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.

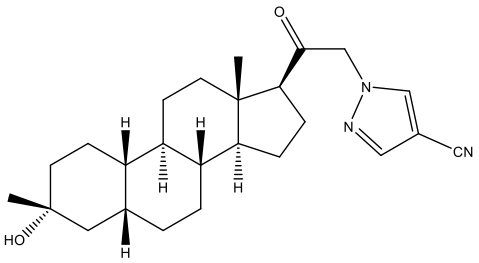
[006] There is a need for neuroactive steroids, in particular 19-NOR C3,3-disubstituted C21-N-pyrazolyl steroids, that display desirable physicochemical properties (e.g., polymorphism, melting point, solubility), are convenient to manufacture and exhibit bioavailability profiles that provide sufficient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

[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:

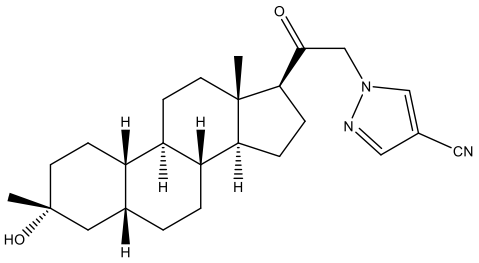
(i) a particle size distribution which is defined by a D_{90} of about 1 µm to about 100 µm;

(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;

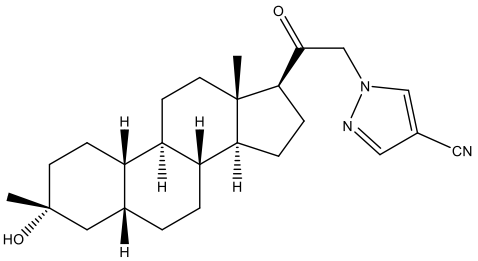
(v) a solid fraction of about 0.5 to about 0.95;

(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**);

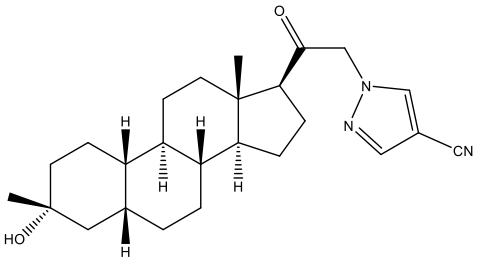
(ii) a filler;

(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;

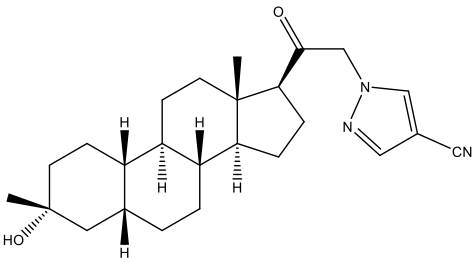
(v) about 0.1% (w/w) to about 5% (w/w) of a lubricant; and

(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;

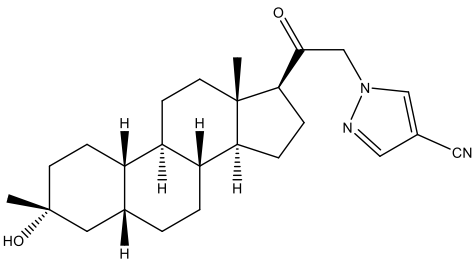
(iv) about 10 mg of croscarmellose sodium;

(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;

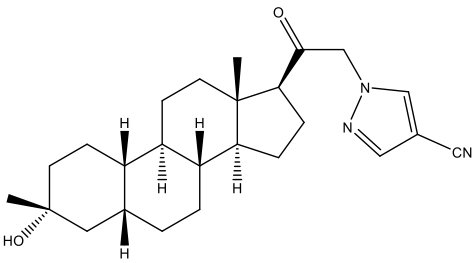
(iv) about 12.5 mg of croscarmellose sodium;

(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;

