on the GRC. Accumulated evidence has now indicated that in addition to the benzodiazepine and barbiturate binding site, the GRC contains a distinct site for neuroactive steroids. See, e.g., Lan, N. C. et al., Neurochem. Res. (1991) 16:347–356.

[004] Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3α–hydroxy-5-reduced pregnan-20-one and 3α-21-dihydroxy-5-reduced pregnan-20-one, metabolites of hormonal steroids progesterone and deoxycorticosterone, respectively. The ability of these steroid metabolites to alter brain excitability was recognized in 1986 (Majewska, M. D. *et al.*, *Science* 232:1004-1007 (1986); Harrison, N. L. *et al.*, *J. Pharmacol. Exp. Ther.* 241:346-353 (1987)).

[005] Compound of Formula (I), a neuroactive steroid described herein, has been shown to be a positive allosteric modulator of $GABA_A$ receptors that targets synaptic and extrasynaptic $GABA_A$ receptors. As a positive allosteric modulator of $GABA_A$ receptors, Compound 1 serves as a therapeutic agent to treat CNS related disorders, e.g., depression (e.g., postpartum depression and major depressive disorder) and anxiety.

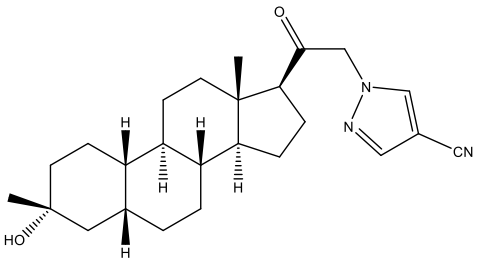
[006] There is a need for neuroactive steroids, in particular 19-NOR C3,3-disubstituted C21-N-pyrazolyl steroids, that display desirable physicochemical properties (e.g., polymorphism, melting point, solubility), are convenient to manufacture and exhibit bioavailability profiles that provide sufficient drug exposures to treat diseases.

[007] As such, the development and manufacture of pharmaceutical formulations with the necessary bioavailability, chemical stability and physical stability and material properties required to produce safe and efficacious oral drug products for the treatment of brain and/or CNS-related disease and disorders remains a significant challenge.

[008] Accordingly, there remains an unmet need to develop pharmaceutical compositions comprising neuroactive steroids and methods of manufacturing said pharmaceutical compositions, whereby the pharmaceutical compositions have the efficacy and safety profiles required by regulatory agencies to produce a commercializable drug product.

SUMMARY ~~OF THE INVENTION~~

[008a] In a first aspect of the present disclosure, there is provided a pharmaceutical composition comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



(**I**),

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) comprises at least one of the following features:

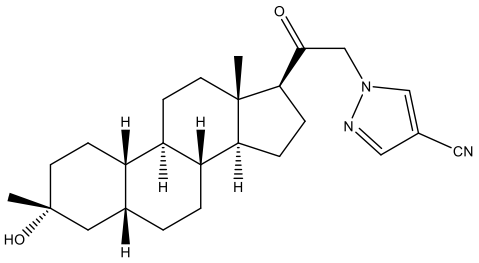
(i) a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm;

(ii) a yield pressure of about 40 MPa to about 200 MPa;

(iii) a strain rate sensitivity of less than about 10%; and

(iv) a contact angle of about 60 degrees to about 110 degrees, wherein the contact angle is measured using a sessile drop technique.

[008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a crystalline form of the compound of formula (**I**)



(**I**),

wherein the pharmaceutical composition comprises at least one of the following features:

(i) a true density of about 1.0 g/cc to about 2.5 g/cc;

(ii) a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc, wherein the tapped density of the pharmaceutical composition is higher than the bulk density;

(iii) a Carr Index of about 10 to about 38;

(iv) about 0.2% to about 90% of the pharmaceutical composition is retained when passed through a 710/25 (microns/mesh) sieve, about 0.2% to about 75% of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve, and about 0.1% to about 55% of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve;

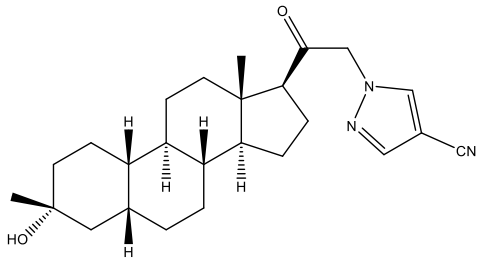
(v) a solid fraction of about 0.5 to about 0.95;

(vi) a flow rate index (FRI) of about 0.1 kg/sec to about 4 kg/sec; and

(vii) the pharmaceutical composition releases at least about 50% of the compound of formula (**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus.

[008c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

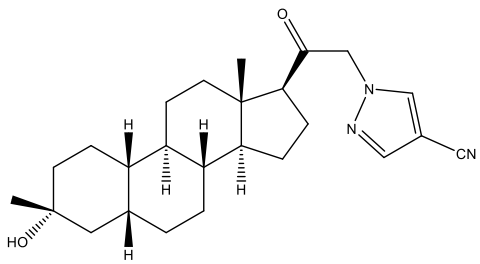
(ii) a filler;

(iii) a lubricant; and

(iv) a glidant.

[008d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(i) about 0.4% (w/w) to about 60% (w/w) of a crystalline form of the compound of formula (**I**)



(**I**),

(ii) about 0% (w/w) to about 90% (w/w) of a brittle filler;

(iii) about 0% (w/w) to about 90% (w/w) of a ductile filler;

(iv) about 0% (w/w) to about 15% (w/w) of a disintegrant;

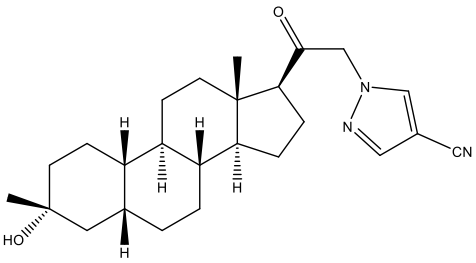
(v) about 0.1% (w/w) to about 5% (w/w) of a lubricant; and

(vi) about 0.1% (w/w) to about 5% (w/w) of a glidant.

[008e] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(A):

(i) about 20 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 105.9 mg of mannitol;

(iii) about 26.2 mg of silicified microcrystalline cellulose;

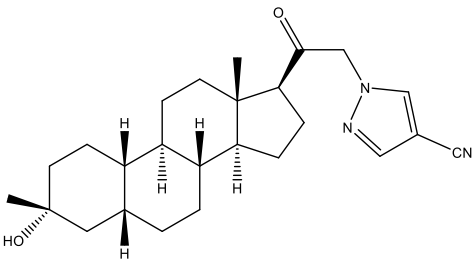
(iv) about 10 mg of croscarmellose sodium;

(v) about 1.7 mg of colloidal silicon dioxide; and

(vi) about 2.9 mg of sodium stearyl fumarate;

(B):

(i) about 25 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 132 mg of mannitol;

(iii) about 32.7 mg of the silicified microcrystalline cellulose;

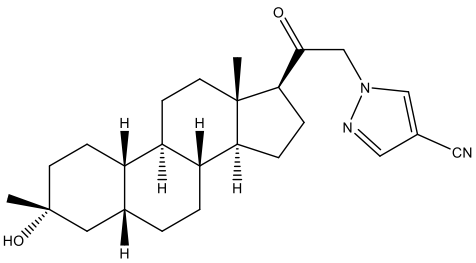
(iv) about 12.5 mg of croscarmellose sodium;

(v) about 2.1 mg of colloidal silicon dioxide; and

(vi) about 3.6 mg of sodium stearyl fumarate;

(C):

(i) about 30 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 159 mg of mannitol;

(iii) about 39.3 mg of the silicified microcrystalline cellulose;

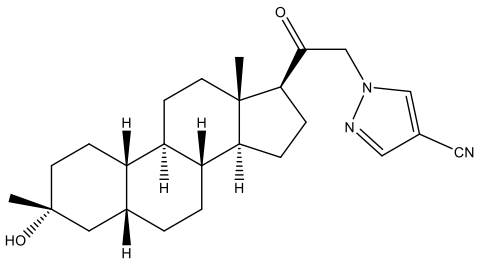
(iv) about 15 mg of croscarmellose sodium;

(v) about 2.5 mg of colloidal silicon dioxide; and

(vi) about 4.4 mg of sodium stearyl fumarate;

(D):

(i) about 40 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 212 mg of mannitol;

(iii) about 52.4 mg of the silicified microcrystalline cellulose;

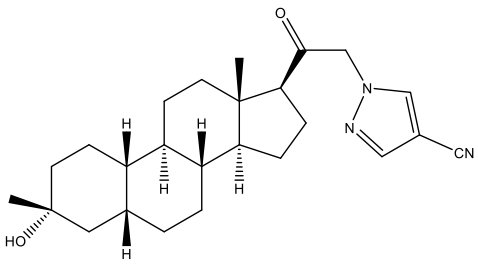
(iv) about 20 mg of croscarmellose sodium;

