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(54) Title: ENZALUTAMIDE NANOCRYSTALS, METHODS AND COMPOSITIONS

(57) Abstract: Described herein are processes for preparing enzalutamide nanocrystals, compositions and pharmaceutical compositions comprising them, and therapeutic methods using them.

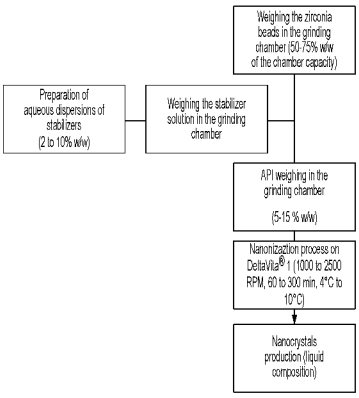

FIG. 1

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ENZALUTAMIDE NANOCRYSTALS, METHODS AND COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application 63/433,168, filed December 16, 2022, the entire contents of which are incorporated herein by reference.

FIELD

[0002] Described herein are processes for preparing nanocrystals of enzalutamide, compositions comprising them, including oral pharmaceutical compositions, and therapeutic methods using them.

BACKGROUND

[0003] Enzalutamide is a small molecule androgen receptor antagonist which has been shown to competitively inhibit androgen binding to androgen receptors, and consequently, inhibits nuclear translocation of androgen receptors and their interaction with DNA. Enzalutamide has been indicated for use in the treatment of patients with castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer. Enzalutamide is poorly water-soluble at physiological pH, which may impact its bioavailability and/or *in vivo* performance.

[0004] Oral solid compositions of enzalutamide have been approved for use. XTANDI® is available in film-coated tablet and liquid-filled soft gelatin capsule dosage forms. The tablets are available in 40 mg and 80 mg doses. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides, with, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, polyvinyl acetate and black iron oxide as the inactive ingredients. The recommend dose of XTANDI® is 160 mg once daily. Thus, patients must take four 40 mg capsules, four 40 mg tablets, or two 80 mg tablets daily, as a single event/time dose. Further, XTANDI® includes certain inactive ingredients (e.g., caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, or butylated hydroxytoluene) that

may affect the health (e.g., gastrointestinal health) of patients particularly, with the consideration that about 75% of the prostate cancer cases in the world occur after 65 years old.

[0005] Thus, as explained above and in more details below, there remains a need for enzalutamide pharmaceutical compositions (e.g., oral enzalutamide pharmaceutical compositions), as well as processes for preparing them

SUMMARY

[0006] Described herein are compositions comprising nanocrystals of enzalutamide, wherein the enzalutamide nanocrystals have an average particle size diameter of $\leq$ 250 nm. The enzalutamide nanocrystals may have an average particle size diameter of 180 nm to 220 nm. The enzalutamide nanocrystals may have a polydispersity index of from 0.05 to 0.30, as measured by dynamic light scattering. The enzalutamide nanocrystals may have a polydispersity index of $\leq$ 0.20, as measured by dynamic light scattering. The enzalutamide nanocrystals may have a saturation solubility in water at 37 ° that is about 20-fold that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 4 hours after being dissolved in water. The enzalutamide nanocrystals may have a saturation solubility in water at 37 ° that is about twice that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 8 hours after being dissolved in water.

[0007] The compositions may further comprise a stabilizer. The stabilizer may comprise one or more selected from (i) low viscosity water-soluble polymeric stabilizers and (ii) non-ionic stabilizers. For example, the compositions may comprise from about 1% to about 10% w/w of the low viscosity water-soluble polymeric stabilizer(s) and from about 0% w/w to about 2% w/w of the non-ionic stabilizer(s). The compositions may comprise one or more low viscosity water-soluble polymeric stabilizers and one or more non-ionic stabilizers. The one or more low viscosity water-soluble polymeric stabilizers may comprise one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000

Daltons. The one or more low viscosity water-soluble polymeric stabilizers may comprise one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000 Daltons. The one or more non-ionic stabilizers may comprise one or more selected from polyethylene glycol sorbitan monooleate, block copolymers of polyethylene oxide and polypropylene oxide, α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate. In specific embodiments, the stabilizer comprises polyvinyl alcohol and polyethylene glycol sorbitan monooleate.

[0008] In accordance with any embodiments, the enzalutamide, low viscosity water-soluble polymeric stabilizer(s) and non-ionic stabilizer(s) may be present in wt/wt a ratio of 10:1-10:0-2, such as a ratio of 10:2-3:1.

[0009] In accordance with any embodiments, the composition may comprise about 10% w/w enzalutamide. In accordance with any embodiments, the composition may comprise about 10% w/w enzalutamide, from about 1% w/w to about 10% w/w low viscosity water-soluble polymeric stabilizer(s), and from 0% to about 2 % w/w non-ionic stabilizer(s). In accordance with any embodiments, the composition may comprise about 10% w/w enzalutamide, about 2% w/w polyvinyl alcohol, and about 1 % w/w polyethylene glycol sorbitan monooleate.

[0010] In accordance with any embodiments, the average particle size of the nanocrystals in the composition may not vary by more than ± 10% after storage at room temperature for 40 days. In accordance with any embodiments, the composition is stable against sedimentation of enzalutamide after storage at room temperature for 3 months.

[0011] In accordance with some embodiments, the composition further comprises water. The composition may be in the form of an aqueous suspension comprising the enzalutamide nanoparticles suspended in an aqueous carrier.

[0012] Also provided are lyophilized compositions prepared from a composition in accordance with any of the foregoing embodiments, optionally further comprising a lyophilization stabilizer.

[0013] Also provided are dry compositions prepared from a composition in accordance with any of the foregoing embodiments, optionally further comprising a granulation excipient.

[0014] In accordance with some embodiments, any composition as described herein does not include hydroxypropyl methyl cellulose (HPMC).

[0015] Also provided are processes for preparing nanocrystals of enzalutamide, comprising wet-milling enzalutamide with an aqueous dispersion comprising one or more low viscosity water-soluble polymeric stabilizers to obtain nanocrystals of enzalutamide having an average particle size diameter of $\leq$ 250 nm. The one or more low viscosity water-soluble polymeric stabilizers comprises one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000 Daltons. The one or more low viscosity water-soluble polymeric stabilizers comprises polyvinyl alcohol. The aqueous dispersion may further comprise one or more non-ionic stabilizers. The one or more non-ionic stabilizers may comprise one or more selected from polyethylene glycol sorbitan monooleate, block copolymers of polyethylene oxide and polypropylene oxide, α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate. In specific embodiments, the non-ionic stabilizer comprises polyvinyl alcohol and polyethylene glycol sorbitan monooleate.

[0016] In accordance with any embodiments, the wet-milling may be conducted in a grinding chamber containing grinding beads in an amount of 50% w/w to 75% w/w, based on the capacity of the grinding chamber. The wet-milling may be conducted with grinding beads having a diameter of from about 0.1 mm to about 0.4 mm. The wet-milling may be conducted with grinding beads having a diameter of from about 0.1 mm to about 0.2 mm. In accordance with any embodiments, the wet-milling may be conducted at temperature from about 4°C to 15 °C. The wet-milling may

be conducted at temperature from about 5°C to 10 °C. In accordance with any embodiments, the wet-milling may be conducted at a speed of from about 1000 rpm to about 2500 rpm.

[0017] In accordance with any embodiments, the enzalutamide may have an average particle size diameter of > 100000 nm prior to the wet-milling. The enzalutamide may have an average particle size diameter on the order of 10000 nm prior to the wet-milling.

[0018] In accordance with any embodiments, the enzalutamide nanocrystals may have an average particle size diameter of from 180 nm to 220 nm.

[0019] Also provided are enzalutamide nanocrystals prepared by a process according to any embodiments disclosed herein, wherein the enzalutamide nanocrystals have an average particle size diameter of ≤ 250 nm. The nanocrystals may have an average particle size diameter of 180 nm to 220 nm. The enzalutamide nanocrystals may have a polydispersity index of from 0.05 to 0.30, as measured by dynamic light scattering. The enzalutamide nanocrystals may have a polydispersity index of ≤ 0.20, as measured by dynamic light scattering. The enzalutamide nanocrystals may have a saturation solubility in water at 37 ° that is about 20-fold that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 4 hours after being dissolved in water. The enzalutamide nanocrystals may have a saturation solubility in water at 37 ° that is about twice that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 8 hours after being dissolved in water.

[0020] Also provided are processes for preparing an oral pharmaceutical composition according to any embodiments disclosed herein, comprising preparing an aqueous composition comprising (i) nanocrystals of enzalutamide, wherein the enzalutamide nanocrystals have an average particle size diameter of ≤ 250 nm; and (ii) a stabilizer, wherein the stabilizer comprises one or more selected from (i) low viscosity water-soluble polymeric stabilizers and (ii) non-ionic stabilizers. The process may further comprise preparing the enzalutamide nanocrystals by wet-milling enzalutamide with an aqueous dispersion comprising a low viscosity water-soluble polymeric stabilizer (e.g., in accordance with any embodiments disclosed herein). The process may further comprise formulating the aqueous composition as an oral liquid pharmaceutical composition. The

process may further comprise drying the aqueous composition to obtain a dried composition. Drying the composition may comprise lyophilizing the composition, granulating the composition, or spray-drying the composition. The process may further comprise formulating the dried composition as a dry oral pharmaceutical composition.

[0021] Also provided are oral pharmaceutical compositions prepared by a process according to any embodiments disclosed herein, and oral pharmaceutical compositions comprising a composition according to any embodiments disclosed herein. An oral pharmaceutical composition may further comprise a penetration enhancer. In some embodiments, the oral pharmaceutical composition does not include hydroxypropyl methyl cellulose (HPMC). The oral pharmaceutical composition may be packaged to provide a daily dose of 50 mg to 160 mg enzalutamide, optionally to provide a daily dose of 50 mg to less than 160 mg enzalutamide.

[0022] In some embodiments, provided are oral liquid pharmaceutical compositions formulated as a bulk product or filled into a capsule. In some embodiments, provided are dry oral pharmaceutical compositions, optionally in a form selected from a powder and granules, optionally filled into a sachet or capsule.

[0023] Also provided are methods of administering enzalutamide, comprising orally administering a composition according to any embodiments described herein, or an oral pharmaceutical composition according to any embodiments described herein, to a subject in need thereof, optionally wherein the composition is administered at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the composition is administered at a daily dose of 50 mg to less than 160 mg enzalutamide. Also provided are methods of treating cancer, comprising orally administering a composition according to any embodiments described herein, or an oral pharmaceutical composition according to any embodiments described herein, to a subject in need thereof, optionally wherein the composition is administered at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the composition is administered at a daily dose of 50 mg to less than 160 mg enzalutamide. Also provided are compositions and oral pharmaceutical compositions according to any embodiments described herein, for use in treating prostate cancer,

optionally wherein the use comprises administering the composition at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the use comprises administering the composition at a daily dose of 50 mg to less than 160 mg enzalutamide. Also provided are uses of compositions and oral pharmaceutical compositions according to any embodiments described herein, in the manufacture of a medicament for treating prostate cancer, optionally wherein the medicament comprises a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the medicament comprises a daily dose of 50 mg to less than 160 mg enzalutamide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. 1 illustrates a process for preparing enzalutamide nanocrystals as described herein, according to a specific implementation.

[0025] FIG. 2 illustrates a size distribution profile for enzalutamide nanocrystals prepared as described herein from different wet-milling formulations.

[0026] FIG. 3 presents physical stability data of enzalutamide compositions described herein.

[0027] FIG. 4 is a comparative profile of enzalutamide saturation solubility (water, 37 °C) before and after nanonization as described herein.

[0028] FIG. 5A-5C illustrate results of a cytotoxicity assay of non-nanosized enzalutamide, XTANDI®, and enzalutamide nanocrystals as described herein (ENC-004).