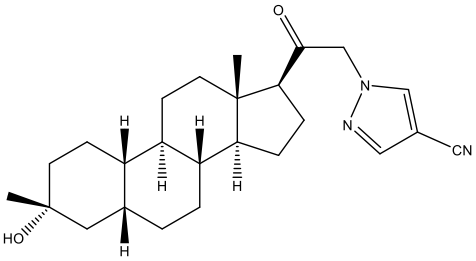
(iv) about 15 mg of croscarmellose sodium;

(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;

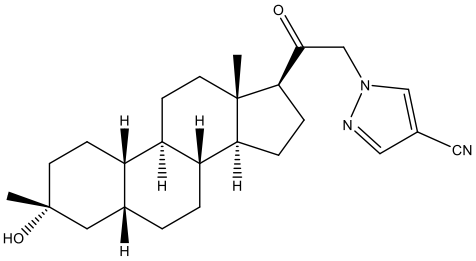
(iv) about 20 mg of croscarmellose sodium;

(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;

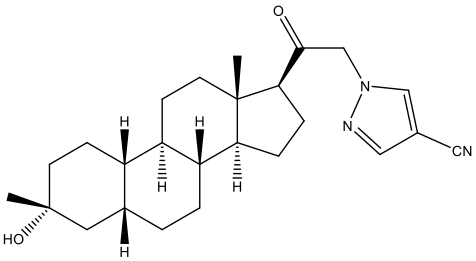
(iv) about 25 mg of croscarmellose sodium;

(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;

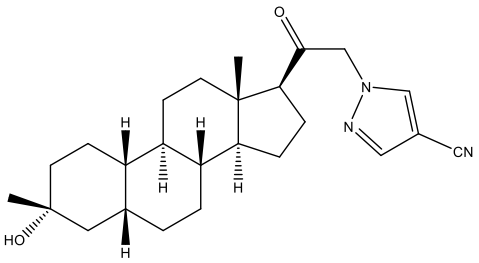
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(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**)



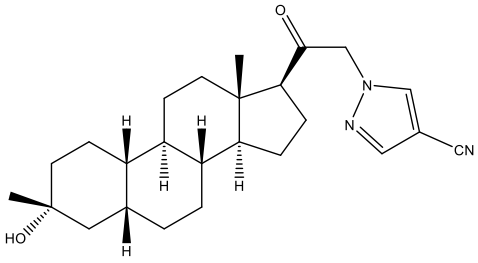
(**I**),

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

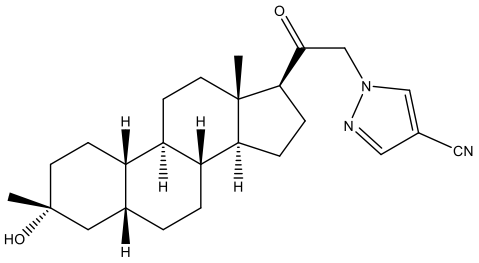
(d) exhibits the following dissolution profile:

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;

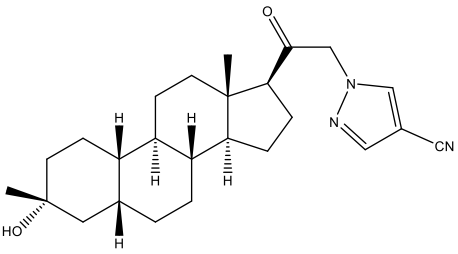
(d) milling the granules to obtain an intragranular phase; and

(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.

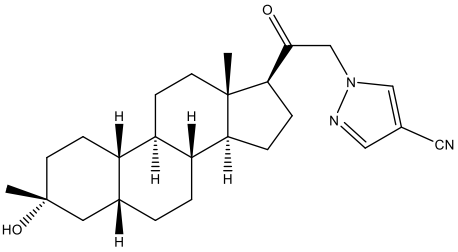
[008k] In another aspect of the present disclosure, there is provided a pharmaceutical composition/composition as disclosed herein or a dosage form as disclosed herein, for use in therapy.

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



(**I**).

