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(54) **Title**: NOVEL COMPOSITIONS

(57) **Abstract**: Provided are pharmaceutical compositions comprising (1 R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form. The compositions are formulated for providing a sustained release of enantiomerically pure (1 R,5S)-1 -(naphthalen-2-yl)-3-azabicyclo[3.1.O)hexane. The compositions are substantially free of the other (-) enantiomer of the compound.

NOVEL COMPOSITIONS

BACKGROUND

[0001] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is an unbalanced triple reuptake inhibitor with the most potency towards norepinephrine reuptake (NE), one-sixth as much towards dopamine reuptake (DA), and one-fourteenth as much towards serotonin reuptake (5-HT).

[0002] There remains a need for novel pharmaceutical compositions comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

BRIEF SUMMARY

[0003] Provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

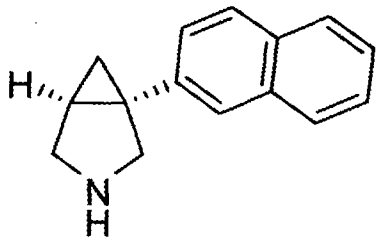
[0004] Further areas of applicability of the present disclosure will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating the preferred embodiment of this disclosure, are intended for purposes of illustration only and are not intended to limit the scope of this disclosure.

DETAILED DESCRIPTION

[0005] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

[0006] As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by referenced in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0007] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, also known as (+)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, is shown as Formula I below.



Formula I

[0008] "(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane" and "(+)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane" are used interchangeably herein.

[0009] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is an unbalanced triple reuptake inhibitor with the most potency towards norepinephrine reuptake (NE), one-sixth as much towards dopamine reuptake (DA), and one-fourteenth as much towards serotonin reuptake (5-HT).

[0010] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may be synthesized as described in U.S. Patent No. 8,461,196 or International Publication No. WO 2013/019271, both of which are incorporated herein by reference in their entirety.

[0011] As used herein, "substantially free of the corresponding (-) enantiomer" means more of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane than the corresponding (-) enantiomer, i.e., (1S,5R)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane. In some embodiments, "substantially free of the corresponding (-) enantiomer" means containing no more than 20% w/w (weight/weight) of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 10% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 5% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 2% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 1% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form.

[0012] As used herein, "(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane" embraces the compound in any form, for example, free or pharmaceutically acceptable salt form, e.g., as a pharmaceutically acceptable acid addition salt. Pharmaceutically acceptable salts are known in the art and include salts that are physiologically acceptable at the dosage amount and form to be administered, for example, hydrochloride salts.

[0013] As used herein, "(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane" is also to be understood as embracing the compound in crystalline and amorphous form including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" may be used interchangeably herein, and are meant to include all crystalline forms of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrates), and conformational polymorphs, as well as mixtures thereof, unless a particular crystalline form is referred to.

[0014] Crystalline and amorphous forms of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may be used in any combination or in forms that are substantially free of one or more of the other crystalline forms or free of the amorphous form.

[0015] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may in some cases also exist in prodrug form. Prodrugs are considered to be any covalently bonded carriers that release the active parent drug *in vivo*.

[0016] As used herein, "concurrently" means the compounds are administered simultaneously or within the same composition. In some embodiments, the compounds are administered simultaneously. In some embodiments, the compounds are administered within the same composition.

[0017] The nominal viscosity of polymers, e.g., hydroxypropyl methylcellulose may be measured, for example, at a 2% concentration in water at 20°C according to the U.S. Pharmacopeia and by other techniques known to those skilled in the art.

[0018] Particle size measurements may be made, for example, by laser diffraction and by other techniques known to those skilled in the art.

[0019] In some embodiments, the pharmaceutical compositions disclosed herein comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, may be administered by any suitable route, including orally, parenterally, transdermally, or by inhalation, including by sustained release, although various other known delivery routes, devices and methods can likewise be employed. In some embodiments, provided is a sustained release pharmaceutical composition, e.g., an oral sustained release pharmaceutical

composition, comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, which provides therapeutically effective levels of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane over a sustained delivery period of approximately 6 hours or longer, e.g., 8 hours or longer, e.g., 12 hours or longer, e.g., 18 hours or longer, e.g., 24 hours or longer.