DETAILED DESCRIPTION

[0029] The present disclosure provides processes for preparing nanocrystals of enzalutamide, compositions comprising them, including oral pharmaceutical compositions, and therapeutic methods using them. The enzalutamide nanocrystals and compositions described herein offer advantages including improved intrinsic drug solubility and dissolution rate (believed to be associated with improved bioavailability) and good physical stability. The enzalutamide compositions described herein may contain the same amount of enzalutamide in a smaller volume

than enzalutamide compositions prepared with non-nanosized enzalutamide or solubilized enzalutamide (e.g., enzalutamide solubilized in caprylocaproyl polyoxylglycerides vehicle), and therefore provide the same dose in a smaller volume. The enzalutamide nanocrystals described herein have an average particle size diameter of ≤ 250 nm, including about 200 nm (e.g., from 180 nm to 220 nm) and are prepared by wet-milling with a stabilizer as described herein. The pharmaceutical compositions described herein may be prepared as liquid or dry pharmaceutical compositions, e.g., as liquid or dry (solid) dosage forms. Exemplary processes, components of intermediate and pharmaceutical compositions, as well as specific illustrative embodiments, are discussed in more detail below.

Definitions

[0030] Technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art to which the present invention pertains, unless otherwise defined. Any suitable materials and/or methods known to those of ordinary skill in the art can be utilized in carrying out the present invention in view of the guidance provided herein; however, specific materials and methods are described for illustrative purposes. Materials, reagents and the like to which reference is made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

[0031] As used herein, the singular forms "a," "an," and "the" designate both the singular and the plural, unless expressly stated to designate the singular only.

[0032] As used herein, "about" when used with a numerical value means the numerical value stated as well as plus or minus 10% of the numerical value. For example, "about 10" should be understood as both "10" and "9-11".

[0033] As used herein, a phrase in the form "A/B" or in the form "A and/or B" means (A), (B), or (A and B); a phrase in the form "at least one of A, B, and C" means (A), (B), (C), (A and B), (A and C), (B and C), or (A, B, and C).

[0034] As used herein, the terms "comprising," "including," and "containing" are used expansively to mean that the described compositions, methods, or kits include at least the stated elements, and may include other elements that are not specified. The phrase "consisting essentially of" is used to include those elements specifically recited and additional elements that do not materially affect the basic and novel characteristics of the claimed invention, such as ingredients that do not materially undermine the solubility of the enzalutamide.

[0035] As used herein, "subject" denotes any mammal, including humans. For example, a subject may be suffering from or at risk of developing a condition that can be treated or prevented with an androgen receptor antagonist, such as enzalutamide, or may be taking androgen receptor antagonist for other purposes.

[0036] The terms "administer," "administration," and "administering" as used herein refer to providing, giving, dosing and/or prescribing, such as by a health professional or his or her authorized agent or under his or her direction, and putting into, taking, or consuming, such as by a health professional or the subject.

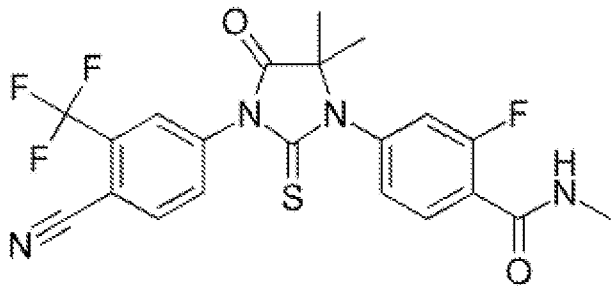
[0037] The terms "treat," "treating," and "treatment" as used herein include alleviating, abating or ameliorating a disease or condition or one or more symptoms thereof, whether or not the disease or condition is considered to be "cured" or "healed," and whether or not all symptoms are resolved.

[0038] As used herein, the phrases "therapeutically effective amount" and "therapeutically effective dose" refer to an amount or dose that provides the specific pharmacological effect for which the drug is administered in a subject in need of such treatment. It is emphasized that a therapeutically effective amount will not always be effective in treating the targeted condition, even though such amount or dose is deemed to be a therapeutically effective amount or dose by those of skill in the art. For convenience only, exemplary doses and therapeutically effective amounts are provided below with reference to adult human subjects. Those skilled in the art can adjust such amounts in accordance with standard practices as needed to treat a specific subject and/or condition/disease.

Enzalutamide

[0039] The compositions described herein comprise enzalutamide. In accordance with the present disclosure, the enzalutamide is formulated in nanocrystal form, as discussed in more detail below. While not wanting to be bound by theory, it is believed that formulating the enzalutamide in nanocrystal form may improve solubility, stability, and bioavailability. For example, the nanoscale size may enhance the dissolution rate and increase the saturation solubility (e.g., achieve *in vivo* saturation without precipitation). Thus, the nanocrystal form may improve bioavailability and/or *in vivo* performance of a composition as described herein. Additionally or alternatively, the enzalutamide compositions described herein may contain the same amount of enzalutamide in a smaller volume than enzalutamide compositions prepared with non-nanosized or solubilized enzalutamide, and therefore provide the same dose in a smaller volume.

[0040] Enzalutamide has the chemical name 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide, the molecular formula $C_{21}H_{16}F_4N_4O_2S$, and a molecular weight of 464.44. It is registered under CAS Registry Number 915087-33-1. The structural formula of enzalutamide is set forth below:



[0041] Enzalutamide compositions have been described in previous patents and patent applications, for example, in WO 2015/118015, US 2020/0397756, and CN108815129. However, as explained herein, there remains a need for enzalutamide pharmaceutical compositions (e.g., oral enzalutamide pharmaceutical compositions) with desirable properties, as well as processes for preparing them.

[0042] As noted above, the enzalutamide nanocrystals described herein have an average particle size ≤ 250 nm, including an average particle size of about 200 nm, or less, such as an average particle size of from 180 nm to 220 nm. Thus, the nanocrystals may have an average particle size of about 200 nm, about 195 nm, about 180 nm, or less. Average particle size can be measured by processes known in the art, such as by dynamic light scattering (DLS).

[0043] In some embodiments, the nanocrystals have a low polydispersity index, indicative of a uniform particle size distribution. In some embodiments, the nanocrystals have a polydispersity index of from about 0.05 to about 0.30 (e.g., from about 5% to about 30%), including from about 0.1 to 0.3 (e.g., 10% to 30%). Polydispersity can be measured by processes known in the art, such as by dynamic light scattering (DLS).

[0044] Thus, in some embodiments, enzalutamide nanocrystals are prepared and/or used that have an average particle size of ≤ 250 nm, including about 200 nm or less, such as from 180 nm to 200 nm. Additionally or alternatively, the enzalutamide nanocrystals have a low polydispersity index, such as a polydispersity index of from about 0.1 to 0.3.

[0045] The compositions described herein may comprise enzalutamide nanocrystals in any suitable amount. For example, the compositions described herein may comprise enzalutamide nanocrystals in any amount suitable for providing a therapeutically effective dose in a suitable amount of pharmaceutical composition for oral administration. A pharmaceutical composition as described herein includes oral liquid pharmaceutical compositions (e.g., in bulk form, in stick packs, or filled into capsules, such as a soft or hard gelatin capsule) and oral dry pharmaceutical compositions (e.g., in powder, granule or tablet form, optionally provided in a stick pack, sachet or capsule, such as a hard gelatin capsule).

[0046] As noted above, currently enzalutamide typically is prescribed at a dose of about 160 mg/day. Thus, pharmaceutical compositions comprising enzalutamide nanocrystals as described herein may include a therapeutically effective amount (e.g., about 160 mg) of enzalutamide in a suitable amount of pharmaceutical composition for oral administration. As noted above, an enzalutamide compositions as described herein may contain the same amount of enzalutamide in

a smaller volume than enzalutamide compositions prepared with non-nanosized enzalutamide, and therefore provide the same dose in a smaller volume. Alternatively, the increased solubility and, potentially, increased bioavailability, of enzalutamide nanocrystals as described herein may support the use of a lower dose as a therapeutically effective amount. Thus, in some embodiments, compositions comprising enzalutamide nanocrystals as described herein may comprise a therapeutically effective amount that is less than 160 mg enzalutamide (such as from 50 mg to less than 160 mg, including about 100 mg enzalutamide) in a suitable amount of composition for oral administration.

[0047] A liquid composition or oral liquid pharmaceutical compositions of enzalutamide nanocrystals as described herein may comprise from about 2.5 mg to about 150 mg of enzalutamide per 1 mL of the composition, including from about 2.5 mg to about 100 mg of enzalutamide per 1 mL of the composition, from about 2.5 mg to about 75 mg of enzalutamide per 1 mL of the composition, from about 2.5 mg to about 50 mg of enzalutamide per 1 mL of the composition, from about 2.5 mg to about 25 mg of enzalutamide per 1 mL of the composition, or from about 2.5 mg to about 7.5 mg of enzalutamide per 1 mL of the composition, such as from 2.5 mg to 150 mg of enzalutamide per 1 mL of the composition, from 2.5 mg to 100 mg of enzalutamide per 1 mL of the composition, from 2.5 mg to 75 mg of enzalutamide per 1 mL of the composition, from 2.5 mg to 50 mg of enzalutamide per 1 mL of the composition, from 2.5 mg to 25 mg of enzalutamide per 1 mL of the composition, or from 2.5 mg to 7.5 mg of enzalutamide per 1 mL of the composition. In alternative embodiments, a dry composition or oral dry pharmaceutical compositions of enzalutamide nanocrystals as described herein may comprise from about 32 mg to about 320 mg of enzalutamide per g of the composition, from about 32 mg to about 50 mg of enzalutamide per g of the composition, from about 32 mg to about 75 mg of enzalutamide per g of the composition, from about 32 to about 100 mg of enzalutamide per g of the composition, from about 32 to about 160 mg of enzalutamide per g of the composition, from about 32 to about 180 mg of enzalutamide per g of the composition, from about 32 to about 225 mg of enzalutamide per g of the composition, or from about 32 to about 280 mg of enzalutamide per g of the composition, such as from 32 mg to 320 mg of enzalutamide per g of the composition, from 32 mg to 50 mg of

enzalutamide per g of the composition, from 32 mg to 75 mg of enzalutamide per g of the composition, from 32 to 100 mg of enzalutamide per g of the composition, from 32 to 160 mg of enzalutamide per g of the composition, from 32 to 180 mg of enzalutamide per g of the composition, from 32 to 225 mg of enzalutamide per g of the composition, or from 32 to 280 mg of enzalutamide per g of the composition.

[0048] In accordance with the present disclosure, an oral pharmaceutical composition of enzalutamide nanocrystals may be prepared by first preparing an aqueous composition comprising (i) enzalutamide nanocrystals; and (ii) a stabilizer; and (iii) optionally, one or more additional pharmaceutically acceptable ingredients, including, optionally, a permeation enhancer. Such a composition may be prepared using pre-formed enzalutamide nanocrystals or may result from a process of preparing enzalutamide nanocrystals as described herein. For convenience, the aqueous composition comprising (i) enzalutamide nanocrystals and (ii) a stabilizer as described herein is referred to herein below from time to time as an "intermediate" composition, although it may be suitable for administration as an oral liquid pharmaceutical composition, as also discussed in more detail below. An oral liquid pharmaceutical composition may be prepared by formulating the aqueous composition (e.g. the "intermediate" composition) as an oral liquid pharmaceutical composition, including optionally adding one or more pharmaceutically acceptable components, such as one or more selected from preservatives, antioxidants, stabilizers, thickeners, etc. Alternatively, a dry oral pharmaceutical composition may be prepared by a process comprising drying the aqueous composition (e.g. the "intermediate" composition) to obtain a dried composition and formulating the dried composition as a dry (e.g., solid) oral pharmaceutical dosage form. In accordance with such embodiments, the amount of enzalutamide in the aqueous composition (e.g., the "intermediate" composition) is not particularly limited, because the aqueous composition can be diluted or concentrated (or dried) to obtain a pharmaceutical composition that comprises a therapeutically effective dose in a suitable amount for oral administration. Exemplary amounts are provided in the discussion that follows for illustration purposes.

Enzalutamide Nanocrystals

[0049] Provided herein are processes for preparing enzalutamide nanocrystals by wet-milling enzalutamide to obtain nanocrystals. In particular, the processes described herein comprise wet-milling enzalutamide with an aqueous dispersion comprising a stabilizer (e.g. one or more low viscosity water-soluble polymeric stabilizers) to obtain nanocrystals of enzalutamide. The processes described herein can be used to obtain enzalutamide nanocrystals having an average particle size diameter of ≤ 250 nm.

