch, starch derivatives; particularly preferably the glidants are selected from the group consisting of colloidal silica and hydrophobic colloidal silica;

and/or

the sweeteners are selected from the group consisting of aspartame, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, and the like; preferably the excipients are microcrystalline cellulose, silicified microcrystalline cellulose, milled lactose, spray dried lactose, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropylcellulose, crospovidone, magnesium stearate, and sodium stearyl fumarate.

The step of formulating the powder into a pharmaceutical composition comprises, preferably consists of, a direct compression step. In a preferred embodiment, this direct compression is carried out by compressing the powder and a suitable filler into a pharmaceutical composition. The process of direct compression is well-known to a person skilled in the art and can be carried out by applying standard parameters.

The pharmaceutical composition can e.g. be any suitable pharmaceutical formulation that is known to a skilled person, such as a solid oral dosage form, such as a tablet.

The process may further comprise a step of coating the pharmaceutical composition. The coating may be a gastroresistant coat or a non-gastroresistant coat. The coating depends on the desired site of action of the API (that is, elagolix or a pharmaceutically acceptable salt thereof).

The invention also relates to a powder obtained by or obtainable by the process of the invention as described herein. The powder may be characterized in that it exhibits the following characteristics:

- (i) bulk density of at least 0.42 g/ml, preferably of at least 0.43 g/ml; and/or
- (ii) tapped density of at least 0.63 g/ml, preferably of at least 0.64 g/ml.

If the filler is lactose monohydrate and preferably the API is elagolix sodium, the powder is preferably characterized by the following characteristics:

- (i) bulk density of at least 0.50 g/ml, preferably of at least 0.53 or 0.54 g/ml; and/or
- (ii) tapped density of at least 0.75 g/ml, preferably of at least 0.80 g/ml.

If the filler is microcrystalline cellulose and preferably the API is elagolix sodium, the powder is preferably characterized by the following characteristics:

- (i) bulk density of at least 0.42 g/ml, preferably of at least 0.43 g/ml; and/or
- (ii) tapped density of at least 0.63 g/ml, preferably of at least 0.64 g/ml.

In a preferred embodiment, both characteristics, (i) and (ii), are present.

The invention also refers to a powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein at least 80%, or at least 90%, or at least 95%, of the one or more filler(s) is/are crystalline, or all of the one or more filler(s) is/are crystalline; and the elagolix or a pharmaceutically acceptable salt is present in amorphous form.

This means that a part of the one or more filler(s) can be crystalline, and a part of the one or more filler(s) can be amorphous.

The ratio of crystalline and amorphous content can e.g. be determined by quantitative DSC.

Advantageously, the part of the one or more filler(s) that is amorphous additionally contributes to improving properties of the pharmaceutical dosage form comprising said powder: For instance, the hardness of a tablet comprising this powder can be improved, and therefore, during formulation, lower compaction pressure can be applied.

All embodiments and methods described above in the context of the process of the invention can also be used for describing the powder of the invention.

When analyzed by scanning electron microscopy (SEM) as described herein, the powder preferably consists of discrete particles of elagolix or a pharmaceutically acceptable salt thereof and filler particles. Furthermore, while the different types of particles may adhere to each other (preferably only a minor amount) to a certain degree, they do not form a composite material wherein e.g., one type of particles forms a matrix which incorporates the respective other type of particles. The particles also do not form granules consisting of several single particles. In one embodiment, the process of the invention provides small particles of elagolix (or a pharmaceutically acceptable salt thereof) as compared with significantly greater filler, e.g., an SEM picture shows filler particles with their longest diameter being ten times the longest diameter of elagolix or a pharmaceutically acceptable salt thereof particles.

Preferably, the powder essentially consists of the elagolix or its pharmaceutically acceptable salt and the one or more filler(s). In one embodiment, "essentially" means that the powder consists of at least 90% or 95% by weight of elagolix or its pharmaceutically acceptable salt and the one or more filler(s). In another embodiment, the powder consists of at least 90% or 95% by weight of elagolix or its pharmaceutically acceptable salt and the one or more filler(s).

In one embodiment, at most 25% of the elagolix or its pharmaceutically acceptable salt are adhered to the one or more filler(s), preferably at most 20%, more preferably at most 15%, and most preferred at most 10% or 5%. The percentage of elagolix adhered to the one or more filler(s) can be determined by any suitable means that is known to a person skilled in the art, such as by applying imaging techniques like IR (infrared)-imaging or other microscopic techniques.

The one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol, sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch; preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;

more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

Preferably, the one or more filler(s) are selected from the group consisting of monohydrate lactose and microcrystalline cellulose. Further preferred, the filler is monohydrate lactose or microcrystalline cellulose.

The invention also refers to a pharmaceutical composition comprising the powder of the invention.

In addition, the invention relates to a dosage form comprising the powder of the invention. Said dosage form can be an oral dosage form, preferably is a solid oral dosage form, more preferably a tablet.

Furthermore, the invention refers to a powder of the invention, a pharmaceutical composition of the invention, or dosage form of the invention, for use in a method of treating GnRH-dependent diseases, such as endometriosis and uterine fibroids.