(v) about 3.3 mg of colloidal silicon dioxide; and

(vi) about 5.8 mg of sodium stearyl fumarate;

(E):

(i) about 50 mg of a crystalline form of the compound of formula (**I**)



(**I**),

(ii) about 265 mg of mannitol;

(iii) about 65.5 mg of the silicified microcrystalline cellulose;

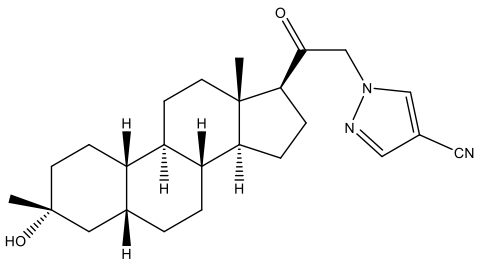
(iv) about 25 mg of croscarmellose sodium;

(v) about 4.2 mg of colloidal silicon dioxide; and

(vi) about 7.3 mg of sodium stearyl fumarate; or

(F):

(i) about 60 mg of a crystalline form of the compound of formula (**I**)



(**I**),

(ii) about 317.7 mg of mannitol;

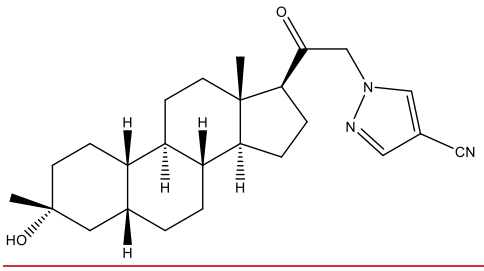
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(iv) about 30 mg of croscarmellose sodium;

(v) about 5 mg of colloidal silicon dioxide; and

(vi) about 8.8 mg of sodium stearyl fumarate.

[008f] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



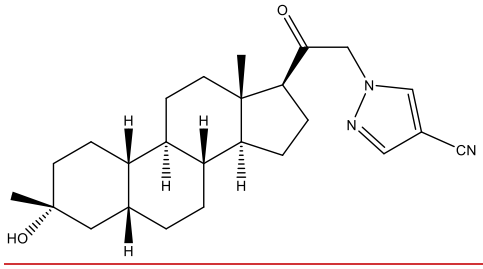
(**I**),

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) have a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm, or about 1 µm to about 20 µm;

optionally, wherein the pharmaceutical composition comprises a filler and one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof.

[008g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

(ii) a filler; and

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition:

(a) has a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc and wherein the tapped density of the pharmaceutical composition is higher than the bulk density;

(b) has an average flow rate index (FRI) of about 0.05 to about 3.1 kg/sec;

(c) releases at least about 50% of the compound of formula (**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus; or

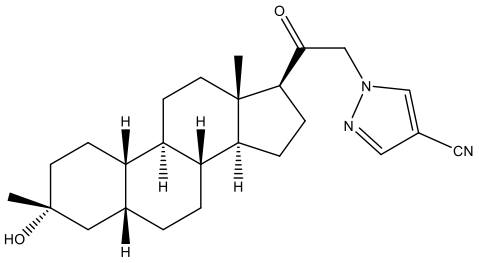
(d) exhibits the following dissolution profile:

at least about 70% of the compound of formula (**I**) is released after about 20 minutes; and at least about 80% of the compound of formula (**I**) is released after about 30 minutes, when tested in about 500 mL to about 900 mL of 50 mM sodium phosphate buffer, pH 6.8 with about 0.2% to about 0.6% SDS in a USP 2 apparatus at about 37°C.

[008h] In another aspect of the present disclosure, there is provided a dosage form intended for oral administration comprising a pharmaceutical composition as disclosed herein, optionally, wherein the dosage form is selected from the group consisting of a powder, a sachet, a stickpack, a capsule, a minitab, and a tablet.

[008i] In yet another aspect of the present disclosure, there is provided a process for making a pharmaceutical composition comprising:

(a) micronizing a crystalline form of the compound of formula (**I**) to obtain a micronized crystalline form of the compound of formula (**I**)



(**I**),

wherein the micronized crystalline form of the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm;

(b) blending the micronized crystalline form of the compound of formula (**I**) with one or more pharmaceutically acceptable excipients to obtain a blend;

(c) granulating the blend to obtain granules;

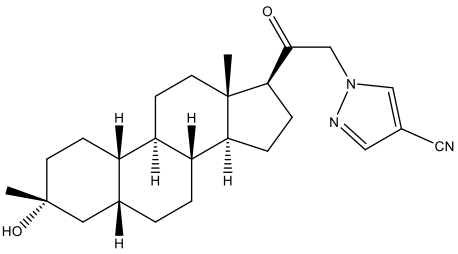
(d) milling the granules to obtain an intragranular phase; and

(e) blending the intragranular phase with one or more extragranular pharmaceutical excipients to obtain the pharmaceutical composition.

[008j] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition/composition as disclosed herein or a dosage form as disclosed herein in the manufacture of a medicament for treating insomnia, major depressive disorder, bipolar disorder, postpartum depression, anxiety, or treatment-resistant depression.

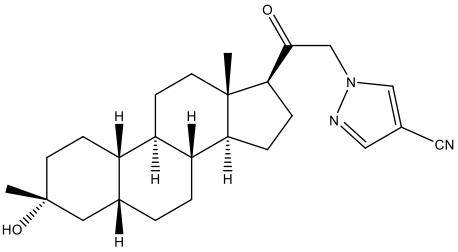
[008k] In another aspect of the present disclosure, there is provided a pharmaceutical composition/composition as disclosed herein or a dosage form as disclosed herein, for use in therapy.

[009] In an ~~aspect~~example, provided herein are pharmaceutical compositions of the compound of formula (**I**)



(I).

[0010] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



(I)

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) comprises at least one of the following features:

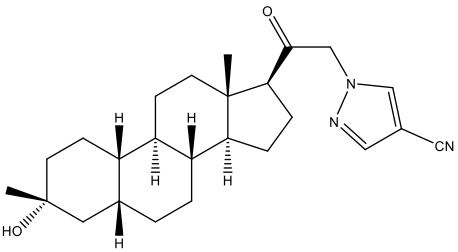
(i) a particle size distribution which is defined by a D_{90} of about 1 μm to about 100 μm;

(ii) a yield pressure of about 40 MPa to about 200 MPa;

(iii) a strain rate sensitivity of less than about 10%; and

(iv) a contact angle of about 60 degrees to about 110 degrees, wherein the contact angle is measured using a sessile drop technique.

[0011] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising a crystalline form of the compound of formula (**I**)



(I)

wherein the pharmaceutical composition comprises at least one of the following features:

(i) a true density of about 1.0 g/cc to about 2.5 g/cc;

(ii) a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc, wherein the tapped density of the pharmaceutical composition is higher than the bulk density;

(iii) a Carr Index of about 10 to about 38;

(iv) about 0.2% to about 90% of the pharmaceutical composition is retained when passed through a 710/25 (microns/mesh) sieve, about 0.2% to about 75% of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve, and about 0.1% to about 55% of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve;

(v) a solid fraction of about 0.5 to about 0.95;

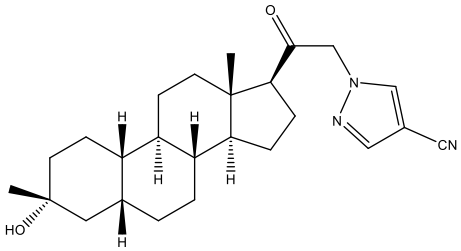
(vi) a flow rate index (FRI) of about 0.1 kg/sec to about 4 kg/sec; and

(vii) the pharmaceutical composition releases at least about 50% of the compound of formula

(**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus.

[0012] In various ~~embodiment~~example**s**, provided herein are pharmaceutical compositions comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**)

(ii) a filler;

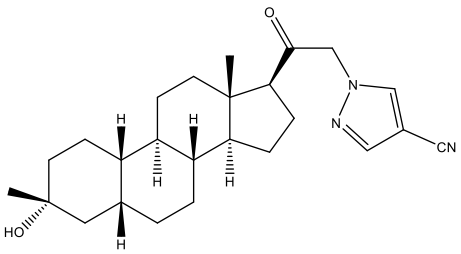
(iii) a lubricant; and

(iv) a glidant.

[0013] In various ~~embodiment~~example**s**, provided herein are pharmaceutical compositions comprising:

(i) about 0.4% (w/w) to about 60% (w/w) of a crystalline form of the compound of formula

(**I**)



(**I**);

(ii) about 0% (w/w) to about 90% (w/w) of a brittle filler;

(iii) about 0% (w/w) to about 90% (w/w) of a ductile filler;

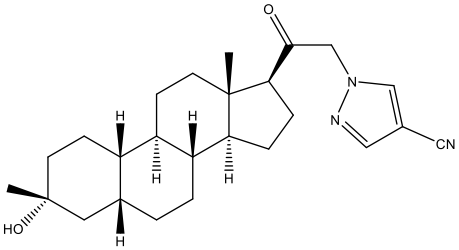
(iv) about 0% (w/w) to about 15% (w/w) of a disintegrant;

(v) about 0.1% (w/w) to about 5% (w/w) of a lubricant; and

(vi) about 0.1% (w/w) to about 5% (w/w) of a glidant.