[0050] In the context of "low viscosity water-soluble polymeric stabilizers", "low viscosity" refers to a viscosity in the range of 2.0 to 6.0 mPa.s-1 when prepared at a concentration of 40g/L. The one or more low viscosity water-soluble polymeric stabilizers may comprise one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10,000 to 60,000 Daltons. However, in some embodiments, a composition as described herein (e.g., a milling composition, an intermediate composition, a pharmaceutical composition) does not include hydroxypropyl methyl cellulose (HPMC). Examples of suitable polyvinyl alcohol (PVA) stabilizers include PVA 4-88, PVA 4-99, PVA 5-88 and PVA 5-99, where the first number indicates viscosity (e.g., of 4-6 mPa.s-1) and the second number indicates degree of alcoholysis (e.g., 86-90 %). Examples of suitable polyvinylpyrrolidone (PVP) stabilizers include PVP having an average molecular weight in a range from 8,000 to 60,000 Daltons, including PVP K-12, PVP K-15, and PVP K-30. In some embodiments, a suitable PVP stabilizer has an average molecular weight of 60,000 Daltons or greater, such as PVP K-30. For embodiments using HPMC, examples of suitable hydroxypropyl methylcellulose stabilizers include hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10,000 to 60,000 Daltons. In some embodiments, the low viscosity water-soluble polymeric stabilizer comprises polyvinyl alcohol, such as PVA 4-88. The low viscosity water-soluble polymeric stabilizer(s) may be used in any suitable amount, such as from 1% w/w to 10% w/w of an aqueous milling composition that also

comprises the enzalutamide (and optionally, one or more non-ionic stabilizers), as discussed in more detail below.

[0051] In some embodiments, the aqueous dispersion further comprises one or more non-ionic stabilizers. The one or more non-ionic stabilizers may comprise one or more selected from polyethylene glycol sorbitan monooleate (polysorbate 80), block copolymers of polyethylene oxide and polypropylene oxide (e.g., Poloxamer 124, Poloxamer 188, Poloxamer 407), α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate. In some embodiments, the non-ionic stabilizer comprises polyethylene glycol sorbitan monooleate (polysorbate 80). The non-ionic stabilizer(s) may be used in any suitable amount, such as from 0% w/w to 2% w/w of an aqueous milling composition that also comprises the enzalutamide and low viscosity water-soluble polymeric stabilizer(s), as discussed in more detail below.

[0052] The wet-milling may be conducted under any suitable conditions for obtaining enzalutamide nanocrystals having an average particle size diameter of $\leq$ 250 nm. It was determined that the enzalutamide concentration and stabilizer present in the wet-milling composition, milling time and milling speed impact the average particle size diameter of the obtained nanocrystals. For example, the higher the concentration of enzalutamide, the shorter the milling time required to obtain nanocrystals with an average particle size diameter of less than 250 nm. Also, higher milling speed was associated with smaller particle size. It also was found that enzalutamide concentration, milling time, and milling speed impact the polydispersity index (PDI) of the obtained nanocrystals. For example, higher concentrations of enzalutamide were associated with lower PDI values.

[0053] In some embodiments, the wet-milling is conducted using a dual centrifuge device, such as the DeltaVita® 1 manufactured by Netzsch, or a similar device with larger capacity. In some embodiments, the wet-milling is conducted in a grinding chamber containing grinding beads in an amount of 50% w/w to 75% w/w, based on the capacity of the grinding chamber. In some embodiments, the wet-milling is conducted with grinding beads having a diameter of from about 0.1 mm to about 0.4 mm, including from 0.1 mm to 0.4 mm, such as from about 0.1 mm to about

0.2 mm, including from 0.1 mm to 0.2 mm. In some embodiments, the wet-milling is conducted at a speed of from about 1000 rpm to about 2500 rpm, including a speed from 1000 rpm to 2500 rpm, or any value therebetween.

[0054] The wet-milling may be conducted for a time effective for obtaining enzalutamide nanocrystals having an average particle size diameter of $\leq$ 250 nm. In some embodiments, the grinding time of the wet-milling process is from about 60 minutes to about 300 minutes, including 60 minutes, 90 minutes, 120 minutes, 150 minutes, 180 minutes, 210 minutes, 240 minutes, 270 minutes, 300 minutes, or any value therebetween.

[0055] The wet-milling may be conducted at a temperature selected to preserve or promote stability of the enzalutamide. In some embodiments, the wet-milling is conducted at a temperature from about 4°C to about 15 °C, such as a temperature from 4°C to 15 °C, including a temperature from about 5°C to about 10 °C, such as a temperature from 5°C to 10 °C.

[0056] The particle size of enzalutamide starting material is not particularly limited. In some embodiments, the enzalutamide has an average particle size diameter of > 100000 nm prior to the wet-milling. In some embodiments, the enzalutamide has an average particle size diameter on the order to 10000 nm prior to the wet-milling.

[0057] As noted above, processes as described herein can be used to obtain enzalutamide nanocrystals having an average particle size diameter of $\leq$ 250 nm, including from about 180 nm to about 220 nm, or smaller, such as about 200 nm, about 195 nm, about 190 nm, about 185 nm, about 180 nm, or smaller. As noted above, average particle size diameter of the nanocrystals may be determined by dynamic light scattering (DLS).

[0058] As noted above, nanocrystals prepared by a process as described herein may have a low polydispersity index, indicative of a uniform particle size distribution. In some embodiments, the nanocrystals have a polydispersity index of from about 0.05 to about 0.30, including from about 0.1 to 0.3. As noted above, the polydispersity index of the nanocrystals may be determined by dynamic light scattering (DLS).

[0059] FIG. 1 illustrates a process of preparing enzalutamide nanocrystals as described herein. As illustrated in the figure, grinding beads (e.g., zirconium beads) are added to a grinding chamber of a wet-milling apparatus (e.g., the DeltaVita® 1 manufactured by Netzsch, or similar device with larger capacity) in an amount of about 50% w/w to about 75% w/w of the capacity of the grinding chamber. The aqueous dispersion comprising the low viscosity water-soluble polymeric stabilizer(s) (and optionally further comprising the non-ionic stabilizers) is prepared at a concentration of from about 2% w/w to about 10% w/w and added to the grinding chamber in an amount of about 30 % w/w to about 45 % w/w of the capacity of the grinding chamber. The enzalutamide starting material is added to the grinding chamber in an amount of about 5% w/w to about 15% w/w of the capacity of the grinding chamber. Wet-milling is conducted at 1000 to 2500 rpm for 60 to 300 minutes at a temperature of from 4°C to 10 °C. The aqueous composition may be recovered from the grinding beads by any suitable method, such as filtration, aspiration, etc.

[0060] After separation from the grinding beads, a process as described herein results in an aqueous composition comprising the enzalutamide nanocrystals and stabilizer(s), e.g., an aqueous dispersion of the enzalutamide nanocrystals and stabilizer(s). Such a composition is referred to herein from time to time as an "intermediate" composition.

Stabilizer

[0061] As noted above, enzalutamide nanoparticles as described herein may be prepared using an aqueous milling composition comprising a stabilizer, and intermediate and pharmaceutical compositions as described herein may comprise a stabilizer. While not wanting to be bound by theory, it is believed that the stabilizer may stabilize the dispersion of nanocrystals (e.g., enzalutamide nanocrystals) in the aqueous vehicle.

[0062] The stabilizer may be one or more selected from low viscosity water-soluble polymeric stabilizers and non-ionic stabilizers. In this context, low viscosity refers to a viscosity in the range of 2.0 to 6.0 mPa.s-1 when prepared at a concentration of 40g/L.

[0063] Examples of suitable low viscosity water-soluble polymeric stabilizers, include, but are not limited to, polyvinyl alcohol, polyvinylpyrrolidone, and hydroxypropyl methylcellulose.

Examples of suitable polyvinyl alcohol (PVA) stabilizers include PVA 4-88, PVA 4-99, PVA 5-88 and PVA -99, where the first number indicates viscosity (e.g., of 4-6 mPa.s-1) and the second number indicates degree of alcoholysis (e.g., 86-90%). Examples of suitable polyvinylpyrrolidone (PVP) stabilizers include PVP having an average molecular weight in a range from 8000 to 60,000 Daltons, including PVP K-12, PVP K-15, and PVP K-30. In some embodiments, a suitable PVP stabilizer has an average molecular weight of 60,000 Daltons or greater, such as PVP K-30. Examples of suitable hydroxypropyl methylcellulose stabilizers include hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10,000 to 60,000 Daltons. In this context, "low viscosity" means having a viscosity in the range of 2.0 to 6.0 mPa.s-1 at a concentration of 40g/L.

[0064] Examples of suitable non-ionic stabilizers, include, but are not limited to, polyethylene glycol sorbitan monooleate (polysorbate 80), block copolymers of polyethylene oxide and polypropylene oxide (e.g., Poloxamer 124, Poloxamer 188, Poloxamer 407), α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate.

[0065] In some embodiments, a composition as described herein comprises polyvinyl alcohol and polyethylene glycol sorbitan monooleate.

[0066] The stabilizer(s) can be present in any suitable amount, such as any amount effective to stabilize the enzalutamide nanocrystals or composition as a whole. In some embodiments, an aqueous composition as described herein (e.g., a milling composition, intermediate composition, or pharmaceutical composition) has a total stabilizer content of from about 1% to about 15% w/w, including from about 1% to about 10% w/w, including from 1% to 10% w/w, such as from about 2% to about 5% w/w, including from 2% to 5% w/w, including about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, or about 10% w/w, such as 2% w/w, 2.5% w/w, 3% w/w, 3.5% w/w, 4% w/w, 4.5% w/w, 5% w/w, 6% w/w, 7% w/w, 8% w/w, 9% w/w, 10%

w/w, based on the weight of the composition, or any value therebetween. When combinations of stabilizers are used, they each may be present in any suitable amount. For example, a composition as described herein that includes more than one stabilizer may comprise a relatively large amount of one and a relatively small amount of the other(s), or may comprise relatively equal amounts of each.

[0067] In some embodiments, the stabilizer may be or comprise polyvinyl alcohol. For example, in some embodiments, an aqueous composition as described herein (e.g., a milling composition, intermediate composition, or pharmaceutical composition) has a polyvinyl alcohol content of from about 1% to about 10% w/w, including from 1% to 10% w/w, such as from about 2% to about 5% w/w, including from 2% to 5% w/w, including about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, or about 10% w/w, such as 2% w/w, 2.5% w/w, 3% w/w, 3.5% w/w, 4% w/w, 4.5% w/w, 5% w/w, 6% w/w, 7% w/w, 8% w/w, 9% w/w, 10% w/w, based on the weight of the composition, or any value therebetween.

[0068] Additionally or alternatively, the stabilizer may be or comprise polyvinylpyrrolidone, such as PVP having an average molecular weight of 60,000 Daltons or greater, such as PVP K-30. For example, in some embodiments, an aqueous composition as described herein (e.g., a milling composition, intermediate composition, or pharmaceutical composition) has a polyvinylpyrrolidone content of from about 1% to about 10% w/w, including from 1% to 10% w/w, such as from about 2% to about 5% w/w, including from 2% to 5% w/w, including about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, or about 10% w/w, such as 2% w/w, 2.5% w/w, 3% w/w, 3.5% w/w, 4% w/w, 4.5% w/w, 5% w/w, 6% w/w, 7% w/w, 8% w/w, 9% w/w, 10% w/w, based on the weight of the composition, or any value therebetween.

[0069] Additionally or alternatively, the stabilizer may be or comprise polyethylene glycol sorbitan monooleate (e.g., polysorbate 80). For example, in some embodiments, an aqueous composition as described herein (e.g., a milling composition, intermediate composition, or

pharmaceutical composition) has a polyethylene glycol sorbitan monooleate (e.g., polysorbate 80) content of from about 1% to about 10% w/w, including from 1% to 10% w/w, such as from about 2% to about 5% w/w, including from 2% to 5% w/w, including about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, or about 10% w/w, such as 2% w/w, 2.5% w/w, 3% w/w, 3.5% w/w, 4% w/w, 4.5% w/w, 5% w/w, 6% w/w, 7% w/w, 8% w/w, 9% w/w, 10% w/w, based on the weight of the composition, or any value therebetween.