The invention also refers to a compressed tablet core consisting of the powder of the invention and 5-15 wt% of one or more disintegrants(s) and optionally 0.1-5 wt% of glidant(s) and/or other excipients.

Methods

1. Determining particle size distribution (PSD)

For the purpose of this invention, particle size distribution (PSD) is determined as the percent volume at each particle size and measured by a laser diffraction method. The particle size distribution (PSD) was measured by laser diffraction using a Malvern Mastersizer 2000 equipped with a Hydro 2000 μ P cell. The measurements were performed in silicon oil AR20 (refractive index = 1.403 (general purpose)). The samples were added as solids under stirring until an obscuration rate of 5-15% was reached. The results were values arising from five measurement cycles with a pre-measurement delay of 5 sec between the cycles. The following parameters were used:

Accessory name: Hydro 2000 μ P

Parameter for analysis

SOP: Elagolix.sop
 Material Name: Fraunhofer
 RI Index: 0
 Dispersant: Silicone oil AR20
 RI Index: 1.403

Result calculation

Model: General purpose – normal sensitivity
 Particle shape: Irregular

Pre-measurement

Stirrer speed: 1500 rpm
 Ultrasonic level: 25% for 240 s
 Pre-measurement delay: 1:30 (mm:ss)

Measurement

Obscuration rate: 10 – 15%
 Time: 12 sec
 Background Measurement: 12 sec
 Measurement Cycles: 5 cycles / sample (delay: 5 sec)

2. Determining bulk and tapped density

The bulk and tapped density was determined using the Tapped Density Tester SVM 121 from ERWEKA, equipped with a 10 mL glass cylinder. Approximately 2 g of the powder was carefully poured into the 10 mL measuring cylinder with a funnel. Bulk density was calculated by dividing the amount of powder (in gram) by the measured volume (mL). The tapped density was then determined as follows:

- Tapp 10 x → Read volume (= V_{10})
- Tapp 500 x (10 + 490) → Read volume (= V_{500})
- Tapp 1250 x (500 + 750) → Read volume (= V_{1250})

(If difference between V_{500} and V_{1250} is bigger than 2 mL, tapp another 1250 x and repeat until difference is below 2 mL). Tapped density = weight/ volume after tapping. As a measure of flowability, the Hausner factor and Carr Index are calculated from bulk and tapped densities as described below.

Calculation:

Bulk density = $m \text{ (mg)} / V \text{ (mL)}$

Tapped density = $m \text{ (mg)} / V_{1250} \text{ (mL)}$

Hausner-Factor = Tapped density / Bulk density

Carr-Index = $[(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] * 100\%$

Hausner Factor	Compressibility (Carr-Index)	Flowability
1.00 – 1.11	< 10	Excellent
1.12 – 1.18	11 – 15	Good
1.19 – 1.25	16 – 20	Fair
1.26 – 1.34	21 – 25	Passable
1.35 – 1.45	26 – 31	Bad/cohesive
1.46 – 1.59	32 – 37	Very bad/ very cohesive
>1.60	> 38	Not flowable at all

3. Dry granulation (slugging)

Dry granulation can be performed on a single punch tablet press Flexitab S (Röltgen Marking System) using a flat round punch (20 mm diameter) and compaction pressures of 150 to 250 bar. To prevent sticking to the die, the punch can be brushed with a little magnesium stearate. The obtained pellets were carefully break up and sieved through an 800 µm or 1000 µm mashed sieve.

Calculation of compaction forces for this punch (20 mm diameter):

Punch	Area [mm ²]	Compaction pressure [bar]	Compaction force [kN]
D20 mm, round	314	150	4.71
D20 mm, round	314	200	6.28
D20 mm, round	314	250	7.85

4. SEM (Scanning Electron Microscope)

The SEM images were recorded with a TM3030Plus from Hitachi. 100-fold, 600-fold, 1200-fold or 1500-fold magnifications were chosen, respectively.

5. Spray drying process

The spray drying process is a process that is well known to a person skilled in the art; selecting the respective parameters lies within the common general knowledge of a skilled person in this field without undue burden. For instance, it is generally known to a skilled person that the critical parameter is the inlet temperature, which should be chosen such that it is about 10°C or more above the boiling point of the solvent (or mixture of solvents) used. The outlet temperature is dependent on the respectively chosen inlet temperature. Determining the respective temperature can be carried out by any suitable means that is known to a person skilled in the art.

As to the spraying rate and the feed rate, it is also known to a person skilled in the art that these parameters are dependent on the power of the pump and the thickness of the suspension, as well as of the diameter of the tubing and valves, and further factors, that are well known to a skilled person. The aspirator and the N₂-pressures are also known to be dependent on the instrument used, in particular on the size of the spray tower.

In the present invention, the spray drying process is preferably carried out with a spray drying nozzle or a rotary atomizer, more preferably with a spray drying nozzle.