[0014] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 0.4% (w/w) to about 36% (w/w) of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 15% (w/w) to about 75% (w/w) of a brittle filler;

(iii) about 10% (w/w) to about 60 % (w/w) of a ductile filler;

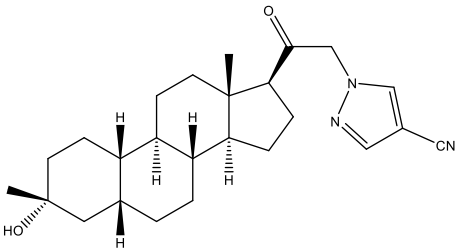
(iv) about 3% (w/w) to about 12% (w/w) of a disintegrant;

(v) about 0.25% (w/w) to about 5% (w/w) of a glidant; and

(vi) about 0.5% (w/w) to about 3% (w/w) of a lubricant.

[0015] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 10% (w/w) to about 15% (w/w) of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 60% (w/w) to about 70% (w/w) of a brittle filler;

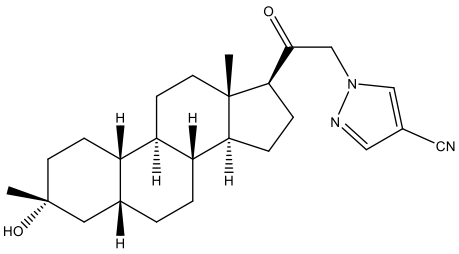
(iii) about 10% (w/w) to about 20 % (w/w) of a ductile filler;

(iv) about 4% (w/w) to about 8% (w/w) of a disintegrant;

(v) about 0.5% (w/w) to about 2% (w/w) of a glidant; and

(vi) about 1% (w/w) to about 2% (w/w) of a lubricant.

[0016] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising: (i) about 20 mg of a crystalline form of the compound of formula (**I**)



(I);

(ii) about 105.9 mg of mannitol;

(iii) about 26.2 mg of silicified microcrystalline cellulose;

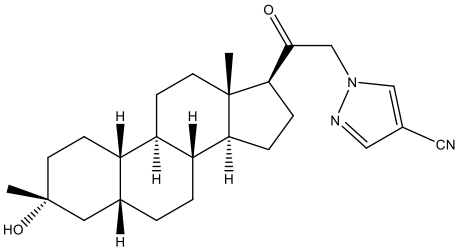
(iv) about 10 mg of croscarmellose sodium;

(v) about 1.7 mg of colloidal silicon dioxide; and

(vi) about 2.9 mg of sodium stearyl fumarate.

[0017] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 25 mg of a crystalline form of the compound of formula (**I**)



(I);

(ii) about 132 mg of mannitol;

(vii) about 32.7 mg of the silicified microcrystalline cellulose;

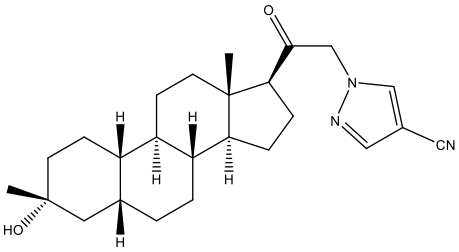
(viii) about 12.5 mg of croscarmellose sodium;

(ix) about 2.1 mg of colloidal silicon dioxide; and

(x) about 3.6 mg of sodium stearyl fumarate.

[0018] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 30 mg of a crystalline form of the compound of formula (**I**)



(I);

(ii) about 159 mg of mannitol;

(iii) about 39.3 mg of the silicified microcrystalline cellulose;

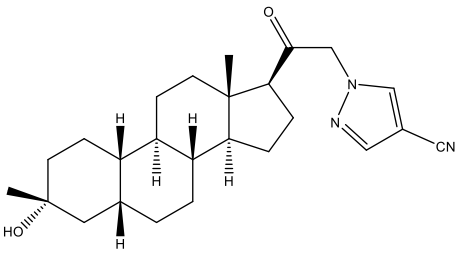
(iv) about 15 mg of croscarmellose sodium;

(v) about 2.5 mg of colloidal silicon dioxide; and

(vi) about 4.4 mg of sodium stearyl fumarate.

[0019] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 40 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 212 mg of mannitol;

(vii) about 52.4 mg of the silicified microcrystalline cellulose;

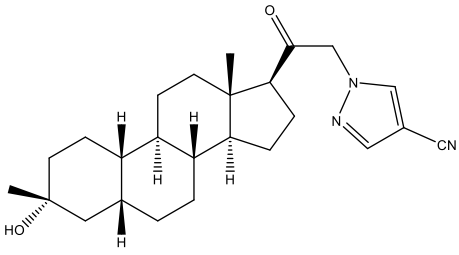
(viii) about 20 mg of croscarmellose sodium;

(ix) about 3.3 mg of colloidal silicon dioxide; and

(x) about 5.8 mg of sodium stearyl fumarate.

[0020] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) about 50 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 265 mg of mannitol;

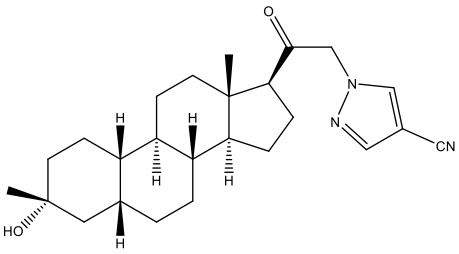
(iii) about 65.5 mg of the silicified microcrystalline cellulose;

(iv) about 25 mg of croscarmellose sodium;

(v) about 4.2 mg of colloidal silicon dioxide; and

(vi) about 7.3 mg of sodium stearyl fumarate.

[0021] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising: (i) about 60 mg of a crystalline form of the compound of formula (**I**)



(I);

(ii) about 317.7 mg of mannitol;

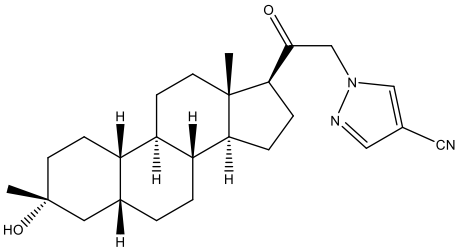
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(iv) about 30 mg of croscarmellose sodium;

(v) about 5 mg of colloidal silicon dioxide; and

(vi) about 8.8 mg of sodium stearyl fumarate.

[0022] In various ~~embodiment~~example**s**, provided herein are pharmaceutical compositions comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



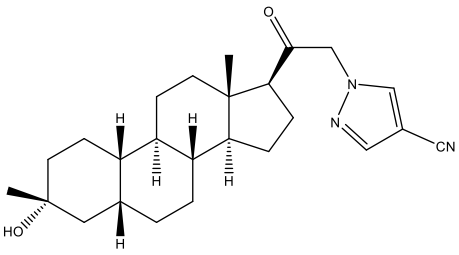
(I);

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) have a

particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm.

[0023] In various ~~embodiment~~example**s**, provided herein are pharmaceutical compositions comprising:

(i) a plurality of particles of a crystalline form of the compound of formula (**I**)



(I);

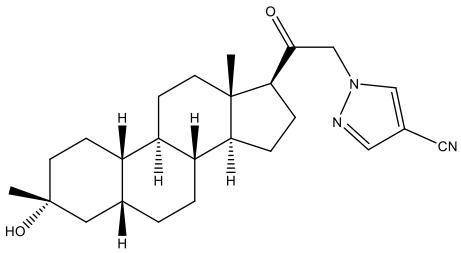
(ii) a filler; and

(vii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof, wherein the plurality of particles of the crystalline form of

the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 20 µm.

[0024] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

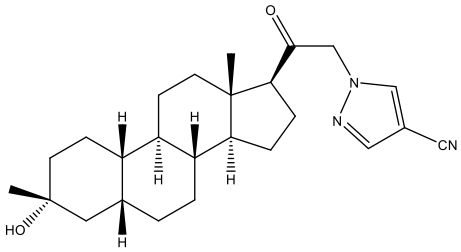
(ii) a filler; and

(vii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition has a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc and wherein the tapped density of the pharmaceutical composition is higher than the bulk density.

[0025] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

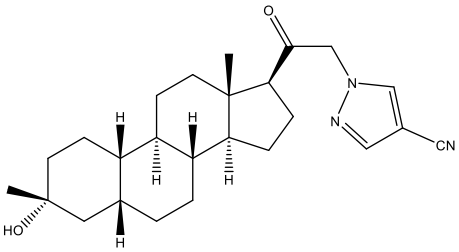
(ii) a filler; and

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition has an average flow rate index (FRI) of about 0.05 to about 3.1 kg/sec.