Other Components

[0070] A composition as described herein may comprise one or more other components suitable for an intermediate of a pharmaceutical composition, or suitable for an oral pharmaceutical composition formulated as a liquid or dry (solid) composition. For example, a composition as described herein optionally may further comprise one or more pharmaceutically acceptable excipients such as viscosity adjusting agents (*e.g.*, thickeners), diluents, pH adjusting agents, colorants, flavoring agents, taste-masking agents, preservatives, etc. In some embodiments, a composition as described herein further comprises a permeation enhancer. Non-limiting examples of selected additional components are set forth below.

Lyophilization Excipients

[0071] As discussed in more detail below, an aqueous composition as described herein (e.g., an "intermediate" composition) may be subjected to a drying process (such as lyophilization) to obtain a dry (solid) composition, which can be formulated as a dry (e.g., solid) oral pharmaceutical composition. In relation to such embodiments, the composition may comprise a lyophilization excipient. The lyophilization excipient may be any compound suitable for use in oral pharmaceutical compositions that may protect the nanocrystals during the lyophilization process, such as any cryoprotectant or lyoprotectant suitable for use in oral pharmaceutical compositions. For example, one or more of maltose, glycine, lactose, dextran, mannitol, and trehalose may be used as a lyophilization excipient. When present, a lyophilization excipient may be used in any suitable amount effective to protect the nanocrystals during the lyophilization process, such as

from about 0.1% w/w to about 50% w/w, including from 0.1% to 50% w/w, based on the weight of the aqueous composition before drying.

Wet Granulation Excipients

[0072] As discussed in more detail below, an aqueous composition as described herein (e.g., an "intermediate" composition) may be subjected to a granulation process (such as wet granulation) to obtain a dry (solid) composition, which can be formulated as a dry (e.g., solid) oral pharmaceutical composition. In relation to such embodiments, the composition may comprise a wet granulation excipient. The wet granulation excipient may be any compound suitable for use in oral pharmaceutical compositions that facilitates granulation, such as one or more selected from disintegrants (e.g., povidone, crospovidone, corn starch, etc.) wetting agents (polaxamers, carboxymethylcellulose, etc.), binders (povidone, corn starch, hydroxyethylmethyl cellulose, hypromellose, lactose monohydrate, etc.), glidants (glyceryl monoestearate, talc, etc.), and diluents (microcrystalline cellulose, corn starch, lactose monohydrate, etc.). When present, a granulation excipient may be used in any suitable amount effective to facilitate the wet granulation process.

Permeation Enhancer

[0073] A composition as described herein (e.g., a pharmaceutical composition), optionally may comprise a permeation enhancer. When present, the permeation enhancer may enhance the solubility of components of the composition (e.g., the enzalutamide), and/or may enhance *in vivo* permeation of the enzalutamide. In some embodiments, the permeation enhancer may improve (shorten) the dissolution rate of the enzalutamide in the composition. Additionally or alternatively, the permeation enhancer may act as a paracellular junction modulator (rather than a mucolytic agent that can cause damage to the intestinal mucosa).

[0074] In some embodiments, a permeation enhancer is a surfactant (e.g., an anionic surfactant). The permeation enhancer may be one or more selected from sodium salts of a medium chain fatty acid, C10 – C18 alcohol sulfates, bile salt derivatives (e.g. sodium taurocholate, sodium glycocholate, sodium taurodeoxycholate and sodium deoxycholate), coconut oil derivatives (e.g.,

methyl ester sulfonates (MES), sodium lauryl sulfate (SLS), sodium coco Sulfate (SCS), and sodium laureth sulfate (SLES); cocoyl chloride, etc.); potassium cocoyl glycinate and sodium cocoyl glycinate, and palm oil derivatives (e.g. palmitic acid, palm kernel oil, etc.). In this context, the term "fatty acid" means a carboxylic acid having the formula RCOOH, where R represents an aliphatic group, such as an alkyl group, that comprises from 4 to 22 carbon atoms. Fatty acids can be saturated, monounsaturated, or polyunsaturated. A fatty acid can have a medium-chain length (e.g., medium chain fatty acid), wherein the fatty acids may be saturated or unsaturated. As used herein, "medium chain fatty acid" refers to a fatty acid that consists of 6 to 14 carbon atoms, such as caproic acid (C6), caprylic acid (C8), capric acid (C10), and lauric acid (C12).

[0075] Examples of suitable sodium salts of a medium chain fatty acid for use as a permeation enhancer, include, but are not limited to, sodium caprate and sodium caprylate. Examples of suitable bile salt derivatives for use as a permeation enhancer, include, but are not limited to, sodium cholate, sodium taurocholate (e.g., sodium deoxycholate, sodium taurodeoxycholate). Examples of suitable coconut oil derivatives and/or palm oil derivatives for use as a permeation enhancer, include, but are not limited to, methyl ester sulfonates (MES), sodium lauryl sulfate (SLS), sodium coco sulfate (SCS), sodium laureth sulfate (SLES), cocoyl chloride), potassium cocoyl glycinate, sodium cocoyl glycinate, palmitic acid and palm kernel oil. Thus, for example, a composition as described herein may comprise one or more permeation enhancers selected from sodium caprate, sodium caprylate, sodium cholate, sodium deoxycholate, and sodium lauryl sulfate. A composition as described herein may comprise one permeation enhancer compound, or a combination of permeation enhancers, such as a combination of any two or more of the permeation enhancers listed above.

[0076] The permeation enhancers(s) can be present in any suitable amount, such as any amount effective to achieve the desired impact on solubility and/or permeation. When combinations of permeation enhancers are used, they each may be present in any suitable amount. For example, a composition as described herein that includes more than one permeation enhancer may comprise a relatively large amount of one and a relatively small amount of the other(s), or may comprise relatively equal amounts of each.

[0077] In some embodiments, the permeation enhancer is or comprises sodium caprate. For example, in some embodiments, a composition as described herein has a sodium caprate content of from about 0.25% w/w to about 50% w/w, including about 0.25% w/w, about 0.5% w/w, about 1% w/w, about 5 % w/w, about 10 % w/w, about 20 % w/w, about 25 % w/w, about 30 % w/w, about 40 % w/w, or about 50 % w/w, relative to the amount of enzalutamide, or any value therebetween.

[0078] Additionally or alternatively, in some embodiments, the permeation enhancer is or comprises sodium caprylate. For example, in some embodiments, a composition as described herein has a sodium caprylate content of from about 1% w/w to about 50% w/w, including about 1% w/w, about 5 % w/w, about 10 % w/w, about 20 % w/w, about 25 % w/w, about 30 % w/w, about 40 % w/w, or about 50 % w/w, relative to the amount of enzalutamide, or any value therebetween.

[0079] Additionally or alternatively, in some embodiments, the permeation enhancer is or comprises sodium cholate (e.g., sodium deoxycholate). For example, in some embodiments, a composition as described herein has a sodium cholate (e.g., sodium deoxycholate) content of from about 0.25% w/w to about 10% w/w, including about 0.25% w/w, 0.5% w/w, 0.25% w/w, about 1 % w/w, about 2 % w/w, about 3 % w/w, about 4 % w/w, about 5 % w/w, or about 6 % w/w, about 7 % w/w, about 8 % w/w, about 9 % w/w, or about 10 % w/w, relative to the amount of enzalutamide, or any value therebetween.

[0080] Additionally or alternatively, in some embodiments, the permeation enhancer is or comprises sodium lauryl sulfate. For example, in some embodiments, a composition as described herein has a sodium lauryl sulfate content of about 1% w/w to about 50% w/w, including about 1% w/w, about 5 % w/w, about 10 % w/w, about 20 % w/w, about 25 % w/w, about 30 % w/w, about 40 % w/w, or about 50 % w/w, relative to the amount of enzalutamide, or any value therebetween.

Antioxidants

[0081] Any embodiments of compositions described herein may comprise one or more antioxidants. Non-limiting examples of suitable antioxidants include butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT), ascorbic palmitate, sodium metabisulfite, sodium thiosulfate, propyl gallate, gamma linoleic acid, ascorbic acid, ethylenediaminetetraacetic acid (EDTA), alpha tocopherol, and DL-methionine. Thus, in accordance with any of the foregoing embodiments, a composition as described herein may comprise an antioxidant. For example, a composition as described herein may comprise one or both of BHA and BHT. The antioxidant(s) may be present in any suitable amount, such as from 0.001% to about 10% w/w of the composition.

Sweetening Agents/Flavoring Agents

[0082] A composition as described herein (e.g., a pharmaceutical composition) may comprise one or more of sweetening agent(s) and/or one or more flavoring agent(s). Examples of suitable sweetening agents include, but are not limited to, sucralose, glycyrrhizic acid and its salts (*e.g.*, ammonium glycyrrhizinate), saccharin, aspartame, acesulfame potassium, cyclamate, erythritol, and neotame. Thus, in accordance with any of the foregoing embodiments, a composition as described herein may comprise a sweetening agent. For example, a composition as described herein may comprise one or more sweetening agent(s) selected from sucralose and ammonium glycyrrhizinate. The sweetening agent(s) may be present in any suitable amount.

[0083] Examples of suitable flavoring agents include, but are not limited to, vanilla flavor, banana flavor, grapefruit flavor, strawberry flavor, raspberry flavor, bubble gum flavor, and caramel flavor. Thus, in accordance with any of the foregoing embodiments, a composition as described herein may comprise a flavoring agent. For example, a composition as described herein may comprise vanilla flavor. The flavoring agent(s) may be present in any suitable amount.

Compositions

[0084] The following are disclosed as specific illustrative embodiments of compositions as described herein. As noted above, in specific embodiments of any of the composition embodiments

described herein (e.g., a milling composition, an intermediate composition, a pharmaceutical composition), the enzalutamide nanocrystals are obtained by a process as described herein. Except where expressly described as a dry composition, the compositions described herein (e.g., a milling composition, an intermediate composition, a pharmaceutical composition), may further comprise water.

[0085] Provided herein are aqueous compositions (e.g., milling compositions, intermediate compositions, or pharmaceutical compositions), comprising:

(i) about 5% to about 15% w/w of enzalutamide nanocrystals;

(ii) about 1% to about 10% w/w (including about 2% to about 5% w/w) of a polymeric stabilizer, wherein the stabilizer comprises one or more low viscosity water-soluble polymers (e.g., polyvinyl alcohol), and

(iii) about 0 % to about 2% w/w of a non-ionic stabilizer (e.g., polyethylene glycol sorbitan monooleate).

[0086] In some embodiments, the aqueous composition comprises:

(i) about 10% to about 15% w/w of enzalutamide nanocrystals;

(ii) about 2% to about 3% w/w of polyvinyl alcohol; and

iii) about 0.5 to about 1% w/w of polyethylene glycol sorbitan monooleate.

[0087] In accordance with any of the foregoing embodiments, the aqueous composition may be an aqueous dispersion comprising the enzalutamide nanocrystals dispersed in an aqueous vehicle.

[0088] In accordance with any of the foregoing embodiments, the aqueous composition may be an intermediate formulation that is subject to further processing to obtain a pharmaceutical composition. For example, an aqueous composition as described above may be subjected to further processing to formulate the aqueous composition as an oral liquid pharmaceutical composition. Such further processing may include one or more of adjusting the concentration of the solution and adding one or more pharmaceutically acceptable components. Alternatively, an aqueous composition as described above may not require further processing to be suitable for use as an oral

liquid pharmaceutical composition; that is an aqueous composition as described above may be an oral liquid pharmaceutical composition.

[0089] In some embodiments, an aqueous composition as described above is subjected to further processing to formulate the aqueous composition as a dry oral pharmaceutical composition. For example, an aqueous composition as described above may be subjected to a drying process (such as granulation and/or lyophilization and/or spray drying) to obtain a dry (solid) composition. In some embodiments, such a dried composition is formulated into a dry oral pharmaceutical composition for administration. As noted above, in some embodiments, a dry oral pharmaceutical composition may comprise a lyophilization excipient. Additionally or alternatively, in some embodiments, a dry oral pharmaceutical composition may comprise a granulation excipient.