With regard to the temperature of the spray (inlet temperature), there is no specific restriction provided that the components of the mixture (that is, the elagolix or its pharmaceutically acceptable salt, the solvent(s) used, and the filler(s) used) can withstand the temperature of the process. This is generally the case when choosing an inlet temperature being about 10 °C or more above the boiling point of the solvent (or mixture of solvent(s)) used. Preferably, the spray is carried out at an inlet temperature in the range of from about 40 °C to about 200 °C, more preferably in the range of from about 50 °C to about 150 °C, more preferably in the range of from about 60 °C to about 90 °C.

Preferably, the spray is carried out at a pressure (N₂-Flow pressure in [mmHg]) in the range of from about 10 to about 100, more preferably in the range of from about 20 to about 80, more preferably in the range from about 25 to about 50. The pressure and the nozzle used are interrelated parameters. It is within the knowledge of the skilled person to adjust accordingly these parameters.

It is further known to a skilled person that 1 mmHg corresponds to 0.0013 bar(abs).

In an example, when using a Büchi Mini Spray Dryer B290, the following parameters are chosen:

Parameter:	Set point:
(i) spraying rate (pump) [%]	25-35, preferably 30
(ii) N ₂ -Flow (pressure) [mmHg]	30-45, preferably 38
(v) T (inlet) [°C]	80-90, preferably 85
(iii) Aspirator [%]	70-80, preferably 75
(iv) T (cooling) [°C]	-1 – 1, preferably 0
(vi) T (outlet) [°C]	55-65; preferably around 57-60
(v) Nozzle cleaner	0
(vi) Feed rate [g/min]	12.5-14.5, preferably 13.6 or 12.8

Examples

Example 1: Co spray-drying elagolix sodium with the filler lactose monohydrate

Sample preparation:

5 g elagolix sodium was dissolved in 30 g ethanol (absolute, >99.9%) and 10 g lactose monohydrate (filler) was added leading to a suspension.

Spray drying parameter:

This mixture was spray dried using a Büchi Mini Spray Dryer B290 and following parameters:

Parameter	Set-point
Spraying rate (pump) [%]	30
N2-Flow (pressure) [mmHg]	38
Aspirator [%]	75
T (Cooling) [°C]	0
T (Inlet) [°C]	85
T (Outlet) [°C]	60
Nozzle Cleaner	0
Feed rate [g/min]	13.6

7.5 g of a white not electrostatic powder was obtained. Bulk and tapped densities were determined and the Hausner ratio and Carr-Index were calculated.

Figure 2 A is an SEM image of the co spray-dried elagolix sodium with the filler lactose monohydrate. Fig. 2 C is a 600-fold magnification.

Example 2: Co spray-drying elagolix sodium with the filler microcrystalline cellulose (MCC)

Sample preparation:

5 g elagolix sodium was dissolved in 30 g ethanol (absolute, >99.9%) and 10 g microcrystalline cellulose (filler) was added leading to a suspension.

Spray drying parameter:

This mixture was spray dried using a Büchi Mini Spray Dryer B290 and following parameters:

Parameter	Set-point
Spraying rate (pump) [%]	30
N2-Flow (pressure) [mmHg]	38
Aspirator [%]	75
T (Cooling) [°C]	0
T (Inlet) [°C]	85
T (Outlet) [°C]	57-59
Nozzle Cleaner	0
Feed rate [g/min]	12.8

7.7 g of a white not electrostatic powder was obtained. Bulk and tapped densities were determined and the Hausner ratio and Carr-Index were calculated.

Figure 2 B is an SEM image of the co spray-dried elagolix sodium with the filler microcrystalline cellulose. Fig. 2 D is a 1500-fold magnification.

Analytics of Example 1, 2, and Example 2 of WO 2017/007895:

Bulk and tapped densities of Example 1 and 2 were determined and the Hausner ratio and Carr-Index were calculated and compared. For comparison reasons, the bulk density of the elagolix drug substance depicted in Table 2 (Example 2) of WO 2017/007895 is also shown in the following table. This elagolix drug substance was prepared as indicated in Example 2 of WO 2017/007895 by applying an acoustic mixing technique, wherein the mixing time was between 0 and 60 minutes. The bulk density indicated in the below table corresponds to the highest bulk density. This bulk density was obtained after a mixing time of the elagolix drug substance for 30 minutes.

Mix/Compound	Bulk density [g/mL]	Tapped density [g/mL]	Hausner Factor	Carr-Index
elagolix sodium spray dried	0.16	0.24	1.5	33
lactose monohydrate	0.62	0.72	1.2	14
Example 1 elagolix sodium + lactose monohydrate Co-Spray dried	0.54	0.80	1.5	33
<u>Table 2 (Example 2) of</u> <u>WO 2017/007895</u>	0.367	-	-	-
elagolix sodium spray dried	0.16	0.24	1.5	33
cellulose microcrystalline (MCC)	0.36	0.48	1.35	26
Example 2 elagolix sodium + MCC Co-Spray dried	0.43	0.64	1.47	32

As can be seen, the bulk densities of Examples 1 and 2 were improved to 0.54 g/mL and 0.43 g/mL for lactose and MCC, respectively. Additionally, the bulk densities of Examples 1 and 2 were also improved compared to the bulk density of elagolix drug substance, which was prepared as indicated in Example 2 of WO 2017/007895 by applying an acoustic mixing technique.