[0026] In various ~~embodiment~~examples, provided herein are pharmaceutical compositions comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

(ii) a filler; and

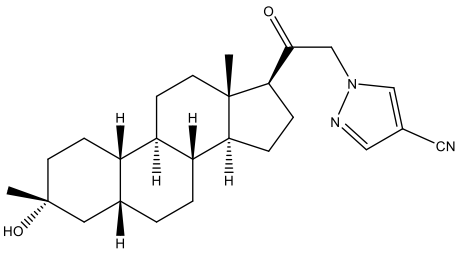
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition releases at least about 50% of the compound of formula

(**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus.

[0027] In various ~~embodiment~~example<u>s</u>, provided herein are pharmaceutical compositions comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

(ii) a filler; and

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof;

wherein the pharmaceutical composition exhibits the following dissolution profile:

at least about 70% of the compound of formula (**I**) is released after about 20 minutes; and

at least about 80% of the compound of formula (**I**) is released after about 30 minutes,

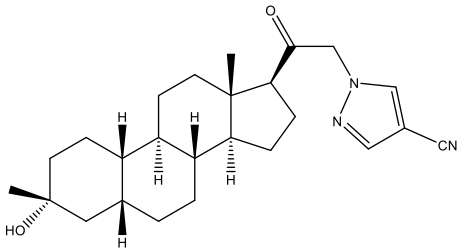
when tested in about 500 mL to about 900 mL of 50 mM sodium phosphate buffer, pH 6.8 with about 0.2% to about 0.6% SDS in a USP 2 apparatus at about 37°C.

[0028] In another ~~aspect~~example, provided herein are dosage forms intended for oral administration comprising a pharmaceutical composition described herein.

[0029] In another ~~aspect~~example, provided herein are methods of making a pharmaceutical composition described herein.

[0030] In various ~~embodiment~~examples, provided herein is a process for making a pharmaceutical composition comprising:

(a) micronizing a crystalline form of the compound of formula (**I**) to obtain a micronized crystalline form of the compound of formula (**I**)



(**I**),

wherein the micronized crystalline form of the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of about 1 μm to about 100 μm;

(b) blending the micronized crystalline form of the compound of formula (**I**) with one or more pharmaceutically acceptable excipients to obtain a blend;

(c) granulating the blend to obtain granules;

(d) milling the granules to obtain an intragranular phase; and

(e) blending the intragranular phase with one or more extragranular pharmaceutical excipients to obtain the pharmaceutical composition.

[0031] In another ~~aspect~~example, provided herein are pharmaceutical compositions comprising the compound of formula (**I**) useful for the treatment of the various conditions, diseases, and disorders described herein. In various ~~embodiment~~examples, the condition, disease, or disorder is insomnia. In various ~~embodiment~~examples, the condition, disease, or disorder is major depressive disorder. In various ~~embodiment~~examples, the condition, disease, or disorder is bipolar disorder. In various ~~embodiment~~examples, the condition, disease, or disorder is insomnia. In various ~~embodiment~~examples, the condition, disease, or disorder is postpartum depression. In various ~~embodiment~~examples, the condition, disease, or disorder is anxiety. In various ~~embodiment~~examples, the condition, disease, or disorder is treatment-resistant depression.

BRIEF DESCRIPTION OF THE DRAWINGS

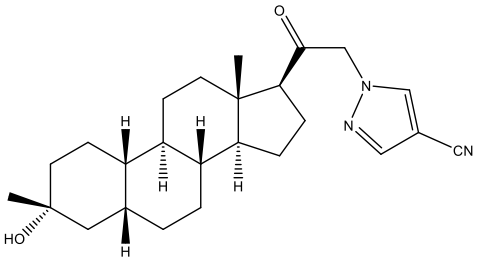
[0032] FIG. 1A is an exemplary X-ray powder diffraction pattern of crystalline Form A of Compound 1.

[0033] FIG. 1B shows exemplary thermogravimetric analysis (upper) and differential scanning calorimetry (lower) curves for crystalline Form A of Compound 1.

CLAIMS

We claim:

1. A pharmaceutical composition comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



(**I**),

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) comprises at least one of the following features:

(i) a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm;

(ii) a yield pressure of about 40 MPa to about 200 MPa;

(iii) a strain rate sensitivity of less than about 10%; and

(iv) a contact angle of about 60 degrees to about 110 degrees, wherein the contact angle is measured using a sessile drop technique.

2. The pharmaceutical composition of claim 1, wherein the plurality of particles of the crystalline form of the compound of formula (**I**) (a) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 20 µm~~.~~, or

~~3. The pharmaceutical composition of claim 1 or 2, wherein the plurality of particles of the crystalline form of the compound of formula (I) has a particle size distribution which is defined by a D_{90} of~~ about 1 µm to about 13 µm~~.~~;

~~4. The pharmaceutical composition of any one of claims 1-3, wherein the plurality of particles of the crystalline form of the compound of formula (I)~~ (b) have a contact angle of about 70 degrees to about 80 degrees, ~~wherein the contact angle is measured using a sessile drop technique.~~ or

~~5. The pharmaceutical composition of any one of claims 1-4, wherein the plurality of particles of the crystalline form of the compound of formula (I) have a contact angle of~~ about 70 degrees to about 75 degrees, wherein the contact angle is measured using a sessile drop technique; and/or ~~.~~

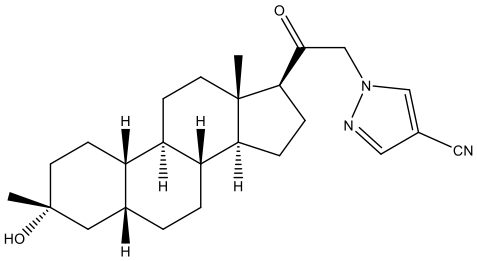
~~6.~~ ~~The pharmaceutical composition of any one of claims 1-5, wherein~~ (c) the yield pressure of the crystalline form of the compound of formula (**I**) is about 60 MPa to about 100 MPa~~.~~,

~~7.~~ ~~The pharmaceutical composition of any one of claims 1-6, wherein the yield pressure of the crystalline form of the compound of formula (I) is~~ about 70 MPa to about 95 MPa~~.~~, or

~~8.~~ ~~The pharmaceutical composition of any one of claims 1-7, wherein the yield pressure of the crystalline form of the compound of formula (I) is~~ about 80 MPa to about 90 MPa.

~~9.~~3. A pharmaceutical composition comprising a crystalline form of the compound of formula

(**I**)



(**I**),

wherein the pharmaceutical composition comprises at least one of the following features:

(i) a true density of about 1.0 g/cc to about 2.5 g/cc;

(ii) a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc, wherein the tapped density of the pharmaceutical composition is higher than the bulk density;

(iii) a Carr Index of about 10 to about 38;

(iv) about 0.2% to about 90% of the pharmaceutical composition is retained when passed through a 710/25 (microns/mesh) sieve, about 0.2% to about 75% of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve, and about 0.1% to about 55% of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve;

(v) a solid fraction of about 0.5 to about 0.95;

(vi) a flow rate index (FRI) of about 0.1 kg/sec to about 4 kg/sec; and

(vii) the pharmaceutical composition releases at least about 50% of the compound of formula (**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus.

~~10.~~4. The pharmaceutical composition of claim ~~3~~9, wherein

(a) the true density is about 1.1 g/cc to about 2.0 g/cc~~.~~, or

~~11. The pharmaceutical composition of claim 9 or 10, wherein the true density is~~ about 1.2 g/cc to about 1.6 g/cc;~~.~~

~~12. The pharmaceutical composition of any one of claims 9-11, wherein~~ (b) the tapped density is about 0.3 g/cc to about 0.9 g/cc,~~.~~

~~13. The pharmaceutical composition of any one of claims 9-12, wherein the tapped density is~~ about 0.35 g/cc to about 0.85 g/cc,~~.~~

~~14. The pharmaceutical composition of any one of claims 9-13, wherein the tapped density is~~ about 0.4 g/cc to about 0.85 g/cc,~~.~~

~~15. The pharmaceutical composition of any one of claims 9-14, wherein the tapped density is~~ about 0.6 g/cc to about 0.85 g/cc,~~.~~

~~16. The pharmaceutical composition of any one of claims 9-15, wherein the tapped density is~~ or about 0.7 g/cc to about 0.8 g/cc;~~.~~

~~17. The pharmaceutical composition of any one of claims 9-16, wherein~~ (c) the bulk density is about 0.2 g/cc to about 0.7 g/cc,~~.~~

~~18. The pharmaceutical composition of any one of claims 9-17, wherein the bulk density is~~ about 0.3 g/cc to about 0.65 g/cc,~~.~~

~~19. The pharmaceutical composition of any one of claims 9-17, wherein the bulk density is~~ about 0.4 g/cc to about 0.7 g/cc~~.~~,

~~20. The pharmaceutical composition of any one of claims 9-19, wherein the bulk density is~~ or about 0.5 g/cc to about 0.65 g/cc;~~.~~

~~21. The pharmaceutical composition of any one of claims 9-20, wherein~~ (d) about 0.5% to about 75%, ~~of the pharmaceutical composition is retained when passed through a 710/25 (microns/ mesh) sieve.~~

~~22. The pharmaceutical composition of any one of claims 9-21, wherein~~ or about 0.5% to about 60% of the pharmaceutical composition is retained when passed through a 710/25 (microns/mesh) sieve;~~.~~

~~23. The pharmaceutical composition of any one of claims 9-22, wherein~~ (e) about 2% to about 50%~~, of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve.~~

~~24. The pharmaceutical composition of any one of claims 9-23, wherein~~ or about 5% to about 35% of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve~~;~~.