Methods of Manufacture of Pharmaceutical Compositions

[0090] The present disclosure provides processes for preparing pharmaceutical compositions (e.g., pharmaceutical compositions as described herein) for the oral administration of enzalutamide. As noted above, the compositions prepared by a process described herein typically include (i) enzalutamide nanocrystals and (ii) a stabilizer, initially prepared in an aqueous vehicle, e.g., as a result of the nanosizing process or prepared from preformed nanocrystals. Thus, processes as described herein can avoid or reduce the use of organic solvents during the manufacturing process.

[0091] As described above, the preparation of enzalutamide nanocrystals as described herein results in an aqueous composition comprising the enzalutamide nanocrystals and stabilizer, in an aqueous vehicle (e.g., water) As noted above, the resulting aqueous composition may be a dispersion of enzalutamide nanocrystals nanocrystals dispersed in an aqueous solvent.

[0092] In some embodiments, the aqueous composition resulting from the nanosizing process (e.g., the "intermediate" composition) is suitable for use as an oral liquid pharmaceutical composition. Thus, an aqueous composition as herein may be packaged in a bulk package (e.g., a bottle), in a unit dose package (e.g., unit dose bottles, vials or pouches) or filled into capsules.

[0093] As noted above, in some embodiments, the aqueous composition is formulated to obtain an oral liquid pharmaceutical composition. For example, an enhancer and/or one or more other pharmaceutically acceptable components may be added to obtain an oral liquid pharmaceutical composition. An oral liquid pharmaceutical composition as described herein may be packaged in a bulk package (e.g., a bottle), in a unit dose package (e.g., unit dose bottles, vials or pouches) or filled into capsules.

[0094] As noted above, in some embodiments, the aqueous composition is dried to obtain a dry (solid) composition that may be formulated as a dry oral pharmaceutical composition. For example, an aqueous composition as described above may be subject to a drying step, such as a granulation and/or lyophilization step and/or spray drying step, to obtain a dried composition (e.g., a solid composition). As noted above, such a composition may comprise one or more lyophilization excipients, such as one or more of maltose, glycine, lactose, dextran, mannitol, and trehalose. Additionally or alternatively, such a composition may comprise one or more granulation excipients that facilitates the granulation process, such as one or more selected from disintegrants (e.g., povidone, crospovidone, corn starch, etc.) wetting agents (polaxamers, carboxymethylcellulose, etc.), binders (povidone, corn starch, hydroxyethylmethyl cellulose, hypromellose, lactose monohydrate, etc.), glidants (glyceryl monoestearate, talc, etc.), and diluents (microcrystalline cellulose, corn starch, lactose monohydrate, etc.).

[0095] The dried composition may be obtained as, or subject to further processing to obtain, a powder or granules, or compressed into tablets. The dried composition may be formulated as a dray oral pharmaceutical composition. A dry oral pharmaceutical composition as described herein may be in the form of a powder or granules (optionally packaged in a sachet or stick pack or filled into a capsule), or tablets, for example.

[0096] As noted above, an enzalutamide pharmaceutical composition as described herein may be packaged into unit dosage forms (unit doses) containing a pharmaceutically effective dose of enzalutamide, such as about 160 mg or less (such as from 50 mg to less than 160 mg, including about 100 mg enzalutamide) per unit dosage form (per unit dose).

Therapeutic Methods/Uses

[0097] The present disclosure also provides uses of the pharmaceutical compositions described herein in treatment methods comprising orally administering an oral pharmaceutical composition as described herein to a subject in need thereof. For example, the subject may be a human subject suffering from prostate cancer, and typically is a male subject although also could be a female subject. The prostate cancer may be advanced prostate cancer, including prostate cancer that does not response to hormone therapy or surgical treatment to lower testosterone, or that has spread to other parts of the body. The composition may be administered at any therapeutically effective dose by any suitable dosing regimen. For example, a pharmaceutical composition described herein that comprises enzalutamide (e.g., enzalutamide nanocrystals) may be administered once daily in an amount that provides a daily dose of enzalutamide of about 160 mg, or less (such as from 50 mg to less than 160 mg, including about 100 mg enzalutamide).

[0098] As noted above, the compositions described herein may exhibit advantageous properties. As noted above, enzalutamide may exhibit low solubility in water. The low solubility and/or slow dissolution rate of enzalutamide in biological fluids can be a limiting factor for its absorption and bioavailability. The pharmaceutical compositions described herein include enzalutamide in nanocrystal form (e.g., enzalutamide nanocrystals) which may exhibit improved water solubility and faster dissolution rates as compared to enzalutamide that is not nanosized. For example, without being bound by theory, it is believed a nanoscale size may enhance dissolution rate, and enhance the intrinsic solubility and saturation concentration of the enzalutamide, resulting in increased bioavailability. The use of an enhancer (in some embodiments) may further improve bioavailability, such as by enhancing intestinal permeation flux and reducing the risk of *in situ* precipitation. Thus, for example, enzalutamide compositions as described herein may exhibit a bioavailability equal to or greater than that of XTANDI®, and/or may require a lower dose for therapeutic efficacy. Additionally or alternatively, the enzalutamide compositions described herein may contain the same amount of enzalutamide in a smaller volume than enzalutamide compositions prepared with non-nanosized enzalutamide, and therefore provide the same dose in

a smaller volume, offer advantages such as improve convenience and easier administration for the patient.

[0099] The following specific examples are included as illustrative examples of the methods and compositions described herein. These examples are in no way intended to limit the scope of disclosure. Other aspects of the disclosure will be apparent to those skilled in the art to which the disclosure relates.

EXAMPLES

Example 1: Preparation of Enzalutamide Nanocrystals

[0100] Nanocrystals of enzalutamide were prepared by a process as described above and outlined in FIG. 1, using the following components.

Sample	Components (w/w%)					
	Enzalutamide	Polyvinyl alcohol (4-88)	PVP (K-30)	PVP (K-15)	Polysorbate 80	Purified water
ENC-001	10	3	-	-	-	87
ENC-002	10	-	3	-	-	87
ENC-003	10	-	-	3	-	87
ENC-004	10	2	-	-	1	87
ENC-005	10	-	2	-	1	87
ENC-006	10	-	-	2	1	87

[0101] The average particle size diameter and polydispersity index (PDI) of the nanocrystals obtained from each formulation were measured by dynamic light scattering. The results are reported in the table below, which shows the impact of the stabilizer on the average particle size. The nanocrystal size distribution profile determined at the time of manufacture is shown in FIG. 2. As seen in the figure, all samples showed a unimodal size distribution, with particles at nanometer scale.

Sample	Average size (nm)	Size D10 (nm)	Size D90 (nm)	PDI (%)
ENC-001	187	121	236	13.2
ENC-002	315	169	480	24.0
ENC-003	825	524	798	22.8
ENC-004	194	124	257	16.1
ENC-005	259	165	329	12.1
ENC-006	248	153	320	11.3

Example 2: Stability of Enzalutamide Nanocrystals

[0102] The physical stability of the enzalutamide nanocrystals obtained in Example 1 was assessed over 42 days at room temperature, with assessments performed at 7, 21, and 42 days. Results are presented in the table below. As seen in the table, only relatively small variations in size and polydispersity index (PDI) were observed (e.g., ± 10% or less). The composition comprising polyvinyl alcohol (4-88) as a low-viscosity polymeric stabilizer showed the greatest stability.

Sample	7 Days		21 Days		42 Days	
	Average diameter (nm)	PDI (%)	Average diameter (nm)	PDI (%)	Average diameter (nm)	PDI (%)
ENC-001	200	9.0	202	16.3	207	19.8
ENC-002	379	28.1	395	16.2	390	21.5
ENC-003	425	1.0	508	5.1	523	19.8
ENC-004	202	19.2	207	5.0	205	14.2
ENC-005	290	19.2	278	14.6	280	3.9
EMC-006	274	20.9	283	24.1	275	16.1

[0103] Physical stability of the same formulations was analyzed using the LUMisizer dispersion analyser equipment manufactured by LUM GmbH, simulating 3.5 months of storage. An "Instability Index" was calculated by the SEPView® software of the LUMisizer to create a

dimensionless (quantitative) number reflecting physical formulation stability, ranging from 0 (more stable) to 1 (more unstable). (More stable formulations have a slower sedimentation rate; thus, sedimentation rate is used to calculate the stability index.) FIG. 3 presents the sedimentation kinetics results graphically, and shows that formulation ENC-003 exhibited the most rapid sedimentation (most quickly lost physical stability), while formulations ENC-001 and ENC-004 exhibited the slowest sedimentation rates, and therefore were more physically stable. Formulations ENC-005 and ENC-006 exhibited essentially the same results and so are plotted on the same curve. Visual inspection of the samples revealed that formulations ENC-001 and ENC-004 showed the lowest sedimentation rate, which is an indication of greater physical stability of these formulations.

Example 3. Impact of Formulation and Process Parameters

[0104] Nanocrystals were produced using different formulations and process parameters, varying the amount of enzalutamide (from 2 to 15 %), PVA 4-88 (from 2 to 5 %) and polysorbate 80 (from 0 to 2 %), and varying milling time (from 90 to 240 minutes) and milling speed (from 1000 to 2000 RPM). The obtained nanocrystals were analyzed for size and PDI by DLS. Results are set forth below. Some test conditions were excluded for resulting in unacceptably inefficient grinding: enzalutamide concentrations greater than 15%, grinding time less than 90 minutes; speed less than 1000 RPM.

Sample	ENZA (% w/w)	PVA 4- 88 (% w/w)	Polysorbate 80 (%, w/w)	Speed (RPM)	Time (min)	Average size (nm)	Average PDI (%)
E1N	2	2	0	1000	240	237.7	18.7
E2N	15	2	0	1000	90	509.9	29.0
E3N	2	5	0	1000	90	320.7	24.4
E4N	15	5	0	1000	240	191.6	20.7
E5N	2	2	2	1000	90	281.7	25.1
E6N	15	2	2	1000	240	204.5	21.2
E7N	2	5	2	1000	240	244.9	21.0
E8N	15	5	2	1000	90	287.5	22.4
E9N	2	2	0	2000	90	190.1	19.1
E10N	15	2	0	2000	240	243.5	21.5
E11N	2	5	0	2000	240	169.9	16.2

Sample	ENZA (% w/w)	PVA 4- 88 (% w/w)	Polysorbate 80 (%, w/w)	Speed (RPM)	Time (min)	Average size (nm)	Average PDI (%)
E12N	15	5	0	2000	90	182.5	10.8
E13N	2	2	2	2000	240	234.7	27.6
E14N	15	2	2	2000	90	254.7	22.8
E15N	2	5	2	2000	90	231.6	13.9
E16N	15	5	2	2000	240	191.7	18.9
E17N	8.5	3.5	1	1500	165	185.9	17.9
E18N	8.5	3.5	1	1500	165	187.6	16.9
E19N	8.5	3.5	1	1500	165	188.3	10.4

[0105] As the foregoing shows, varying the formulation and/or process parameters impacted the size and PDI of the nanocrystals. Nanocrystals with a size ranging from 169.9 to 320.7 nm and a PDI from 10.4 % to 29.0 % were obtained. From the statistical analysis, it was determined that enzalutamide concentration, milling time, and milling speed have the most significant impact on the average size and PDI of the nanocrystals.

Example 4: Saturation Solubility Of Enzalutamide Nanocrystals

[0106] The saturation solubility of enzalutamide nanocrystals in water was evaluated in an orbital shaker for 24 hours at 37°C, using nanocrystals of formulation ENC-004 and non-nanosized enzalutamide (having an average particle size of about 6,000 nm), each formulated at 0.5 mg/ml. As seen in FIG. 4, nanonization increased the saturation solubility relative to non-nanonized enzalutamide by about 20-fold in 4 hours (considered to be an important time frame relevant to absorption). After that time, solubility decreased, probably due to recrystallization of enzalutamide.