The Hausner factor, which is an indicator for flowability, remains the same as for the API (elagolix sodium) alone. Nevertheless, the electrostatic character could be reduced tremendously, compared to the ethanol-spray dried pure elagolix.

Example 3: Co-spray dried tablet with dissolution testing

1. Tableting

The co-spraydried mixtures were pressed into tablets (200 mg) according to below listed formula. All components of the tablet mixture were first sieved through an 800 µm meshed sieve and then thoroughly mixed together using a TURBULA® T2F three dimensional shaker-mixer (WAB) for 5 min (level 34). Tablets were then pressed on a single punch tablet press Flexitab S (Röntgen Marking System) with a 9 x 19 mm die (lower punch height: 9 mm) using 100 bar compaction pressure (hold time: 0 sec; return time: 3 sec).

	[g]	[%]
Co-spraydried mixture	0.600	60

Cellulose microcrystalline (MCC)	0.340	34
Croscarmellose sodium	0.050	5
Aerosil (silicium dioxide)	0.005	0.5
Magnesium stearate	0.005	0.5
SUM [g]:	1.000	

2. Dissolution analysis

Dissolution was performed on a paddle apparatus (Agilent) according to USP II. Following conditions were used: HCl 0.1N, 900 mL, 37°C, 75 rpm, detection at 246nm wavelength.

Figure 4 depicts the dissolution profile of the elagolix sodium co-spray dried tablets with lactose and cellulose microcrystalline. The x-axis shows the time in minutes. The y-axis shows the drug release of elagolix sodium in percent (%).

Claims

1. Process for the preparation of a powder comprising as active pharmaceutical ingredient (API) elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid) or a pharmaceutically acceptable salt thereof, wherein the process comprises the following steps:

- a) providing a solution comprising elagolix or a pharmaceutically acceptable salt thereof, and a suitable solvent or mixture of solvents;
- b) combining the solution of elagolix or a pharmaceutically acceptable salt thereof with one or more filler in its crystalline form, thereby obtaining a suspension;
- c) co spray-drying the suspension of step (b), and
- d) obtaining the powder.

2. Process according to claim 1, wherein in step (a) the pharmaceutically acceptable salt of elagolix is selected from the group consisting of sodium elagolix, hydrochloric acid salt of elagolix, and sulfuric acid salt of elagolix; preferably the salt is sodium elagolix.

3. Process according to claim 1 or 2, wherein the solvent or mixture of solvents is selected to the effect that the following conditions (i) to (iii) are met:

- (i) the elagolix or pharmaceutically acceptable salt used in step (a) is fully dissolved in the solvent or mixture of solvents;
- (ii) the one or more filler(s) used in step (b) is (are) at most only partially dissolved, or not dissolved at all in the solvent or mixture of solvents, thereby forming a suspension; and
- (iii) the solvent or mixture of solvents is suitable for spray drying.

4. Process according to any of claims 1 to 3, wherein the solvent or mixture of solvents is selected from the group consisting of

water, alcohols, such as methanol, ethanol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol (n-butanol), 2-butanol, iso-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, cyclohexanol, glycerol, or C1-C6 alcohols and the like;

nitriles, such as acetonitrile or propionitrile;

amides, such as formamide, N,N- dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, or hexamethyl phosphoric triamide and the like;

sulfoxides, such as dimethylsulfoxide and the like;

or any mixtures of two or more solvents thereof;
preferably, alcohols or a mixture thereof are used.

5. Process according to claim 4, wherein the solvent or mixture of solvents is a polar solvent or a polar mixture of solvents,
preferably the solvent or mixture of solvents is selected from the group consisting of methanol, ethanol, isopropyl alcohol, and n-butanol; more preferably the solvent or mixture of solvents comprises ethanol,
even more preferably the solvent is a single solvent, preferably an alcohol, and most preferred, the solvent is ethanol.

6. Process according to any of claims 1 to 5, wherein the ratio of the amount of elagolix or its pharmaceutically acceptable salt (or a mixture of different forms of elagolix) to the amount of the one or more filler(s) of step (b) is in a range of from about 1 : 0.5 to about 1 : 3.5; preferably in a range of from about 1 : 1 to about 1 : 3; more preferably in a range of from about 1 : 1 to about 1 : 2.5; and most preferred the ratio is about 1 : 2.

7. Process according to any of claims 1 to 6, wherein the solution of step (a) consists of elagolix or its pharmaceutically acceptable salt, and the solvent or mixture of solvents.

8. Process according to any of claims 1 to 7, wherein the one or more filler(s) of step (b) is/are selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol, sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch;
preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;
more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

9. Powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein the bulk density of said powder is at least 0.38 g/ml, and/or the tapped density of said powder is at least 0.63 g/ml.

10. Powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein the one or more filler(s) is/are at least partially crystalline, and the elagolix or a pharmaceutically acceptable salt is present in amorphous form.
11. Powder according to claim 10, wherein the powder essentially consists of the elagolix or its pharmaceutically acceptable salt and the one or more filler(s).
12. Pharmaceutical composition or dosage form comprising the powder as defined in any one of claims 9 to 11.
13. Compressed tablet core consisting of the powder according to any of claims 9 to 11 and 5-15 wt% of one or more disintegrants(s) and optionally 0.1-5 wt% of glidant(s) and/or other excipients.
14. Powder as defined in any one of claims 9 to 11, pharmaceutical composition or dosage form as defined in claim 12, or compressed tablet core as defined in claim 13, for use in the treatment of GnRH-dependent diseases, such as endometriosis and uterine fibroids.
15. Process for the preparation of a pharmaceutical dosage form, preferably a tablet, comprising elagolix or a pharmaceutically acceptable salt thereof, wherein the process comprises a step of formulating a powder as defined in any of claims 9-11 into a pharmaceutical dosage form, wherein the process preferably comprises carrying out a process according to any one of claims 1 to 8 for preparing said powder.

AMENDED CLAIMS

received by the International Bureau on 17 January 2020 (17.01.2020)

1. Process for the preparation of a powder comprising as active pharmaceutical ingredient (API) elagolix (also known under the IUPAC name (R)-4-((2-(5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-(trifluoromethyl)benzyl)-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-1-phenylethyl)amino)butanoic acid) or a pharmaceutically acceptable salt thereof, wherein the process comprises the following steps:

- a) providing a solution comprising elagolix or a pharmaceutically acceptable salt thereof, and a suitable solvent or mixture of solvents;
- b) combining the solution of elagolix or a pharmaceutically acceptable salt thereof with one or more filler in its crystalline form, thereby obtaining a suspension;
- c) co spray-drying the suspension of step (b), and
- d) obtaining the powder.

2. Process according to claim 1, wherein in step (a) the pharmaceutically acceptable salt of elagolix is selected from the group consisting of sodium elagolix, hydrochloric acid salt of elagolix, and sulfuric acid salt of elagolix; preferably the salt is sodium elagolix.

3. Process according to claim 1 or 2, wherein the solvent or mixture of solvents is selected to the effect that the following conditions (i) to (iii) are met:

- (i) the elagolix or pharmaceutically acceptable salt used in step (a) is fully dissolved in the solvent or mixture of solvents;
- (ii) the one or more filler(s) used in step (b) is (are) at most only partially dissolved, or not dissolved at all in the solvent or mixture of solvents, thereby forming a suspension; and
- (iii) the solvent or mixture of solvents is suitable for spray drying.

4. Process according to any of claims 1 to 3, wherein the solvent or mixture of solvents is selected from the group consisting of

water, alcohols, such as methanol, ethanol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol (n-butanol), 2-butanol, iso-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, cyclohexanol, glycerol, or C1-C6 alcohols and the like;
nitriles, such as acetonitrile or propionitrile;

amides, such as formamide, N,N- dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, or hexamethyl phosphoric triamide and the like;

sulfoxides, such as dimethylsulfoxide and the like;

or any mixtures of two or more solvents thereof;

preferably, alcohols or a mixture thereof are used.

5. Process according to claim 4, wherein the solvent or mixture of solvents is a polar solvent or a polar mixture of solvents,

preferably the solvent or mixture of solvents is selected from the group consisting of methanol, ethanol, isopropyl alcohol, and n-butanol; more preferably the solvent or mixture of solvents comprises ethanol,

even more preferably the solvent is a single solvent, preferably an alcohol, and most preferred, the solvent is ethanol.

6. Process according to any of claims 1 to 5, wherein the ratio of the amount of elagolix or its pharmaceutically acceptable salt (or a mixture of different forms of elagolix) to the amount of the one or more filler(s) of step (b) is in a range of from about 1 : 0.5 to about 1 : 3.5; preferably in a range of from about 1 : 1 to about 1 : 3; more preferably in a range of from about 1 : 1 to about 1 : 2.5; and most preferred the ratio is about 1 : 2.

7. Process according to any of claims 1 to 6, wherein the solution of step (a) consists of elagolix or its pharmaceutically acceptable salt, and the solvent or mixture of solvents.

8. Process according to any of claims 1 to 7, wherein the one or more filler(s) of step (b) is/are selected from the group consisting of microcrystalline cellulose or silicified microcrystalline cellulose; lactose such as lactose monohydrate and agglomerated lactose such as Tablettose 70 or Tablettose 80; sugar alcohols and preferably mannitol, erythritol, sorbitol and xylitol; inorganic fillers such as anhydrous calcium salt such as calcium hydrogenphosphate, and starches such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch;

preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose, silicified microcrystalline cellulose, lactose monohydrate, lactose, and pregelatinized starch;

more preferably the one or more filler(s) is/are selected from the group consisting of microcrystalline cellulose and lactose monohydrate (such as lactose monohydrate known under the trade name "CapsuLac®60").

9. Powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein the bulk density of said powder is at least 0.38 g/ml, and/or the tapped density of said powder is at least 0.63 g/ml.
10. Powder comprising elagolix or a pharmaceutically acceptable salt thereof and one or more filler(s), wherein the one or more filler(s) is/are at least partially crystalline, and the elagolix or a pharmaceutically acceptable salt is present in amorphous form.
11. Powder according to claim 10, wherein the powder essentially consists of the elagolix or its pharmaceutically acceptable salt and the one or more filler(s), preferably wherein the filler is lactose monohydrate or microcrystalline cellulose.
12. Pharmaceutical composition or dosage form comprising the powder as defined in any one of claims 9 to 11.
13. Compressed tablet core consisting of the powder according to any of claims 9 to 11 and 5-15 wt% of one or more disintegrants(s) and optionally 0.1-5 wt% of glidant(s) and/or other excipients.
14. Powder as defined in any one of claims 9 to 11, pharmaceutical composition or dosage form as defined in claim 12, or compressed tablet core as defined in claim 13, for use in the treatment of GnRH-dependent diseases, such as endometriosis and uterine fibroids.
15. Process for the preparation of a pharmaceutical dosage form, preferably a tablet, comprising elagolix or a pharmaceutically acceptable salt thereof, wherein the process comprises a step of formulating a powder as defined in any of claims 9-11 into a pharmaceutical dosage form, wherein the process preferably comprises carrying out a process according to any one of claims 1 to 8 for preparing said powder.
16. Powder obtained by or obtainable by the process as defined in any of claims 1 to 8.

Statement under Art. 19 (1) PCT

Amended claim 11 now additionally defines the preferred embodiment that the filler is lactose monohydrate or microcrystalline cellulose. Amended claim 11 thereby now reflects the results depicted in the table on page 31 of the application as filed, wherein it is shown that the bulk density of elagolix sodium combined with lactose monohydrate (example 1) and the bulk density of elagolix sodium combined with microcrystalline cellulose (example 2) is improved when compared to the bulk density depicted in table 2 (example 2) of prior art as reflected by WO 2017/007895 (referred to as D1 in the International Search Report).

Amended claim 11, via back-reference to claim 10, requires that the one or more filler(s) is/are at least partially crystalline.

New claim 16 refers to a powder obtained by or obtainable by the process as defined in any of claims 1 to 8. The powder referred to in claim 16 is a powder comprising elagolix or a pharmaceutically acceptable salt thereof, exhibiting a bulk density being at least 0.38 g/ml, and/or a tapped density being at least 0.63 g/ml.

The at least partial crystallinity of the filler(s), in combination with the solution of elagolix and thereby arriving at a suspension, applied in a co-spray-drying process; substantially contributes to arriving at the advantages of the present invention.

The specifically tested fillers microcrystalline cellulose and lactose monohydrate represent an example of fillers that are at least partially crystalline: An effect has been shown for elagolix sodium being combined with the filler lactose monohydrate and for elagolix sodium being combined with the filler microcrystalline cellulose. As the technical effect demonstrated can be extrapolated to any filler(s) that is/are at least partially crystalline, the claims are supported over the whole claimed scope.

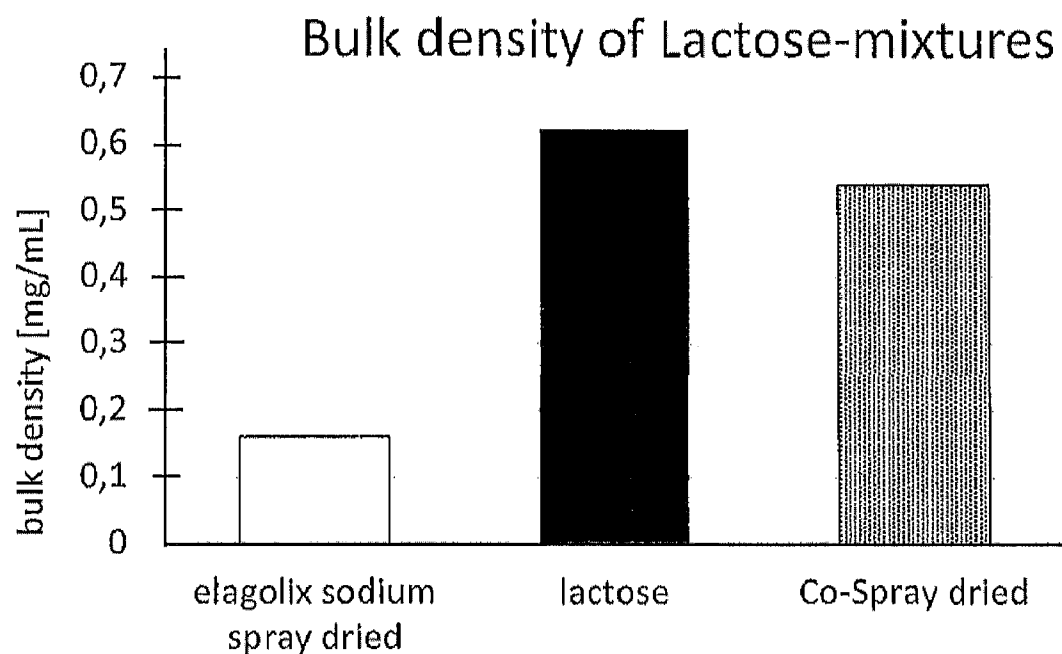
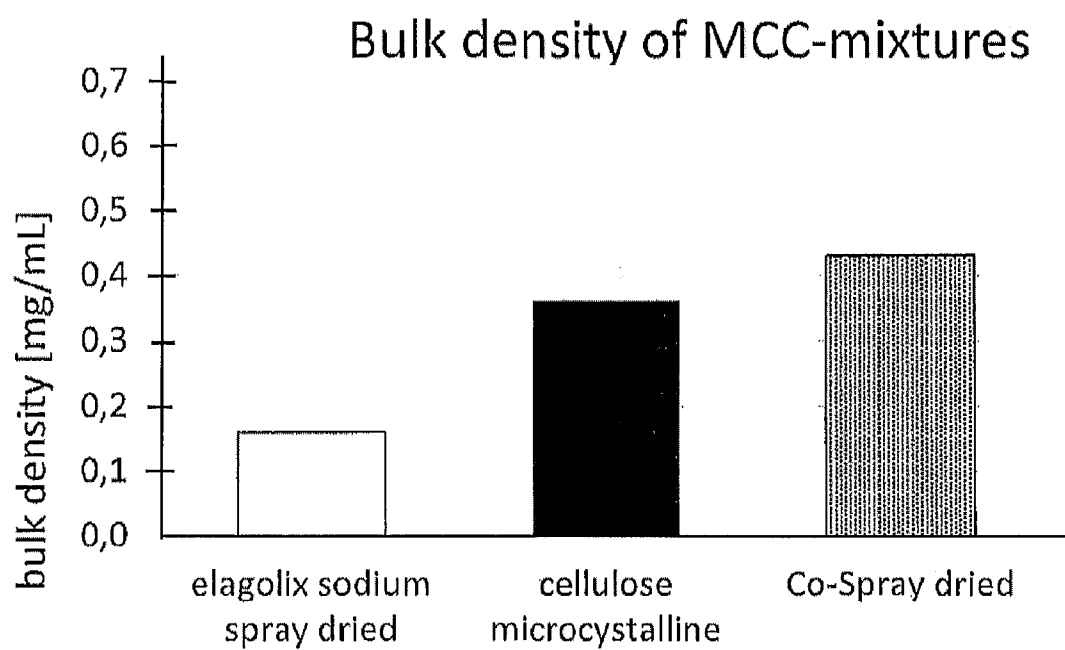
Figure 1A**Figure 1B**