~~25. The pharmaceutical composition of any one of claims 9-24, wherein~~ (f) about 0.5% to about 30%, or ~~of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve.~~

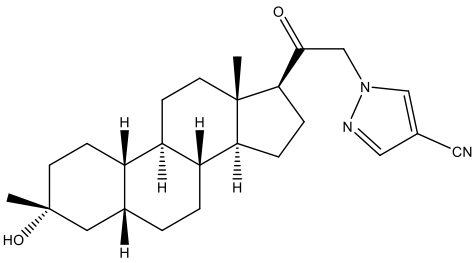
~~26. The pharmaceutical composition of any one of claims 9-25, wherein~~ about 1% to about 25% of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve~~.~~; and/or

~~27. The pharmaceutical composition of any one of claims 9-26, wherein~~ (g) the solid fraction is about 0.55 to about 0.95, or~~.~~

~~28. The pharmaceutical composition of any one of claims 9-27, wherein the solid fraction is~~ about 0.6 to about 0.85.

~~29.~~5. A pharmaceutical composition comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

(ii) a filler;

(iii) a lubricant; and

(iv) a glidant.

~~30.~~6. The pharmaceutical composition of claim 5~~29~~, wherein the filler comprises a brittle filler, a ductile filler, or combinations thereof~~;~~, optionally,

~~31. The pharmaceutical composition of claim 29 or 30,~~ wherein the filler comprises a brittle filler and a ductile filler~~;~~, or, optionally,

~~32. The pharmaceutical composition of claim 31,~~ wherein the mass ratio of the brittle filler to the ductile filler is in the range of about 1 to 9 to about 9 to 1~~.~~

~~33. The pharmaceutical composition of claim 31 or 32, wherein the mass ratio of the brittle filler to the ductile filler is in the range of~~ about 1 to 5 to about 5 to 1~~.~~,

~~34. The pharmaceutical composition of any one of claims 31-33, wherein the mass ratio of the brittle filler to the ductile filler is in the range of~~ about 1 to 4 to about 4 to 1.

~~35.~~7. The pharmaceutical composition of ~~any one of claims 30-34~~claim 5 or 6, wherein (a) the brittle filler is selected from the group consisting of a sugar, an inorganic material, and combinations thereof~~.~~;

~~36. The pharmaceutical composition of claim 35~~optionally, wherein the sugar is selected from the group consisting of mannitol, lactose, sucrose, fructose, glucose, maltose and combinations thereof~~.~~;

~~37. The pharmaceutical composition of claim 35~~optionally, wherein the inorganic material is selected from the group consisting of dibasic calcium phosphate, hydroxyapatite, sodium carbonate, sodium bicarbonate, calcium carbonate, bentonite, kaolin, and combinations thereof~~.~~;

~~38. The pharmaceutical composition of any one of claims 30-34~~optionally, wherein the brittle filler is selected from the group consisting of mannitol, lactose, dibasic calcium phosphate, and combinations thereof~~.~~;

~~39. The pharmaceutical composition of any one of claims 30-38, wherein~~ (b) the ductile filler is selected from the group consisting of a microcrystalline cellulose, a starch, a polysaccharide, a cellulose, a polyvinylpyrrolidone, a polyvinyl acrylate, and combinations thereof~~.~~;

~~40. The pharmaceutical composition of claim 39~~optionally, wherein the cellulose is selected from the group consisting of a hydroxypropylcellulose, a hypromellose, a carboxymethylcellulose, a methylcellulose, a hydroxypropylmethylcellulose, and combinations thereof~~.~~;

~~41. The pharmaceutical composition of any one of claims 30-38~~optionally, wherein the ductile filler is a microcrystalline cellulose, or~~.~~

~~42. The pharmaceutical composition of any one of claims 30-38, wherein the ductile filler is~~ a starch;~~.~~

~~43. The pharmaceutical composition of claim 30 or 31, wherein~~ (c) the filler comprises mannitol and microcrystalline cellulose and the mass ratio of mannitol to the microcrystalline cellulose is about 1:4 to about 4:1;~~.~~

~~44.~~ ~~The pharmaceutical composition of claim 30 or 31, wherein~~ (d) the filler comprises lactose and microcrystalline cellulose and the mass ratio of lactose to the microcrystalline cellulose is about 1:4 to about 4:1~~.~~;

~~45.~~ ~~The pharmaceutical composition of claim 30 or 31, wherein~~ (e) the filler comprises dibasic calcium phosphate and microcrystalline cellulose and the mass ratio of dibasic calcium phosphate to the microcrystalline cellulose is about 1:4 to about 4:1;~~.~~

~~46.~~ ~~The pharmaceutical composition of claim 30 or 31, wherein~~ (f) the filler comprises mannitol and a starch and the mass ratio of mannitol to the starch is about 1:4 to about 4:1;~~.~~

~~47.~~ ~~The pharmaceutical composition of claim 30 or 31, wherein~~ (g) the filler comprises dibasic calcium phosphate and a starch and the mass ratio of dibasic calcium phosphate to the starch is about 1:4 to about 4:1;~~.~~

~~48.~~ ~~The pharmaceutical composition of any one of claims 29-47, wherein~~ (h) the lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, stearic acid, glyceryl behenate, and combinations thereof;~~.~~

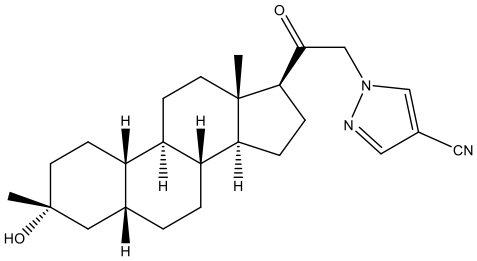
~~49.~~ ~~The pharmaceutical composition of any one of claims 29-48, wherein~~ (i) the glidant is selected from the group consisting of colloidal silicon dioxide, talc, kaolin, bentonite, and combinations thereof; and/or~~.~~

~~50.~~ ~~The pharmaceutical composition of any one of claims 29-49~~(j) optionally, wherein the pharmaceutical composition further comprises a disintegrant;~~.~~

~~51.~~ ~~The pharmaceutical composition of claim 50~~optionally, wherein the disintegrant is selected from the group consisting of sodium starch glycolate, a crospovidone, croscarmellose sodium, and combinations thereof.

~~52.~~8. A pharmaceutical composition comprising:

(i) about 0.4% (w/w) to about 60% (w/w) of a crystalline form of the compound of formula (**I**)



(**I**),

(ii) about 0% (w/w) to about 90% (w/w) of a brittle filler;

(iii) about 0% (w/w) to about 90% (w/w) of a ductile filler;

(iv) about 0% (w/w) to about 15% (w/w) of a disintegrant;

(v) about 0.1% (w/w) to about 5% (w/w) of a lubricant; and

(vi) about 0.1% (w/w) to about 5% (w/w) of a glidant.