Example 5: Cytotoxicity Assay

[0107] The safety of non-nanosized enzalutamide, XTANDI®, and nanocrystals of formulation ENC-004 (described above) were evaluated using intestinal epithelial human cells (Caco2) seeded in 96-well culture plates. All samples were prepared in phosphate buffer saline (PBS). The plates were incubated at 37°C and 5% CO2 with 200 µL of the test material diluted in DMEM supplemented with 1% (v/v) NEAA, 1% (v/v) P/S, and 10% FBS. Samples of non-nanosized

enzalutamide were prepared with 1% DMSO or PBS. All test materials were assessed at concentrations of 10 μg/ml, 100 μg/ml, and 200 μg/ml, at 0.5 hours, 2 hour, and 24 hours. Results are reported in FIG. 5A-5C. As seen in the figure, ENC-004 exhibited a higher viability profile (e.g., reduced toxicity) after incubation for 24 hours as compared to XTANDI®.

WHAT IS CLAIMED IS:

1. A composition comprising nanocrystals of enzalutamide, wherein the enzalutamide nanocrystals have an average particle size diameter of ≤ 250 nm.

2. The composition of claim 1, wherein the enzalutamide nanocrystals have an average particle size diameter of 180 nm to 220 nm.

3. The composition of any one of the preceding claims, wherein the enzalutamide nanocrystals have a polydispersity index of from 0.05 to 0.30, as measured by dynamic light scattering.

4. The composition of any one of the preceding claims, wherein the enzalutamide nanocrystals have a polydispersity index of ≤ 0.20, as measured by dynamic light scattering.

5. The composition of any one of the preceding claims, wherein the enzalutamide nanocrystals have a saturation solubility in water at 37 ° that is about 20-fold that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 4 hours after being dissolved in water.

6. The composition of any one of the preceding claims, wherein the enzalutamide nanocrystals have a saturation solubility in water at 37 ° that is about twice that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 8 hours after being dissolved in water.

7. The composition of any one of the preceding claims, further comprising a stabilizer, wherein the stabilizer comprises one or more selected from (i) low viscosity water-soluble polymeric stabilizers and (ii) non-ionic stabilizers.

8. The composition of claim 7, comprising from about 1% to about 10% w/w of the low viscosity water-soluble polymeric stabilizer(s) and from about 0% w/w to about 2% w/w of the non-ionic stabilizer(s).

9. The composition of claim 7, comprising one or more low viscosity water-soluble polymeric stabilizers and one or more non-ionic stabilizers.

10. The composition of any one of claims 7-9, wherein the one or more low viscosity water-soluble polymeric stabilizers comprises one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000 Daltons.

11. The composition of any one of claims 7-9, wherein the one or more low viscosity water-soluble polymeric stabilizers comprises one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000 Daltons.

12. The composition of any one of claims 7-11, wherein the one or more non-ionic stabilizers comprise one or more selected from polyethylene glycol sorbitan monooleate, block copolymers of polyethylene oxide and polypropylene oxide, α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate.

13. The composition of any one of claims 7-12, wherein the stabilizer comprises polyvinyl alcohol and polyethylene glycol sorbitan monooleate.

14. The composition of any one of claims 7-13, wherein the enzalutamide, low viscosity water-soluble polymeric stabilizer(s) and non-ionic stabilizer(s) are present in wt/wt a ratio of 10:1-10:0-2.

15. The composition of any one of claims 7-13, wherein the enzalutamide, low viscosity water-soluble polymeric stabilizer(s) and non-ionic stabilizer(s) are present in wt/wt a ratio of 10:2-3:1.

16. The composition of any one of the preceding claims, comprising about 10% w/w enzalutamide.

17. The composition of claim 16, comprising about 10% w/w enzalutamide, from about 1% w/w to about 10% w/w low viscosity water-soluble polymeric stabilizer(s), and from 0% to about 2 % w/w non-ionic stabilizer(s).

18. The composition of any one of claims 16-17, comprising about 10% w/w enzalutamide, about 2% w/w polyvinyl alcohol, and about 1 % w/w polyethylene glycol sorbitan monooleate.

19. The composition of any one of the preceding claims, wherein the average particle size of the nanocrystals in the composition does not vary by more than ± 10% after storage at room temperature for 40 days.

20. The composition of any one of the preceding claims, wherein the composition is stable against sedimentation of enzalutamide after storage at room temperature for 3 months.

21. The composition of any one of the preceding claims, further comprising water.

22. The composition of claim 21, wherein the composition is in the form of an aqueous suspension comprising the enzalutamide nanoparticles suspended in an aqueous carrier.

23. A lyophilized composition prepared from a composition of any one of the preceding claims, and further comprising a lyophilization stabilizer.

24. A dry composition comprising the composition of any one of claims 1-20 or 23, and further comprising a granulation excipient.

25. A composition of any one of the preceding claims, wherein the composition does not include hydroxypropyl methyl cellulose (HPMC).

26. A process for preparing nanocrystals of enzalutamide, comprising wet-milling enzalutamide with an aqueous dispersion comprising one or more low viscosity water-soluble polymeric stabilizers to obtain nanocrystals of enzalutamide having an average particle size diameter of $\leq$ 250 nm.

27. The process of claim 26, wherein the one or more low viscosity water-soluble polymeric stabilizers comprises one or more selected from polyvinyl alcohol, polyvinylpyrrolidone having an average molecular weight of 60,000 Daltons or greater, hydroxypropyl methylcellulose having an average molecular weight of 40,000 to 100,000 Daltons, and hydroxypropyl methylcellulose having an average molecular weight of 10000 to 60000 Daltons.

28. The process of claim 26 or 27, wherein the one or more low viscosity water-soluble polymeric stabilizers comprises polyvinyl alcohol.

29. The process of any one of claims 26-28, wherein the aqueous dispersion further comprises one or more non-ionic stabilizers.

30. The process of claim 29, wherein the one or more non-ionic stabilizers comprises one or more selected from polyethylene glycol sorbitan monooleate, block copolymers of polyethylene oxide and polypropylene oxide, α-tocopherol, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene nonylphenol ethers, and polyoxyethylene 15 hydroxy stearate.

31. The process of claim 29 or claim 30, wherein the non-ionic stabilizer comprises polyethylene glycol sorbitan monooleate.

32. The process of any one of claims 26-31, wherein the wet-milling is conducted in a grinding chamber containing grinding beads in an amount of 50% w/w to 75% w/w, based on the capacity of the grinding chamber.

33. The process of any one of claims 26-32, wherein the wet-milling is conducted with grinding beads having a diameter of from about 0.1 mm to about 0.4 mm.

34. The process of any one of claims 26-33, wherein the wet-milling is conducted with grinding beads having a diameter of from about 0.1 mm to about 0.2 mm.

35. The process of any one of claims 26-34, wherein the wet-milling is conducted at temperature from about 4°C to 15 °C.

36. The process of any one of claims 26-35, wherein the wet-milling is conducted at temperature from about 5°C to 10 °C.

37. The process of any one of claims 26-36, wherein the wet-milling is conducted at a speed of from about 1000 rpm to about 2500 rpm.

38. The process of any one of claims 26-37, wherein, prior to the wet-milling, the enzalutamide has an average particle size diameter of > 100000 nm.

39. The process of any one of claims 26-37, wherein, prior to the wet-milling, the enzalutamide has an average particle size diameter on the order of 10000 nm.

40. The process of any one of claims 26-39, wherein the enzalutamide nanocrystals have an average particle size diameter of from 180 nm to 220 nm.

41. Enzalutamide nanocrystals prepared by a process according to any one of claims 26-40, wherein the enzalutamide nanocrystals have an average particle size diameter of ≤ 250 nm.

42. The nanocrystals of claim 41, wherein the nanocrystals have an average particle size diameter of 180 nm to 220 nm.

43. The nanocrystals of claim 41 or claim 42, wherein the nanocrystals have a polydispersity index of from 0.05 to 0.30, as measured by dynamic light scattering.

44. The nanocrystals of any one of claims 41-43, wherein the nanocrystals have a polydispersity index of ≤ 0.20, as measured by dynamic light scattering.

45. The nanocrystals of any one of claims 41-44, wherein the nanocrystals have a saturation solubility in water at 37 ° that is about 20-fold that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 4 hours after being dissolved in water.

46. The nanocrystals of any one of claims 41-45, wherein the enzalutamide nanocrystals have a saturation solubility in water at 37 ° that is about twice that of non-nanosized enzalutamide having an average particle size of about 6,000 nm, when assessed 8 hours after being dissolved in water.

47. A process for preparing an oral pharmaceutical composition of any one of claims 7-25, comprising preparing an aqueous composition comprising:

(i) nanocrystals of enzalutamide, wherein the enzalutamide nanocrystals have an average particle size diameter of $\leq$ 250 nm; and

(ii) a stabilizer, wherein the stabilizer comprises one or more selected from (i) low viscosity water-soluble polymeric stabilizers and (ii) non-ionic stabilizers.

48. The process of claim 47, further comprising preparing the enzalutamide nanocrystals by wet-milling enzalutamide with an aqueous dispersion comprising a low viscosity water-soluble polymeric stabilizer.

49. The process of any one of claims 47-48, further comprising formulating the aqueous composition as an oral liquid pharmaceutical composition.

50. The process of any one of claims 47-49, further comprising drying the aqueous composition to obtain a dried composition.

51. The process of claim 50, wherein drying the composition comprises lyophilizing the composition, granulating the composition, or spray-drying the composition.

52. The process of claim 50 or claim 51, further comprising formulating the dried composition as an oral pharmaceutical composition.

53. An oral pharmaceutical composition prepared by a process according to any one of claims 47-52.

54. An oral pharmaceutical composition comprising a composition according to any one of clams 1-25.

55. An oral pharmaceutical composition according to claim 54, further comprising a penetration enhancer.

56. An oral liquid pharmaceutical composition comprising a composition according to any one of clams 1-22, optionally wherein the composition does not include hydroxypropyl methyl cellulose (HPMC).

57. The oral liquid pharmaceutical composition of claim 56, wherein the composition is formulated as a bulk product or filled into a capsule.

58. A dry oral pharmaceutical composition comprising a composition according to any one of claims 1-20 and 23-24, optionally wherein the composition does not include hydroxypropyl methyl cellulose (HPMC).

59. The dry oral pharmaceutical dosage form of claim 59, in a form selected from a powder and granules, optionally filled into a sachet or capsule.

60. The oral pharmaceutical composition of any one of claims 53-59, wherein the composition is packaged to provide a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the composition is packaged to provide a daily dose of 50 mg to less than 160 mg enzalutamide.

61. A method of administering enzalutamide, comprising orally administering a composition according to any one claims 1-26 or an oral pharmaceutical composition according any one of claims 53-60 to a subject in need thereof, optionally wherein the composition is administered at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the composition is administered at a daily dose of 50 mg to less than 160 mg enzalutamide.

62. A method of treating prostate cancer, comprising orally administering a composition according to any one claims 1-26 or an oral pharmaceutical composition according any one of claims 53-60 to a subject in need thereof, optionally wherein the composition is administered at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the composition is administered at a daily dose of 50 mg to less than 160 mg enzalutamide.

63. A composition according to any one claims 1-26 or an oral pharmaceutical composition according any one of claims 53-60, for use in treating prostate cancer, optionally wherein the use comprises administering the composition at a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the use comprises administering the composition at a daily dose of 50 mg to less than 160 mg enzalutamide.

64. Use of a composition according to any one claims 1-26 or an oral pharmaceutical composition according any one of claims 53-60, in the manufacture of a medicament for treating prostate cancer, optionally wherein the medicament comprises a daily dose of 50 mg to 160 mg enzalutamide, further optionally wherein the medicament comprises a daily dose of 50 mg to less than 160 mg enzalutamide.