[0010] In various 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:

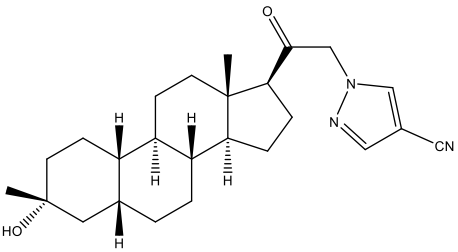
(i) a particle size distribution which is defined by a D_{90} of about 1 μm to about 100 μm;

(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 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;

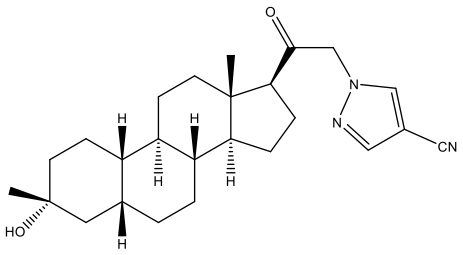
(vi) a flow rate index (FRI) of about 0.1 kg/sec to about 4 kg/sec; and

(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 examples, provided herein are pharmaceutical compositions comprising:

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



(**I**)

(ii) a filler;

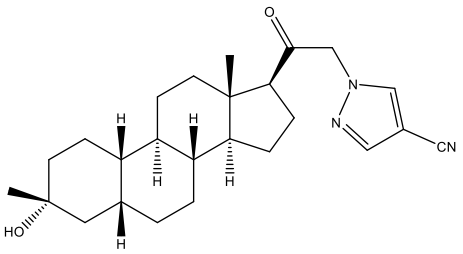
(iii) a lubricant; and

(iv) a glidant.

[0013] In various examples, 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;

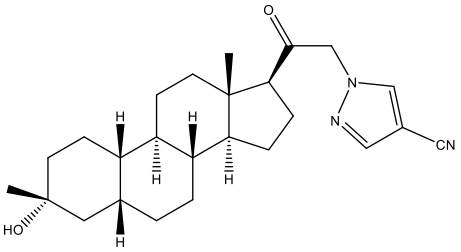
(iv) about 0% (w/w) to about 15% (w/w) of a disintegrant;

(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 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;

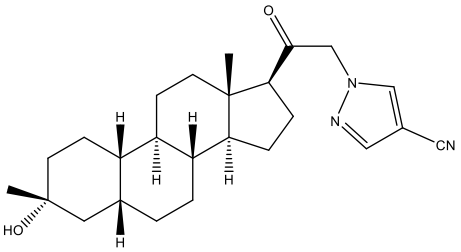
(iv) about 3% (w/w) to about 12% (w/w) of a disintegrant;

(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 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;

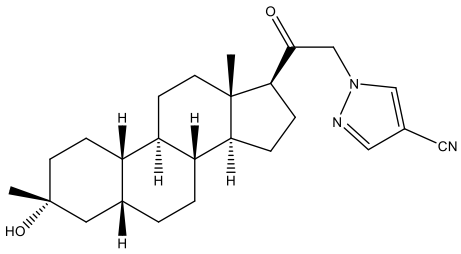
(iv) about 4% (w/w) to about 8% (w/w) of a disintegrant;

(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 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;

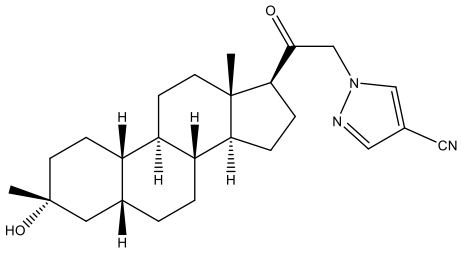
(iv) about 10 mg of croscarmellose sodium;

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

(vi) about 2.9 mg of sodium stearyl fumarate.

[0017] In various 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;

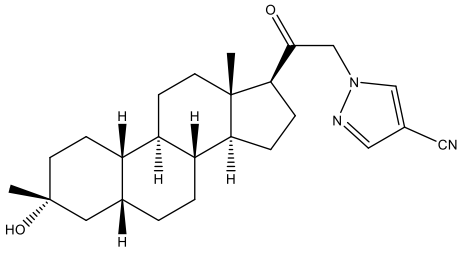
(viii) about 12.5 mg of croscarmellose sodium;

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

(x) about 3.6 mg of sodium stearyl fumarate.