~~53.~~9. The pharmaceutical composition of claim ~~852~~, wherein (a) the amount of the crystalline form of the compound of formula (**I**) is about 0.4% (w/w) to about 40% (w/w), about 0.4% (w/w) to about 36% (w/w), or ~~.~~

~~54. The pharmaceutical composition of claim 52 or 53, wherein the amount of the crystalline form of the compound of formula (I) is~~ about 10% (w/w) to about 40% (w/w), or about 10% (w/w) to about 15% (w/w);~~.~~

~~55. The pharmaceutical composition of any one of claims 52-54, wherein~~ (b) the amount of the brittle filler is about 15% (w/w) to about 75% (w/w), about 30% (w/w) to about 75% (w/w), about 60% (w/w) to about 70% (w/w), or ~~.~~

~~56. The pharmaceutical composition of any one of claims 52-55, wherein the amount of the brittle filler is~~ about 41% (w/w) to about 45% (w/w);~~.~~

~~57. The pharmaceutical composition of any one of claims 52-56, wherein~~ (c) the amount of the ductile filler is about 5% (w/w) to about 25% (w/w),~~.~~ about 10% (w/w) to about 60% (w/w), about 10% (w/w) to about 20% (w/w), or

~~58. The pharmaceutical composition of any one of claims 52-56, wherein the amount of the ductile filler is~~ about 41% (w/w) to about 45% (w/w)~~.~~;

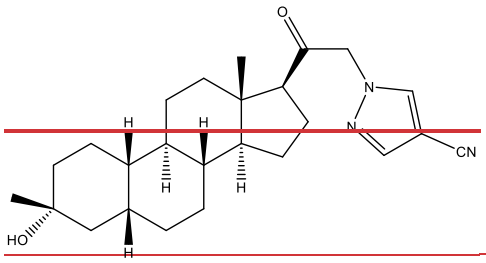
~~59. The pharmaceutical composition of any one of claims 52-58, wherein~~ (d) the amount of the disintegrant is about 2.5% (w/w) to about 10% (w/w), about 3% (w/w) to about 12% (w/w), or about 4% (w/w) to about 8% (w/w);~~.~~

~~60. The pharmaceutical composition of any one of claims 52-59, wherein~~ (e) the amount of the lubricant is about 0.25 % (w/w) to about 3.00 % (w/w), about 0.5% (w/w) to about 3% (w/w), or about 1% (w/w) to about 2% (w/w); and/or~~.~~

~~61. The pharmaceutical composition of any one of claims 52-60, wherein~~ (f) the amount of glidant is about 0.25% (w/w) to about 2.5% (w/w), about 0.5% (w/w) to about 2% (w/w), or about 0.25% (w/w) to about 5% (w/w);~~.~~

~~62.~~ optionally, (g) wherein the ~~A~~ pharmaceutical composition comprises~~ing~~:

(i) about 0.4% (w/w) to about 36% (w/w) of a crystalline form of the compound of formula (**I**);



~~(I);~~

(ii) about 15% (w/w) to about 75% (w/w) of a brittle filler;

(iii) about 10% (w/w) to about 60 % (w/w) of a ductile filler;

(iv) about 3% (w/w) to about 12% (w/w) of a disintegrant;

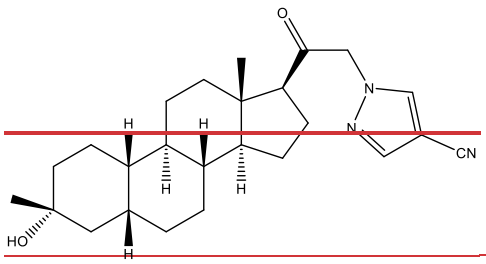
(v) about 0.25% (w/w) to about 5% (w/w) of a glidant; and

(vi) about 0.5% (w/w) to about 3% (w/w) of a lubricant;~~.~~

or

~~63.~~ optionally, (h) wherein the~~A~~ pharmaceutical composition comprises~~ing~~:

(i) about 10% (w/w) to about 15% (w/w) of a crystalline form of the compound of formula (**I**);



~~(I);~~

(ii) about 60% (w/w) to about 70% (w/w) of a brittle filler;

(iii) about 10% (w/w) to about 20 % (w/w) of a ductile filler;

(iv) about 4% (w/w) to about 8% (w/w) of a disintegrant;

(v) about 0.5% (w/w) to about 2% (w/w) of a glidant; and

(vi) about 1% (w/w) to about 2% (w/w) of a lubricant.

~~64.~~10. The pharmaceutical composition of ~~any one of claims 52-63~~claim 8 or 9, wherein (a) the brittle filler is mannitol~~.~~

~~65. The pharmaceutical composition of any one of claims 52-63, wherein the brittle filler is~~ lactose, or~~.~~

~~66. The pharmaceutical composition of any one of claims 52-63, wherein the brittle filler is~~ dibasic calcium phosphate;~~.~~

~~67. The pharmaceutical composition of any one of claims 52-66, wherein~~ (b) the ductile filler is a microcrystalline cellulose, or ~~.~~

~~68. The pharmaceutical composition of any one of claims 52-66, wherein the ductile filler is~~ a starch~~;~~.

~~69. The pharmaceutical composition of any one of claims 52-68, wherein~~ (c) the disintegrant is selected from the group consisting of sodium starch glycolate, a crosslinked polyvinylpyrrolidone, croscarmellose sodium, and combinations thereof~~,~~ optionally,

~~70. The pharmaceutical composition of claim 69,~~ wherein the disintegrant is croscarmellose sodium or~~.~~

~~71. The pharmaceutical composition of claim 69, wherein the disintegrant is~~ a crosslinked polyvinylpyrrolidone~~;~~.

~~72. The pharmaceutical composition of any one of claims 52-70, wherein~~ (d) the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof~~,~~

~~73. The pharmaceutical composition of claim 72~~optionally, wherein the glidant is colloidal silicon dioxide~~;~~.

~~74. The pharmaceutical composition of any one of claims 52-73, wherein~~ (e) the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, glyceryl behenate, stearic acid, and combinations thereof~~.~~; optionally,

~~75. The pharmaceutical composition of claim 74,~~ wherein the lubricant is sodium stearyl fumarate~~.~~;

~~76. The pharmaceutical composition of any one of claims 29-75,~~optionally, (f) wherein the pharmaceutical composition further comprises a binder~~.~~;

~~77. The pharmaceutical composition of claim 76~~optionally, wherein the binder is selected from the group consisting of a hydroxypropylcellulose, a hydroxypropylmethycellulose, a polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, a starch, and combinations thereof~~.~~; and/or

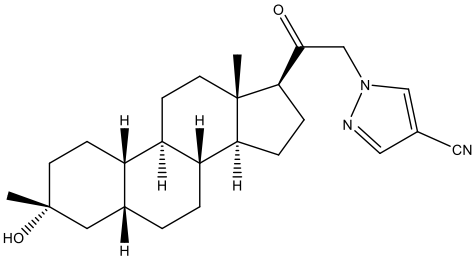
~~78. The pharmaceutical composition of any one of claims 29-77,~~ optionally, (g) wherein the pharmaceutical composition further comprises a wetting agent~~;~~.

~~79. The pharmaceutical composition of claim 78~~optionally, wherein the wetting agent is selected from the group consisting of a poloxamer, sodium dodecyl sulfate, docusate sodium, and combinations thereof.

~~80.~~11. A pharmaceutical composition comprising:

(A):

(i) about 20 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 105.9 mg of mannitol;

(iii) about 26.2 mg of silicified microcrystalline cellulose;

(iv) about 10 mg of croscarmellose sodium;

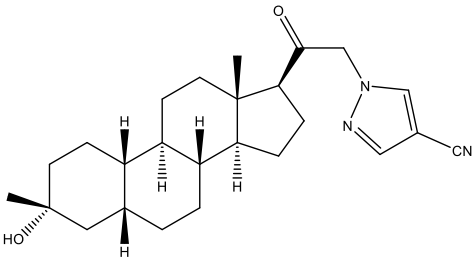
(v) about 1.7 mg of colloidal silicon dioxide; and

(vi) about 2.9 mg of sodium stearyl fumarate;.

~~81. A pharmaceutical composition comprising:~~

(B):

(i) about 25 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 132 mg of mannitol;

(iii) about 32.7 mg of the silicified microcrystalline cellulose;

(iv) about 12.5 mg of croscarmellose sodium;

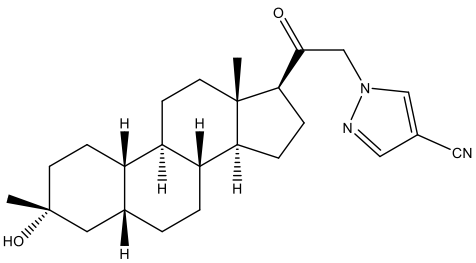
(v) about 2.1 mg of colloidal silicon dioxide; and

(vi) about 3.6 mg of sodium stearyl fumarate;.

~~82. A pharmaceutical composition comprising:~~

(C):

(i) about 30 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 159 mg of mannitol;

(iii) about 39.3 mg of the silicified microcrystalline cellulose;

(iv) about 15 mg of croscarmellose sodium;

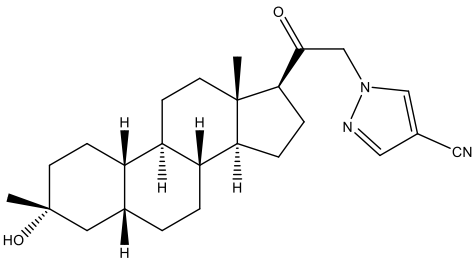
(v) about 2.5 mg of colloidal silicon dioxide; and

(vi) about 4.4 mg of sodium stearyl fumarate;.