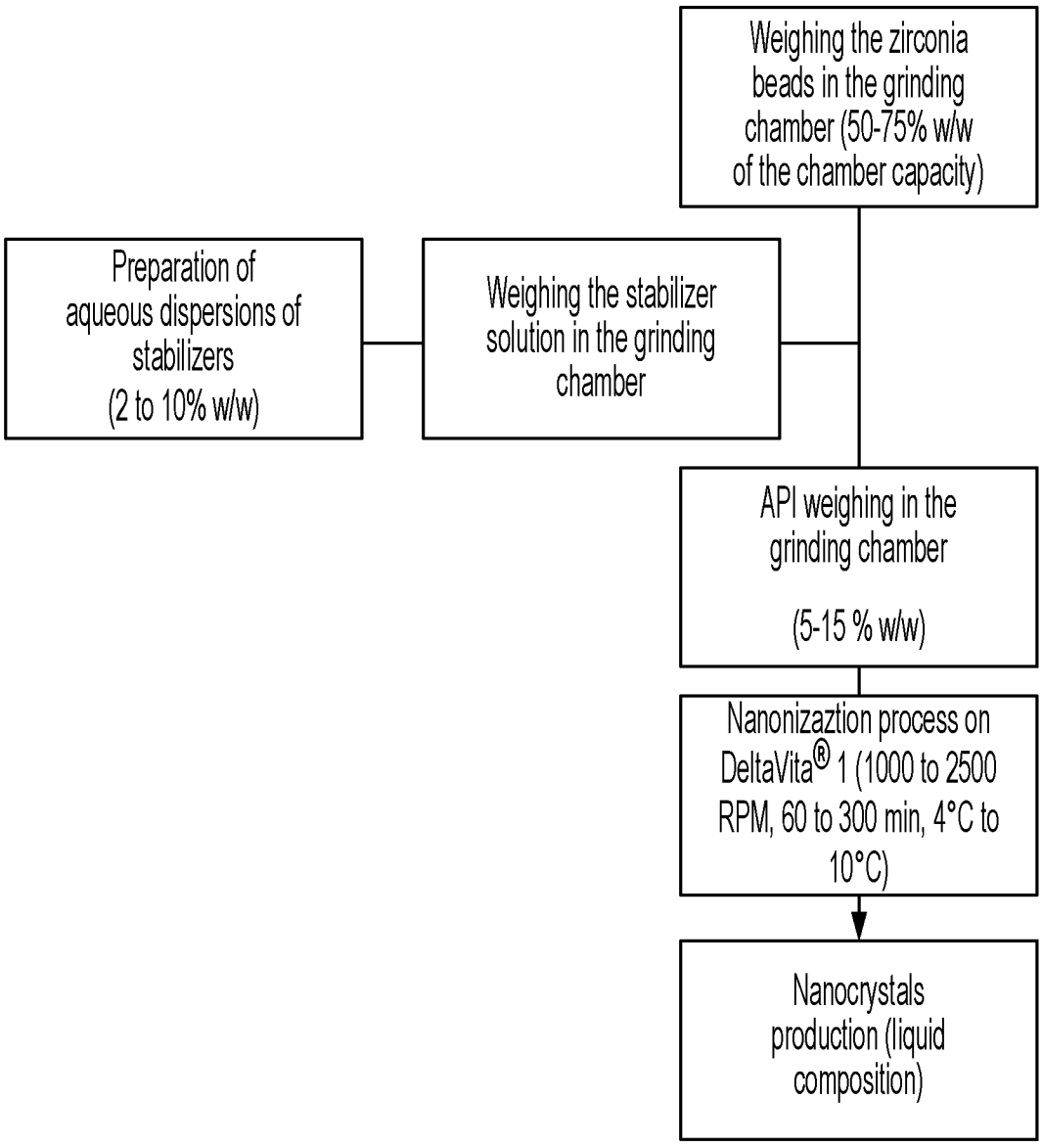
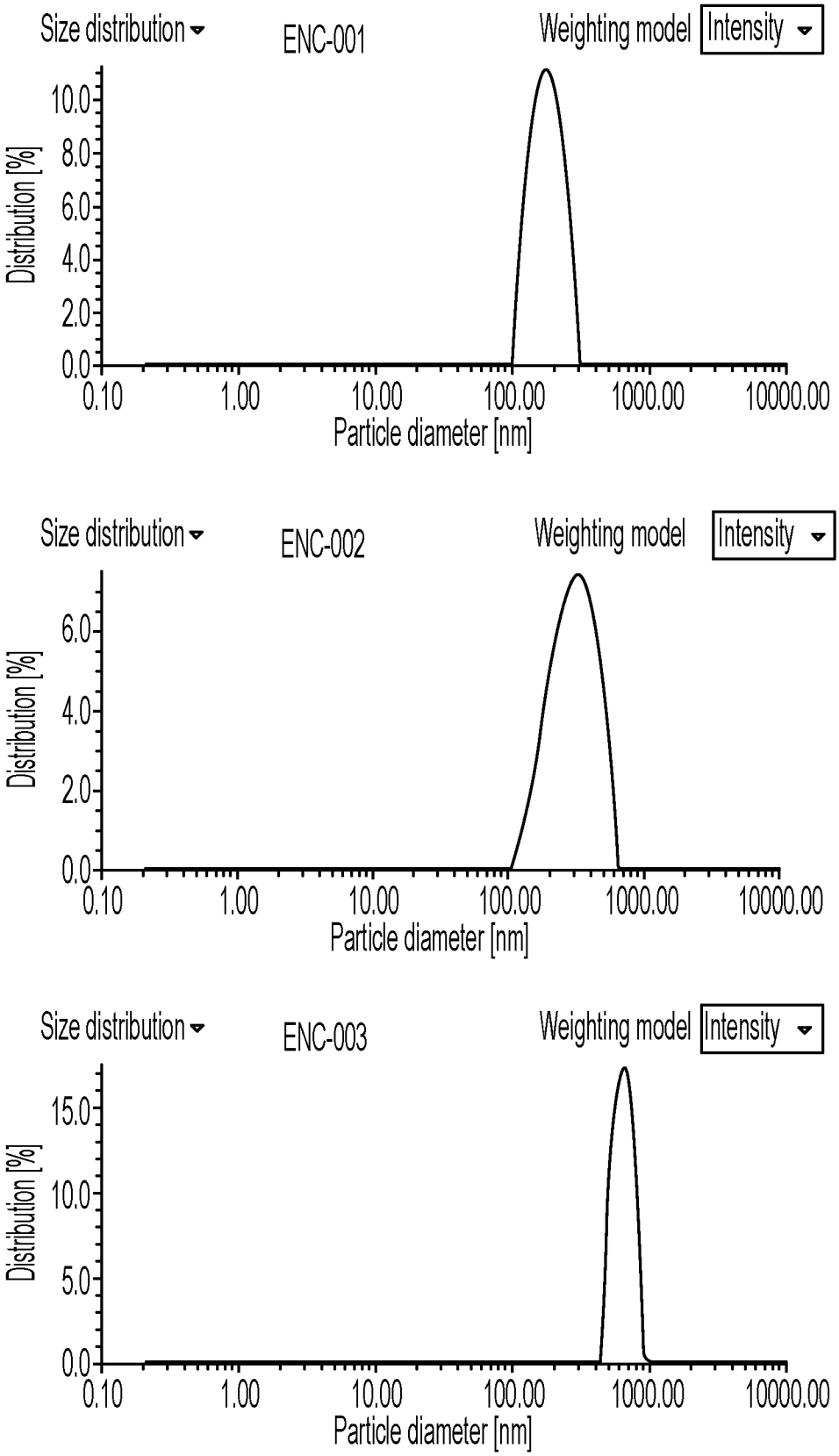

Weighing the zirconia beads in the grinding chamber (50-75% w/w of the chamber capacity)
Preparation of aqueous dispersions of stabilizers (2 to 10% w/w)
Weighing the stabilizer solution in the grinding chamber
API weighing in the grinding chamber (5-15 % w/w)
Nanonizaztion process on DeltaVita® 1 (1000 to 2500 RPM, 60 to 300 min, 4°C to 10°C)
Nanocrystals production (liquid composition)

FIG. 1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ENC-001
Weighting model
Intensity
Distribution [%]
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6.0
4.0
2.0
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1.00
10.00
100.00
1000.00
10000.00
Particle diameter [nm]
Size distribution
ENC-002
Weighting model
Intensity
Distribution [%]
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4.0
2.0
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0.10
1.00
10.00
100.00
1000.00
10000.00
Particle diameter [nm]
Size distribution
ENC-003
Weighting model
Intensity
Distribution [%]
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0.0
0.10
1.00
10.00
100.00
1000.00
10000.00
Particle diameter [nm]