[0018] In various 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;

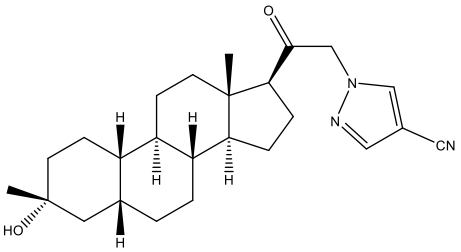
(iv) about 15 mg of croscarmellose sodium;

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

(vi) about 4.4 mg of sodium stearyl fumarate.

[0019] In various 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;

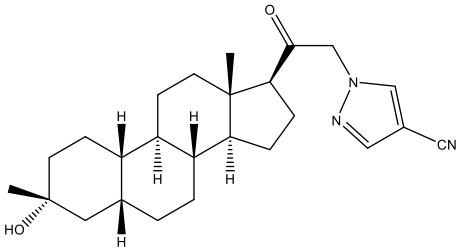
(viii) about 20 mg of croscarmellose sodium;

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

(x) about 5.8 mg of sodium stearyl fumarate.

[0020] In various 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;

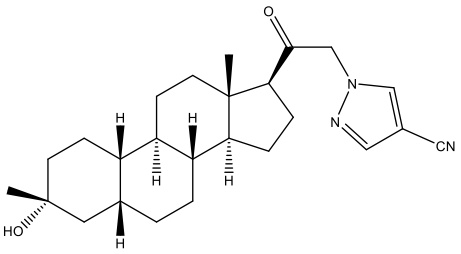
(iv) about 25 mg of croscarmellose sodium;

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

(vi) about 7.3 mg of sodium stearyl fumarate.

[0021] In various 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;

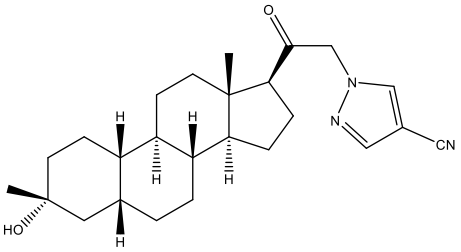
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(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 examples, provided herein are pharmaceutical compositions comprising a plurality of particles of a crystalline form of the compound of formula (**I**)



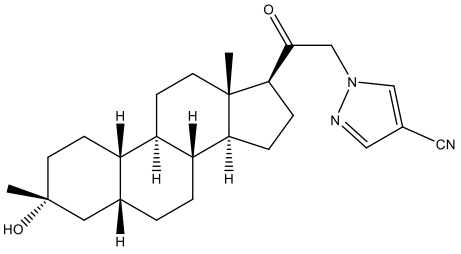
(**I**);

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

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

[0023] In various examples, provided herein are pharmaceutical compositions comprising:

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



(**I**);

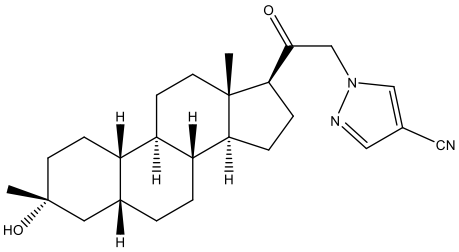
(ii) a filler; and

(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 examples, provided herein are pharmaceutical compositions comprising:

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



(**I**);

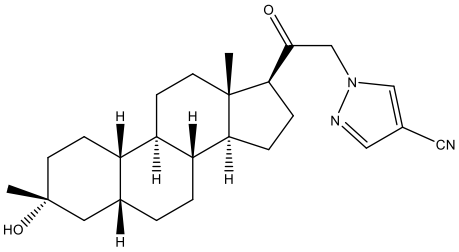
(ii) a filler; and

(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 examples, provided herein are pharmaceutical compositions comprising:

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



(**I**);

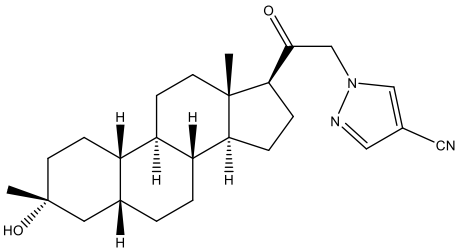
(ii) a filler; and

(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 examples, provided herein are pharmaceutical compositions comprising:

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



(**I**);

(ii) a filler; and

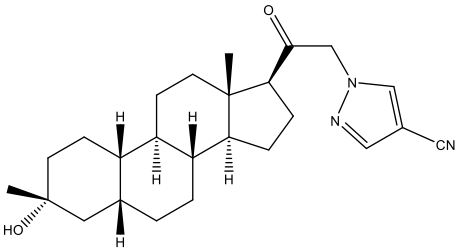
(iii) one or more pharmaceutically acceptable excipients selected from the group consisting of a disintegrant, a binder, a wetting agent, a lubricant, a glidant, and combinations thereof,

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 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 exhibits the following dissolution profile:

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

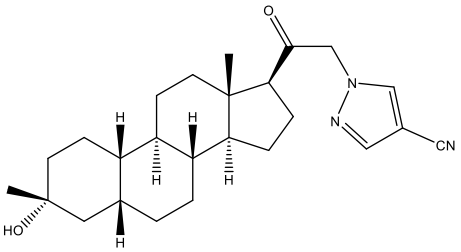
at least about 80% of the compound of formula (**I**) is released after about 30 minutes, when tested in about 500 mL to about 900 mL of 50 mM sodium phosphate buffer, pH 6.8 with about 0.2% to about 0.6% SDS in a USP 2 apparatus at about 37°C.

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

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

[0030] In various 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 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 examples, the condition, disease, or disorder is insomnia. In various examples, the condition, disease, or disorder is major depressive disorder. In various examples, the condition, disease, or disorder is bipolar disorder. In various examples, the condition, disease, or disorder is insomnia. In various examples, the condition, disease, or disorder is postpartum depression. In various examples, the condition, disease, or disorder is anxiety. In various examples, the condition, disease, or disorder is treatment-resistant depression.

BRIEF DESCRIPTION OF THE DRAWINGS

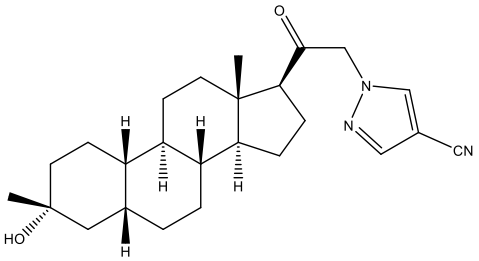
[0032] FIG. 1A is an exemplary X-ray powder diffraction pattern of crystalline Form A of Compound 1.

[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.

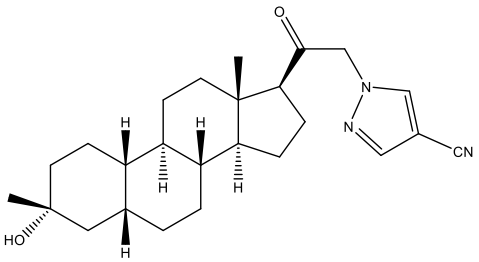
2. The pharmaceutical composition of claim 1, wherein the plurality of particles of the crystalline form of the compound of formula (**I**)

(a) has a particle size distribution which is defined by a D_{90} of about 1 µm to about 20 µm, or about 1 µm to about 13 µm;

(b) have a contact angle of about 70 degrees to about 80 degrees, or about 70 degrees to about 75 degrees, wherein the contact angle is measured using a sessile drop technique; and/or

(c) the yield pressure of the crystalline form of the compound of formula (**I**) is about 60 MPa to about 100 MPa, about 70 MPa to about 95 MPa, or about 80 MPa to about 90 MPa.

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.