~~83. A pharmaceutical composition comprising:~~

(D):

(i) about 40 mg of a crystalline form of the compound of formula (**I**)



(**I**);

(ii) about 212 mg of mannitol;

(iii) about 52.4 mg of the silicified microcrystalline cellulose;

(iv) about 20 mg of croscarmellose sodium;

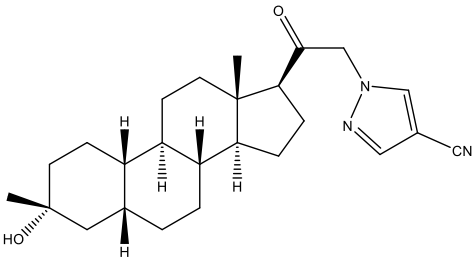
(v) about 3.3 mg of colloidal silicon dioxide; and

(vi) about 5.8 mg of sodium stearyl fumarate;.

~~84. A pharmaceutical composition comprising:~~

(E):

(i) about 50 mg of a crystalline form of the compound of formula (**I**)



(**I**),

(ii) about 265 mg of mannitol;

(iii) about 65.5 mg of the silicified microcrystalline cellulose;

(iv) about 25 mg of croscarmellose sodium;

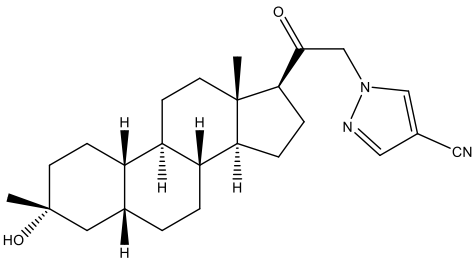
(v) about 4.2 mg of colloidal silicon dioxide; and

(vi) about 7.3 mg of sodium stearyl fumarate; or

~~85. A pharmaceutical composition comprising:~~

(F):

(i) about 60 mg of a crystalline form of the compound of formula (**I**)



(I),

(ii) about 317.7 mg of mannitol;

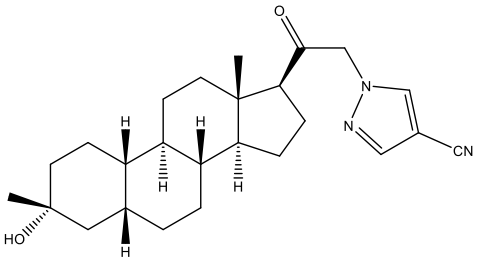
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(iv) about 30 mg of croscarmellose sodium;

(v) about 5 mg of colloidal silicon dioxide; and

(vi) about 8.8 mg of sodium stearyl fumarate.

~~86.~~12. A pharmaceutical composition comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



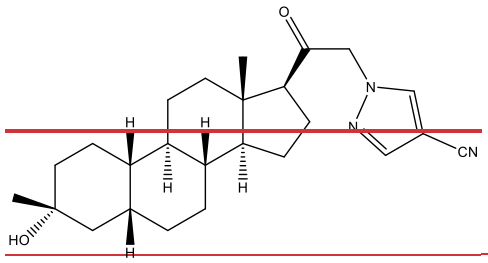
(I),

wherein the plurality of particles of the crystalline form of the compound of formula (**I**) have a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm.~~,~~ or

~~87. The pharmaceutical composition of claim 85, wherein the plurality of particles of the crystalline form of the compound of formula (I) has a particle size distribution which is defined by a D_{90} of~~ about 1 µm to about 20 µm~~.~~; optionally, wherein the pharmaceutical composition comprises a filler and one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof.

~~88. A pharmaceutical composition comprising:~~

~~(i) a plurality of particles of a crystalline form of the compound of formula (I)~~



~~(I);~~

~~(ii) a filler; and~~

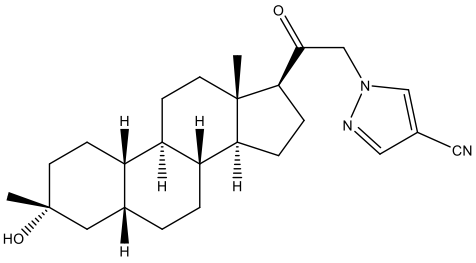
~~(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,~~

~~wherein the plurality of particles of the crystalline form of the compound of formula (I) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 20 µm.~~

~~89. The pharmaceutical composition of claim 88, wherein the plurality of particles of the crystalline form of the compound of formula (I) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 13 µm.~~

~~90.~~13. A pharmaceutical composition comprising:

(i) a crystalline form of the compound of formula (**I**)



(**I**);

(ii) a filler; and

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition: (a) has a bulk density of about 0.2 g/cc to about 0.8 g/cc and a tapped density of about 0.3 g/cc to about 1.1 g/cc and wherein the tapped density of the pharmaceutical composition is higher than the bulk density~~.~~;

(b) has an average flow rate index (FRI) of about 0.05 to about 3.1 kg/sec;

(c) releases at least about 50% of the compound of formula (**I**) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus; or

(d) exhibits the following dissolution profile:

at least about 70% of the compound of formula (**I**) is released after about 20 minutes; and at least about 80% of the compound of formula (**I**) is released after

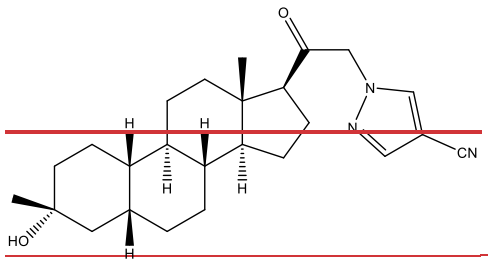
about 30 minutes, when tested in about 500 mL to about 900 mL of 50 mM sodium phosphate buffer, pH 6.8 with about 0.2% to about 0.6% SDS in a USP 2 apparatus at about 37°C.

~~91.~~14. The pharmaceutical composition of claim 13~~90~~, wherein the pharmaceutical composition: (a) has a bulk density of about 0.3 g/cc to about 0.7 g/cc and a tapped density of about 0.5 g/cc to about 0.9 g/cc and wherein the tapped density of the pharmaceutical composition is higher than the bulk density~~.~~;

~~92. The pharmaceutical composition of claim 90, wherein the pharmaceutical composition~~ (b) has a bulk density of about 0.4 g/cc to about 0.7 g/cc and a tapped density of about 0.5 g/cc to about 0.9 g/cc and wherein the tapped density of the pharmaceutical composition is higher than the bulk density~~.~~;

~~93. A pharmaceutical composition comprising:~~

~~(i) a crystalline form of the compound of formula (I)~~



~~(I);~~

~~(ii) a filler; and~~

~~(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,~~

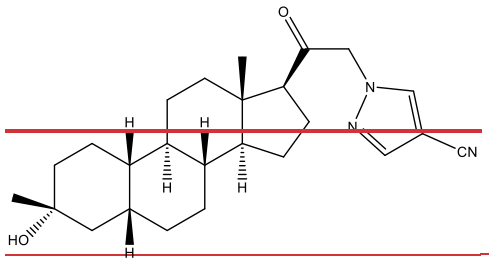
~~wherein the pharmaceutical composition has an average flow rate index (FRI) of about 0.05 to about 3.1 kg/sec.~~

~~94. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition~~ (c) has an average (FRI) of about 0.2 to about 1.5 kg/sec~~.~~, or

~~95. The pharmaceutical composition of claim 93, wherein the pharmaceutical composition has an average (FRI) of~~ about 0.4 to about 0.9 kg/sec; or~~.~~

~~96. A pharmaceutical composition comprising:~~

~~(i) a crystalline form of the compound of formula (I)~~



(I);

(ii) a filler; and

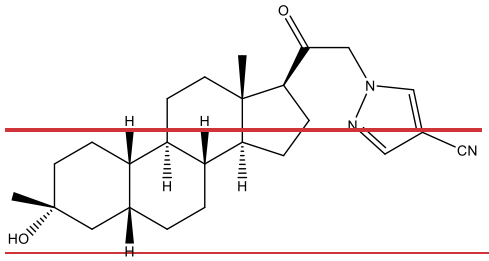
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

wherein the pharmaceutical composition releases at least about 50% of the compound of formula (I) after about 20 minutes, when tested using a USP 1 or a USP 2 apparatus.

97. The pharmaceutical composition of claim 96, wherein the pharmaceutical composition (d) releases at least about 65% of the compound of formula (I) after about 30 minutes, when tested using a USP 1 or a USP 2 apparatus.

98. A pharmaceutical composition comprising:

(i) a crystalline form of the compound of formula (I)



(I);

(ii) a filler; and

(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof;

wherein the pharmaceutical composition exhibits the following dissolution profile:

at least about 70% of the compound of formula (I) is released after about 20 minutes; and

at least about 80% of the compound of formula (I) is released after about 30 minutes, when tested in about 500 mL to about 900 mL of 50 mM sodium phosphate buffer, pH 6.8 with about 0.2% to about 0.6% SDS in a USP 2 apparatus at about 37°C.