FIG. 2

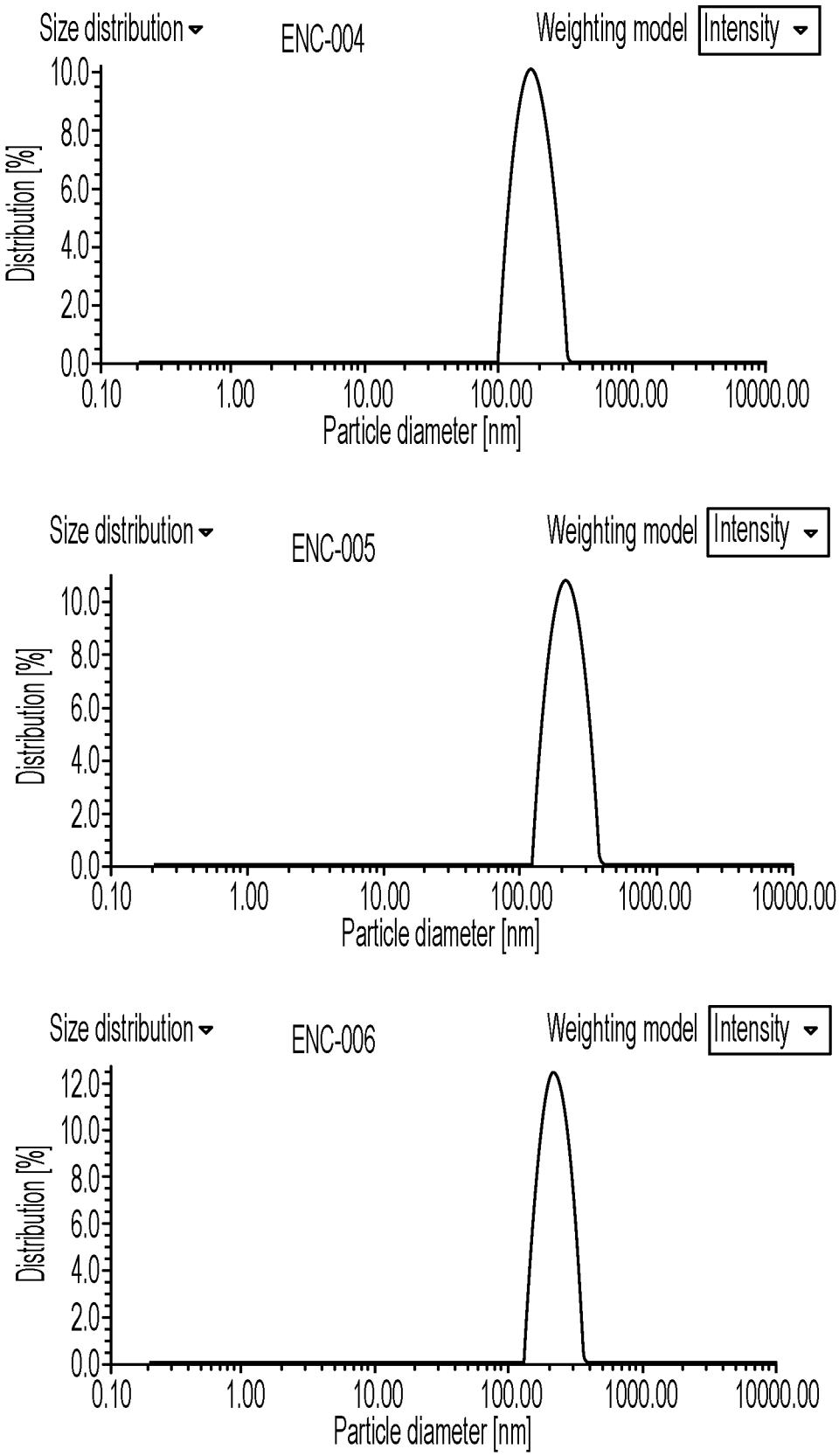

FIG. 2
CONTINUED

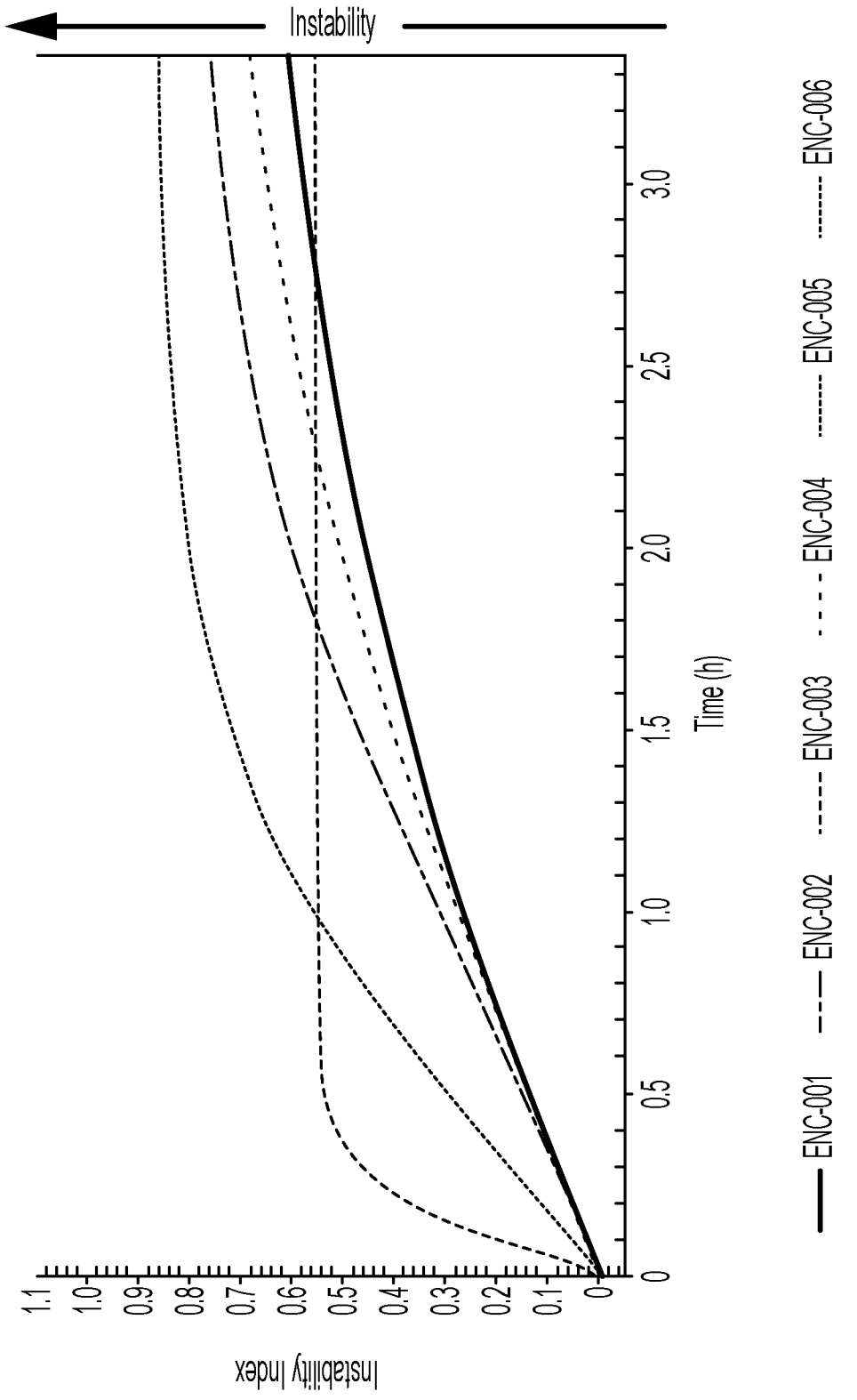
Instability
Instability Index
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1.0
1.5
2.0
2.5
3.0
Time (h)
ENC-001
ENC-002
ENC-003
ENC-004
ENC-005
ENC-006

FIG. 3

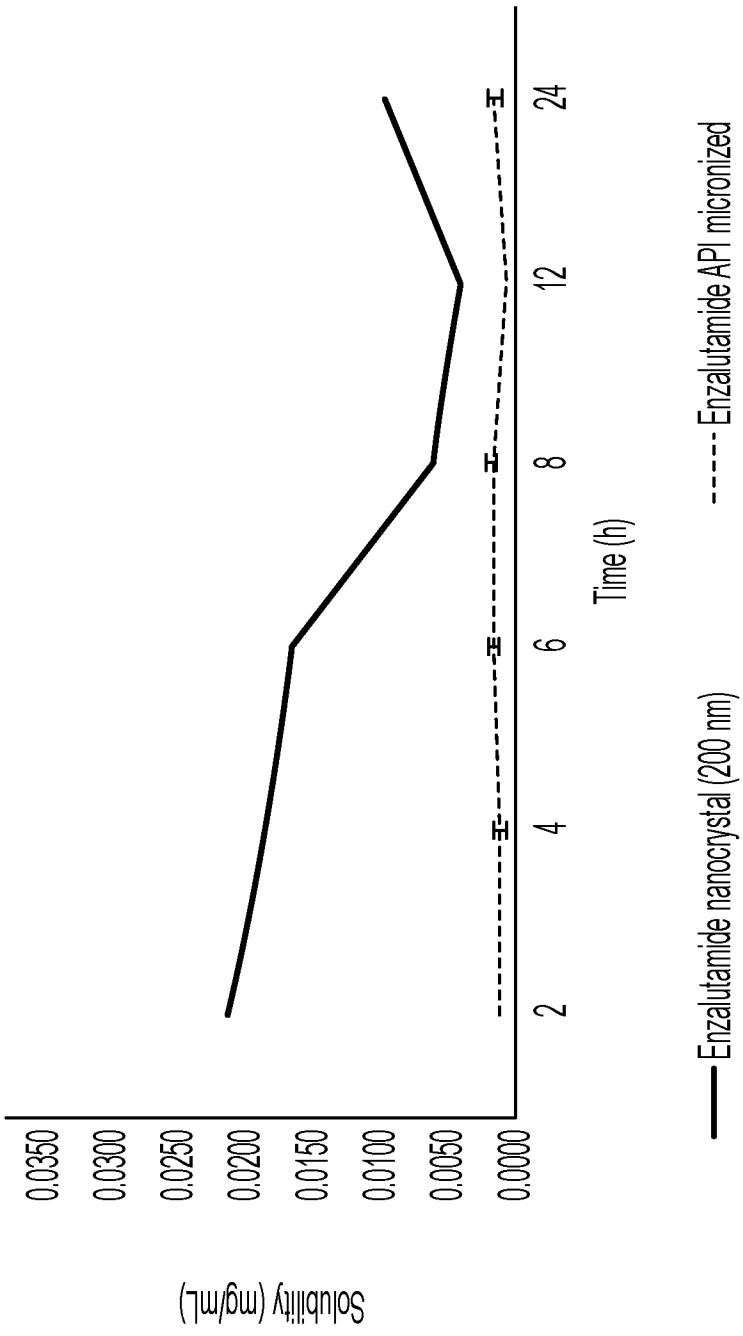
Solubility (mg/mL)
0.0350
0.0300
0.0250
0.0200
0.0150
0.0100
0.0050
0.0000
2
4
6
8
12
24
Time (h)
Enzalutamide nanocrystal (200 nm)
Enzalutamide API micronized

FIG. 4

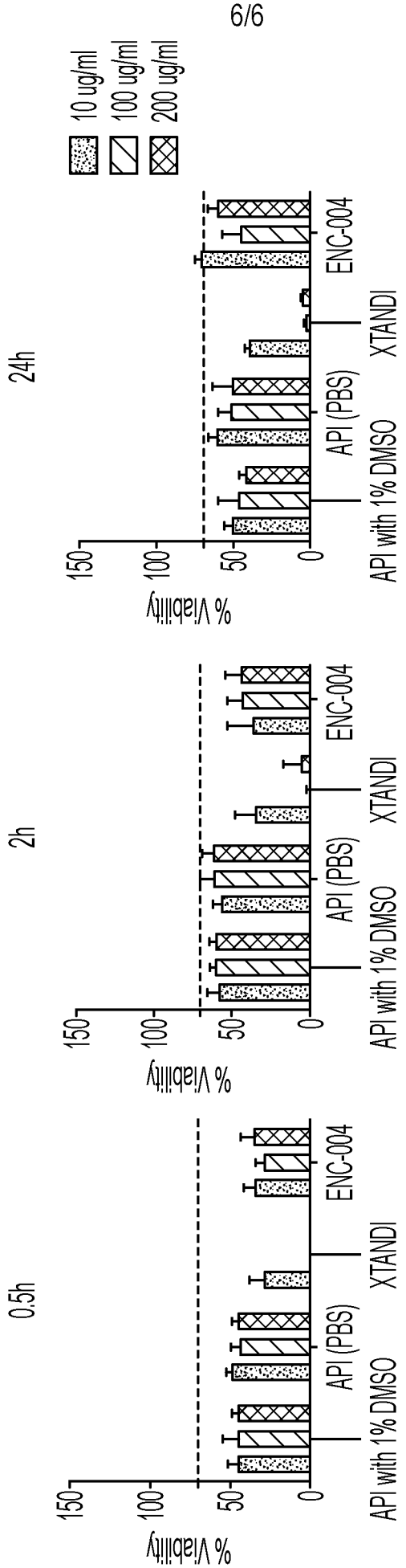

FIG. 5A

FIG. 5B

FIG. 5C

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/062806

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K9/08 A61K9/19 A61K31/4166 A61K47/26
A61K47/32 A61P35/00
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUO XUETING ET AL: "A comparative study on in vitro and in vivo characteristics of enzalutamide nanocrystals versus amorphous solid dispersions and a better prediction for bioavailability based on "spring-parachute" model", INTERNATIONAL JOURNAL OF PHARMACEUTICS, [Online] vol. 628, 25 November 2022 (2022-11-25), page 122333, XP093147591, NL ISSN: 0378-5173, DOI: 10.1016/j.ijpharm.2022.122333 Retrieved from the Internet: URL:https://pdf.sciencedirectassets.com/271189/1-s2.0-S0378517322X00173/1-s2.0-S0378517322008882/main.pdf?X-Amz-Security-Token=IQoJb3JpZ2luX2VjEEwaCXVzLWVhc3QtMSJHMEUCIQDkYIYTawSBXtmt0vQYmLWdlvz4BB3UFa3CdAgaAlg -/--	1-7,21, 22,24, 25, 41-47, 50-54, 56,58, 59,61-64

[X] Further documents are listed in the continuation of Box C.
[X] 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
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"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2024	08/05/2024

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	abstract 1. Introduction; page 1 - page 2 2. Materials and methods; page 2 - page 5 3. Results and discussion; page 5 - page 12 4. Conclusion; page 12 figures; tables -----	32-37,40
X	WO 2020/234448 A1 (HELM AG [DE]) 26 November 2020 (2020-11-26) claims 1-4, 10-53 paragraph [0013] - paragraph [0020] paragraph [0026] paragraph [0031] paragraph [0037] paragraph [0048] paragraph [0066] - paragraph [0091] paragraph [0098] paragraph [0121] - paragraph [0122] paragraph [0133] - paragraph [0134] paragraph [0147] paragraph [0149] - paragraph [0153] paragraph [0155] - paragraph [0156] paragraph [0171] - paragraph [0175] paragraph [0183] - paragraph [0185]; example 3 paragraph [0190] - paragraph [0196]; examples 5, 6 paragraph [0200] - paragraph [0210]; examples 8, 9 ----- -/--	1-4, 7-12,14, 16,17, 21,22, 24,25, 41-44, 47,49-64

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/346207 A1 (GRAHEK ROK [SI] ET AL) 1 December 2016 (2016-12-01)	1,7,10, 11, 13-15, 18-23, 26-31, 38,39, 41,47, 48, 50-55, 61-64
Y	paragraph [0013] - paragraph [0019] paragraph [0133] paragraph [0148] - paragraph [0151] paragraph [0168] - paragraph [0174]; examples reference examples 3-6 figure 2	32-37,40

X	CN 108 815 129 A (TIANJIN SHUANGSHUO PHARMACEUTICAL TECH CO LTD) 16 November 2018 (2018-11-16) claims 1-10 paragraph [0021] - paragraph [0026] paragraph [0041] - paragraph [0043] paragraph [0062] - paragraph [0065]; examples 5, 6	1,2,7, 9-12,21, 22,25, 41,42, 47, 50-54, 58-64

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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