4. The pharmaceutical composition of claim 3, wherein

(a) the true density is about 1.1 g/cc to about 2.0 g/cc, or about 1.2 g/cc to about 1.6 g/cc;

(b) the tapped density is about 0.3 g/cc to about 0.9 g/cc, about 0.35 g/cc to about 0.85 g/cc, about 0.4 g/cc to about 0.85 g/cc, about 0.6 g/cc to about 0.85 g/cc, or about 0.7 g/cc to about 0.8 g/cc;

(c) the bulk density is about 0.2 g/cc to about 0.7 g/cc, about 0.3 g/cc to about 0.65 g/cc, about 0.4 g/cc to about 0.7 g/cc, or about 0.5 g/cc to about 0.65 g/cc;

(d) about 0.5% to about 75%, or about 0.5% to about 60% of the pharmaceutical composition is retained when passed through a 710/25 (microns/mesh) sieve;

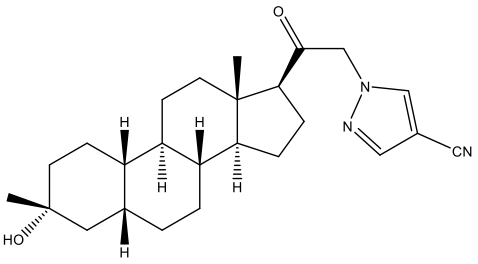
(e) about 2% to about 50%, or about 5% to about 35% of the material is retained when the pharmaceutical composition is passed through a 425/40 (microns/mesh) sieve;

(f) about 0.5% to about 30%, or about 1% to about 25% of the pharmaceutical composition is retained when passed through a 63/230 (microns/mesh) sieve; and/or

(g) the solid fraction is about 0.55 to about 0.95, or about 0.6 to about 0.85.

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.

6. The pharmaceutical composition of claim 5,

wherein the filler comprises a brittle filler, a ductile filler, or combinations thereof;

optionally, wherein the filler comprises a brittle filler and a ductile filler; or,

optionally, 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, about 1 to 5 to about 5 to 1, about 1 to 4 to about 4 to 1.

7. The pharmaceutical composition of claim 5 or 6, wherein

(a) the brittle filler is selected from the group consisting of a sugar, an inorganic material, and combinations thereof;

optionally, wherein the sugar is selected from the group consisting of mannitol, lactose, sucrose, fructose, glucose, maltose and combinations thereof;

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;

optionally, wherein the brittle filler is selected from the group consisting of mannitol, lactose, dibasic calcium phosphate, and combinations thereof;

(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;

optionally, wherein the cellulose is selected from the group consisting of a hydroxypropylcellulose, a hypromellose, a carboxymethylcellulose, a methylcellulose, a hydroxypropylmethylcellulose, and combinations thereof;

optionally, wherein the ductile filler is a microcrystalline cellulose, or a starch;

(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;

(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;

(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;

(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;

(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;

(h) the lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, stearic acid, glyceryl behenate, and combinations thereof;

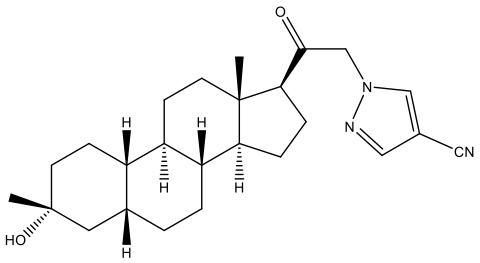
(i) the glidant is selected from the group consisting of colloidal silicon dioxide, talc, kaolin, bentonite, and combinations thereof; and/or

(j) optionally, wherein the pharmaceutical composition further comprises a disintegrant;

optionally, wherein the disintegrant is selected from the group consisting of sodium starch glycolate, a crospovidone, croscarmellose sodium, and combinations thereof.

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.

9. The pharmaceutical composition of claim 8, 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 about 10% (w/w) to about 40% (w/w), or about 10% (w/w) to about 15% (w/w);

(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 about 41% (w/w) to about 45% (w/w);

(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 about 41% (w/w) to about 45% (w/w);

(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);

(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

(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);

optionally, (g) wherein the pharmaceutical composition comprises:

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

optionally, (h) wherein the pharmaceutical composition comprises:

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

10. The pharmaceutical composition of claim 8 or 9, wherein

(a) the brittle filler is mannitol, lactose, or dibasic calcium phosphate;

(b) the ductile filler is a microcrystalline cellulose, or a starch;