99.15. The pharmaceutical composition of any one of claims 1-1498, wherein the crystalline form of the compound of formula (**I**)

(a) comprises crystalline Form A, wherein crystalline Form A exhibits an X-ray powder

diffraction pattern comprising characteristic peaks at the following diffraction angles (2θθ): 9.5° ± 0.2°, 10.8° ± 0.2°, 13.2° ± 0.2°, 14.9° ± 0.2°, 16.0° ± 0.2°, 18.3° ± 0.2°, 18.9° ± 0.2°, 21.1° ± 0.2°, 21.6° ± 0.2°, and 23.5 ° ± 0.2°.; or

100. The pharmaceutical composition of any one of claims 1-98, wherein the crystalline form of the compound of formula (I) (b) comprises crystalline Form C, wherein crystalline Form C exhibits an X-ray powder diffraction pattern comprising characteristic peaks at the following diffraction angles (2θθ): 9.9° ± 0.2°, 11.8° ± 0.2°, 13.4° ± 0.2°, 14.4° ± 0.2°, 14.8° ± 0.2°, 17.0° ± 0.2°, 20.7° ± 0.2°, 21.5° ± 0.2°, and 22.6° ± 0.2°.

101. The pharmaceutical composition of any one of claims 1-100optionally, wherein the crystalline form of the compound of formula (**I**) comprises crystalline Form A and crystalline Form C.

102.16. A dosage form intended for oral administration comprising a pharmaceutical composition of any one of claims 1-15101.

103. The dosage form of claim 102optionally, wherein the dosage form is selected from the group consisting of a powder, a sachet, a stickpack, a capsule, a minitab, and a tablet.

104.17. The dosage form of claim 102 or 10316, wherein the dosage form is (a) a capsule.

105. The dosage form of claim 104optionally, wherein the size of the capsule is selected from the group consisting of 000, 00, 0, 1, 2, 3, 4, and 5;.

106. The dosage form of claim 104 or 105optionally, wherein the total weight of the pharmaceutical composition in the capsule is about 25 mg to about 1000 mg; or.

107. The dosage form of claim 102 or 103, wherein the dosage form is (b) a tablet.

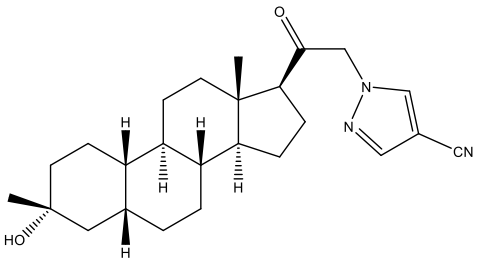
108. The dosage form of claim 107optionally, wherein the total weight of the pharmaceutical composition in the tablet is about 20 mg to about 1000 mg.

109. The dosage form of claim 107 or 108optionally, wherein the tablet further comprises a coating.

110. The dosage form of claim 109optionally, wherein the coating comprises polyvinyl alcohol.

111.18. A process for making a pharmaceutical composition comprising:

(a) micronizing a crystalline form of the compound of formula (**I**) to obtain a micronized crystalline form of the compound of formula (**I**)



(**I**),

wherein the micronized crystalline form of the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm;

(b) blending the micronized crystalline form of the compound of formula (**I**) with one or more pharmaceutically acceptable excipients to obtain a blend;

(c) granulating the blend to obtain granules;

(d) milling the granules to obtain an intragranular phase; and

(e) blending the intragranular phase with one or more extragranular pharmaceutical excipients to obtain the pharmaceutical composition.

~~112.~~19. The process of claim 18~~111~~, wherein,

(A) in step (a), the micronized crystalline form of the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 20 µm~~.~~, or

~~113. The process of claim 111 or 112, wherein, in step (a), the micronized crystalline form of the compound of formula (**I**) has a particle size distribution which is defined by a D_{90} of~~ about 1 µm to about 13 µm~~.~~;

~~114. The process of any one of claims 111-113, wherein,~~ (B.i) in step (b), the one or more pharmaceutically acceptable excipients is selected from the group consisting of a filler, a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof~~.~~;

~~115. The process of any one of claims 111-113, wherein,~~ (B.ii) in step (b), the micronized crystalline compound of formula (**I**) is blended with a filler, a disintegrant, a lubricant, and a glidant;~~.~~

~~116. The process of claim 113 or 115, wherein,~~ (B.iii) in step (b), the filler is selected from the group consisting of a brittle filler, a ductile filler, and combinations thereof~~.~~;

~~117. The process of any one of claims 113-116, wherein,~~ (B.iv) in step (b), the filler comprises a brittle filler and a ductile filler;~~.~~

~~118. The process of claim 116 or 117, wherein,~~ (B.v) in step (b), the brittle filler is selected from the group consisting of mannitol, lactose, dibasic calcium phosphate, and combinations thereof~~.~~;

~~119. The process of claim 116 or 117, wherein,~~ (B.vi) in step (b), the ductile filler is selected from the group consisting of a microcrystalline cellulose, a starch, a polysaccharide, a cellulose, a polyvinylpyrrolidone, a polyvinyl acrylate, and combinations thereof;~~.~~

~~120. The process of any one of claims 111-119, wherein,~~ (B.vii) in step (b), the disintegrant is selected from the group consisting of sodium starch glycolate, a crosslinked polyvinylpyrrolidone, croscarmellose sodium, and combinations thereof;~~.~~

~~121. The process of any one of claims 111-120, wherein,~~ (B.viii) in step (b), the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof;~~.~~

~~122. The process of any one of claims 111-121, wherein,~~ (B.ix) in step (b), the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, glyceryl behenate, stearic acid, and combinations thereof;~~.~~

~~123. The process of any one of claims 111-122, wherein,~~(C) in step (c), the granules have a solid fraction of about 0.5 to about 0.95, or~~.~~

~~124. The process of any one of claims 111-123, wherein, in step (c), the granules have a solid fraction of~~ about 0.6 to about 0.85;~~.~~

~~125. The process of any one of claims 111-124, wherein,~~ (E.i) in step (e), the one or more extragranular excipients is selected from the group consisting of a disintegrant, a lubricant, a glidant, and combinations thereof~~.~~;

~~126. The process of any one of claims 111-125, wherein,~~ (E.ii) in step (e), the intragranular phase is blended with a disintegrant, a lubricant, and a glidant~~.~~;

~~127. The process of claim 125 or 126, wherein,~~ (E.iii) in step (e), the disintegrant is selected from the group consisting of sodium starch glycolate, a crosslinked polyvinylpyrrolidone, croscarmellose sodium, and combinations thereof;~~.~~

~~128. The process of any one of claims 125-127, wherein,~~ (E.iv) in step (e), the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof;~~.~~

~~129. The process of any one of claims 125-128, wherein,~~ (E.v) in step (e), the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, glyceryl behenate, stearic acid, and combinations thereof;~~.~~

~~130. The process of any one of claims 111-129,~~ optionally, (F) wherein the process further comprises compressing the pharmaceutical blend into a tablet~~.~~,

~~131. The process of claim 130, wherein~~ optionally, wherein (I) the tablet comprises a coating, wherein the coating comprises one or more film-forming polymers selected from the group consisting of a hypromellose, an ethylcellulose, a polyvinylpyrrolidone, a polyacrylate, a plasticizer, and combinations thereof~~.~~,

~~132.~~ ~~The process of claim 131, wherein~~ optionally, wherein (II) the coating comprises a colorant selected from the group consisting of titanium dioxide, an aluminum lake, an iron oxide, carbon black, and combinations thereof; and/or~~.~~

~~133.~~ ~~The process of any one of claims 111-129, wherein~~ optionally, wherein (G) the process further comprises filling a capsule with the pharmaceutical blend~~,~~.

~~134.~~ ~~The process of claim 133, wherein~~ optionally, wherein (I) the capsule is size 000, 00, 0, 1, 2, 3, 4, or 5~~.~~.

~~135.~~ ~~The process of claim 133 or 134, wherein~~ (II) the capsule comprises a gelatin, a polysaccharide, a starch, a hypromellose, or combinations thereof; and/or~~.~~

~~136.~~ ~~The process of any one of claims 133-135, wherein~~ (III) the capsules comprise a colorant; optionally, wherein the colorant is selected from the group consisting of titanium dioxide, an aluminum lake, an iron oxide, carbon black, and combinations thereof.

~~137.~~20. Use of a pharmaceutical composition/composition of any one of claims 1-15 or a dosage form of claims 16 or 17 in the manufacture of a medicament for~~A method of~~ treating insomnia, ~~the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110.~~

~~138.~~ ~~A method of treating~~ major depressive disorder, ~~the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110.~~

~~139.~~ ~~A method of treating~~ bipolar disorder, ~~the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110.~~

~~140.~~ ~~A method of treating~~ postpartum depression, ~~the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110.~~

~~141.~~ ~~A method of treating~~ anxiety, ~~the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110.~~

~~142.~~ ~~A method of treating~~ or treatment-resistant depression~~, the method comprising administering to a subject in need thereof a pharmaceutical composition/composition of any one of claims 1-101 or a dosage form of any one of claims 102-110~~.

21. A pharmaceutical composition/composition of any one of claims 1-15 or a dosage form of claims 16 or 17, for use in therapy.