Figure 2

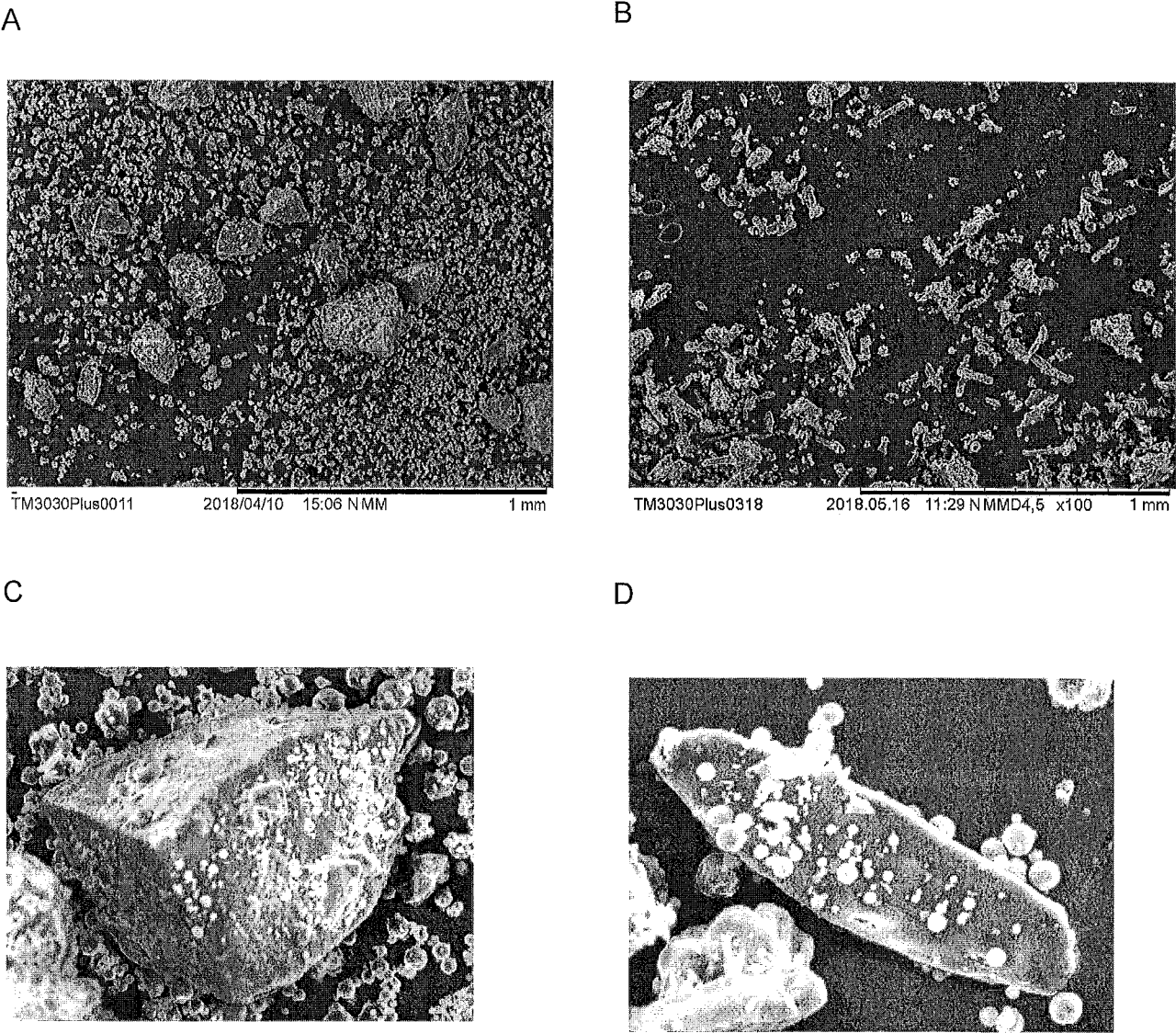


Figure 3

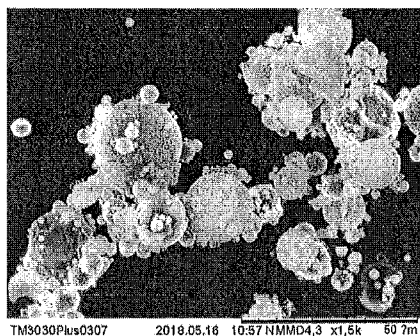
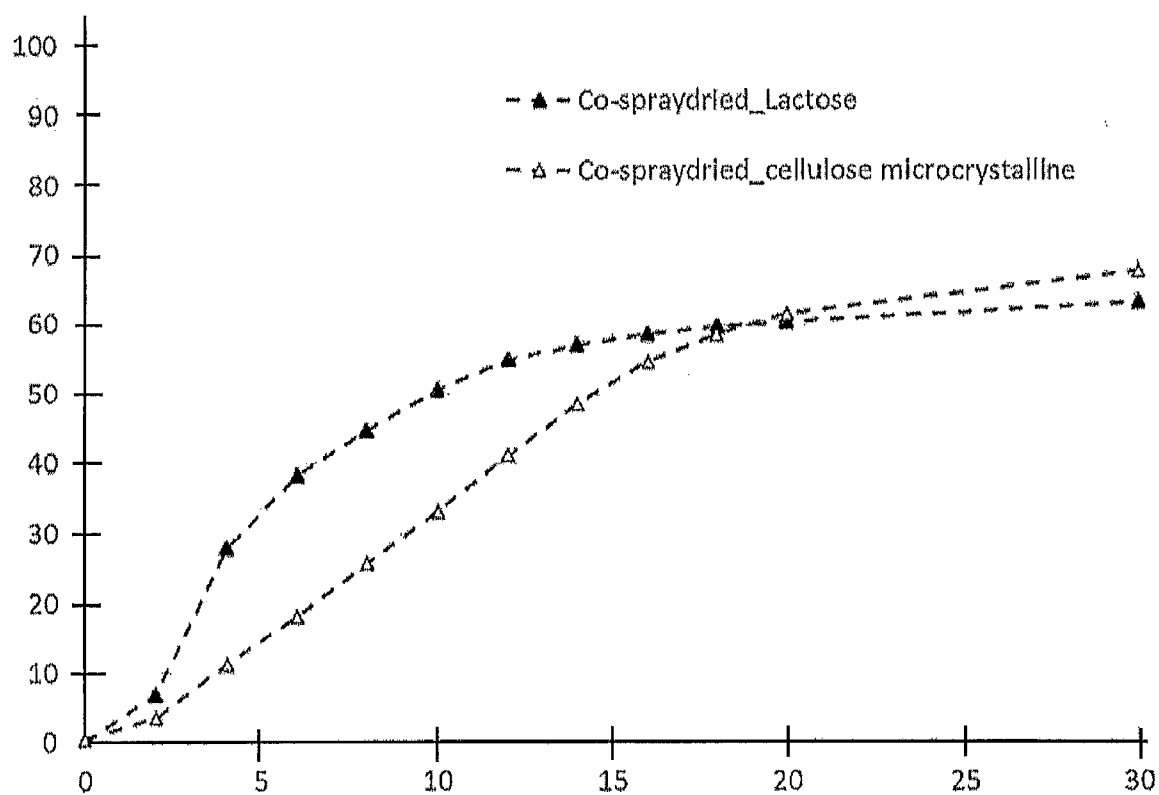


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/072927

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K31/513
ADD.

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 data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, COMPENDEX, FSTA, INSPEC, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/007895 A1 (ABBVIE INC [US]) 12 January 2017 (2017-01-12) cited in the application examples	9-15
A	----- WO 2009/062087 A1 (NEUROCRINE BIOSCIENCES INC [US]; GALLAGHER DONALD [US]; TREIBER LASZLO) 14 May 2009 (2009-05-14) cited in the application page 6, line 13 - page 7, line 8 examples 8,9 -----	1-15



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

"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

11 November 2019

Date of mailing of the international search report

18/11/2019

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/072927

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