(c) the disintegrant is selected from the group consisting of sodium starch glycolate, a crosslinked polyvinylpyrrolidone, croscarmellose sodium, and combinations thereof,

optionally, wherein the disintegrant is croscarmellose sodium or a crosslinked polyvinylpyrrolidone;

(d) the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof,

optionally, wherein the glidant is colloidal silicon dioxide;

(e) the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, glyceryl behenate, stearic acid, and combinations thereof;

optionally, wherein the lubricant is sodium stearyl fumarate;

optionally, (f) wherein the pharmaceutical composition further comprises a binder;

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

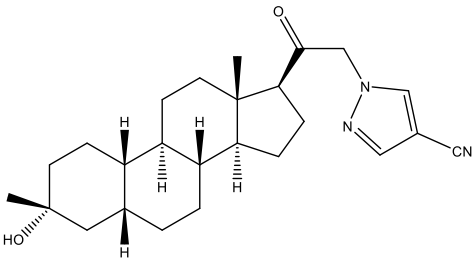
optionally, (g) wherein the pharmaceutical composition further comprises a wetting agent;

optionally, wherein the wetting agent is selected from the group consisting of a poloxamer, sodium dodecyl sulfate, docusate sodium, and combinations thereof.

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;

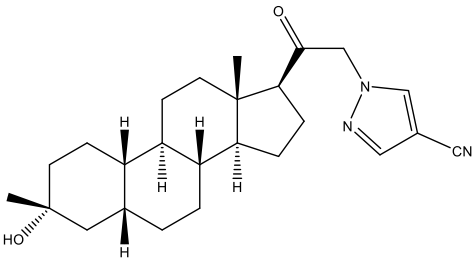
(iv) about 10 mg of croscarmellose sodium;

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

(vi) about 2.9 mg of sodium stearyl fumarate;

(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;

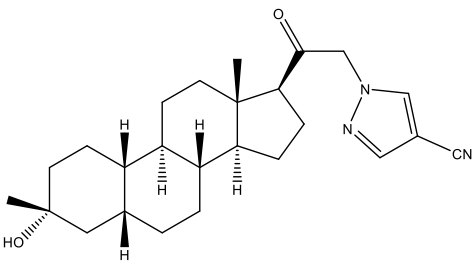
(iv) about 12.5 mg of croscarmellose sodium;

(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;

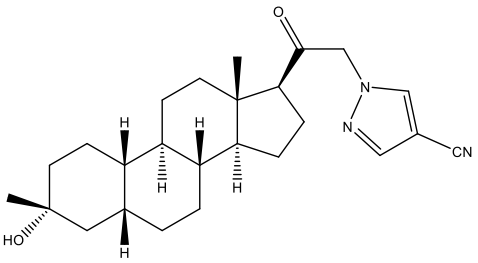
(iv) about 15 mg of croscarmellose sodium;

(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;

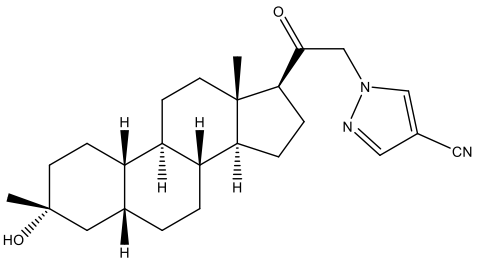
(iv) about 20 mg of croscarmellose sodium;

(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;

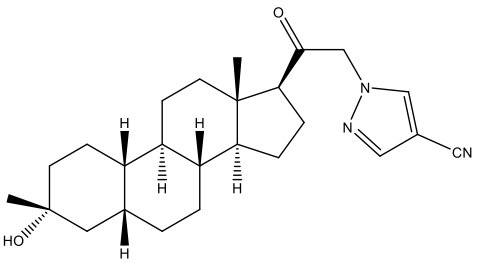
(iv) about 25 mg of croscarmellose sodium;

(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;

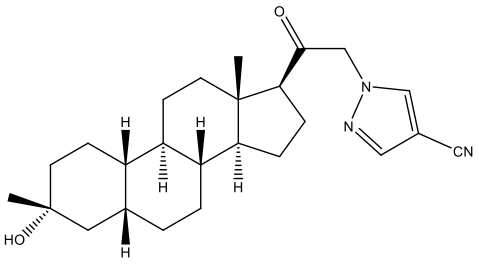
(iii) about 78.6 mg of the silicified microcrystalline cellulose;

(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.

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



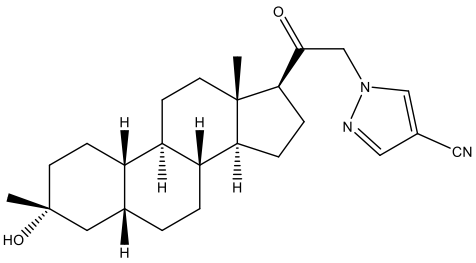
(**I**),

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 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.

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.

14. The pharmaceutical composition of claim 13, 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;

(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;

(c) has an average (FRI) of about 0.2 to about 1.5 kg/sec, or about 0.4 to about 0.9 kg/sec; or

(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.

15. The pharmaceutical composition of any one of claims 1-14, 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 (2θ): 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

(b) comprises crystalline Form C, wherein crystalline Form C exhibits an X-ray powder diffraction pattern comprising characteristic peaks at the following diffraction

angles (2θ): 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°,

optionally, wherein the crystalline form of the compound of formula (**I**) comprises crystalline Form A and crystalline Form C.

16. A dosage form intended for oral administration comprising a pharmaceutical composition of any one of claims 1-15, 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.

17. The dosage form of claim 16, wherein the dosage form is

(a) a capsule,

optionally, wherein the size of the capsule is selected from the group consisting of 000, 00, 0, 1, 2, 3, 4, and 5;

optionally, wherein the total weight of the pharmaceutical composition in the capsule is about 25 mg to about 1000 mg; or

(b) a tablet,

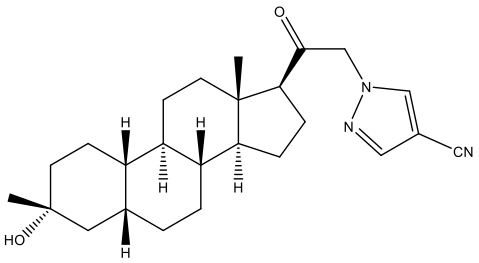
optionally, wherein the total weight of the pharmaceutical composition in the tablet is about 20 mg to about 1000 mg,

optionally, wherein the tablet further comprises a coating,

optionally, wherein the coating comprises polyvinyl alcohol.

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.

19. The process of claim 18, 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 about 1 µm to about 13 µm;

(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;

(B.ii) in step (b), the micronized crystalline compound of formula (**I**) is blended with a filler, a disintegrant, a lubricant, and a glidant;

(B.iii) in step (b), the filler is selected from the group consisting of a brittle filler, a ductile filler, and combinations thereof;

(B.iv) in step (b), the filler comprises a brittle filler and a ductile filler;

(B.v) in step (b), the brittle filler is selected from the group consisting of mannitol, lactose, dibasic calcium phosphate, and combinations thereof;

(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;

(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;

(B.viii) in step (b), the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof;

(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;

(C) in step (c), the granules have a solid fraction of about 0.5 to about 0.95, or about 0.6 to about 0.85;

(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;

(E.ii) in step (e), the intragranular phase is blended with a disintegrant, a lubricant, and a glidant;

(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;

(E.iv) in step (e), the glidant is selected from colloidal silicon dioxide, talc, and combinations thereof;

(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;

optionally, (F) wherein the process further comprises compressing the pharmaceutical blend into a tablet,

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,

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

optionally, wherein (G) the process further comprises filling a capsule with the pharmaceutical blend,

optionally, wherein (I) the capsule is size 000, 00, 0, 1, 2, 3, 4, or 5, (II) the capsule comprises a gelatin, a polysaccharide, a starch, a hypromellose, or combinations thereof; and/or (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.

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 treating insomnia, major depressive disorder, bipolar disorder, postpartum depression, anxiety, or treatment-resistant depression.

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.