[0020] In some embodiments, (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is released from a pharmaceutical composition as disclosed herein and delivered into the blood plasma or other target site of activity in the subject (including, but not limited to, areas of the brain such as the prefrontal cortex, frontal cortex, thalamus, striatum, ventral tegmental area, other cortical areas, hippocampus, hypothalamus, or nucleus accumbens) in a sustained release profile characterized in that from about 0% to 20% of the active compound is released and delivered (as determined, e.g., by measuring blood plasma levels) within 0 to 2 hours, from 20% to 50% of the active compound is released and delivered within about 2 to 12 hours, from 50% to 85% of the active compound is released and delivered within about 3 to 20 hours, and greater than 75% of the active compound is released and delivered within about 5 to 18 hours.

[0021] In some embodiments, (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is released from a pharmaceutical composition as disclosed herein and delivered into the blood plasma or other target site of activity in the subject (including, but not limited to, areas of the brain such as the prefrontal cortex, frontal cortex, thalamus, striatum, ventral tegmental area, other cortical areas, hippocampus, hypothalamus, or nucleus accumbens) in a sustained release profile characterized in that at least 20% of the active compound is released and delivered (as determined, e.g., by measuring blood plasma levels) within 4 or less hours after administration, e.g., at least about 30%, e.g., at least about 40%, e.g., about 20-80%, e.g., about 30-70%, e.g., about 40-60% is released and delivered within 4 hours or less after administration.

[0022] In some embodiments, (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is released from a pharmaceutical composition as disclosed herein and delivered into the blood plasma or other target site of activity in the subject (including, but not limited to, areas of the brain such as the prefrontal cortex, frontal cortex, thalamus, striatum, ventral tegmental area, other cortical areas, hippocampus, hypothalamus, or

nucleus accumbens) in a sustained release profile characterized in that at least 50% of the active compound is released and delivered (as determined, e.g., by measuring blood plasma levels) within 8 hours or less after administration, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., about 50-90%, e.g., about 60-90%, e.g., about 60-80% is released and delivered within 8 hours or less after administration.

[0023] In some embodiments, at least 20% of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, e.g., at least about 30%, e.g., at least about 40%, e.g., about 20-80%, e.g., about 30-70%, e.g., about 30-60%, e.g., about 40-60%, e.g., about 50-60%, e.g., about 50%, e.g., about 60%, is released and dissolved within 4 hours or less (e.g., within about 2-4 hours, e.g., about within 3-4 hours, e.g., about 4 hours) from a pharmaceutical composition as disclosed herein as measured in 900 mL water using USP Apparatus 2 paddle, at 50 rpm and at 37°C±0.5. In addition, in some embodiments, at least 50% of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, e.g., at least about 60%, e.g., at least about 70%, e.g., at least about 80%, e.g., about 50-90%, e.g., about 60-90%, e.g., about 60-80% is released and dissolved within 8 hours or less (e.g., within about 6-8 hours, e.g., within about 7-8 hours, e.g., about 8 hours) from a pharmaceutical composition as disclosed herein as measured in 900 mL water using USP Apparatus 2 paddle, at 50 rpm and 37°C±0.5.

[0024] In some embodiments, the C_{max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, as disclosed herein is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30% of the C_{max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition. In some embodiments, the C_{max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, as disclosed herein is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{max} obtained

after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

[0025] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, as disclosed herein is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, of the C_{max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition. In some embodiments, the C_{max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, as disclosed herein is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

[0026] In some embodiments, the pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, e.g., a sustained release pharmaceutical composition, comprises a lubricant, e.g., magnesium stearate, a carrier, e.g., lactose monohydrate, or a combination thereof.

[0027] Provided is a pharmaceutical composition (Composition 1), e.g., a sustained release pharmaceutical composition, comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

[0028] Further provided is Composition 1 as follows:

1.1 Composition 1 wherein the composition is sustained release.

1.2 Composition 1 or 1.1 wherein the pharmaceutical composition is substantially free of the corresponding (-) enantiomer.

1.3 Composition 1, 1.1, or 1.2 wherein the composition comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.

1.4 Any of Compositions 1 or 1.1-1.3 wherein the composition comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.

1.5 Any of Compositions 1 or 1.1-1.4 wherein the composition comprises less than or equal to 5% w/w of the corresponding (-) enantiomer.

1.6 Any of Compositions 1 or 1.1-1.5 wherein the composition comprises less than or equal to 2% w/w of the corresponding (-) enantiomer.

1.7 Any of Composition 1 or 1.1-1.6 wherein the composition comprises less than or equal to 1% w/w of the corresponding (-) enantiomer.

1.8 Any of Compositions 1 or 1.1-1.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.

1.9 Composition 1.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.

1.10 Composition 1.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.

1.11 Any of Compositions 1 or 1.1-1.10 comprising 1 mg to 1800 mg, e.g., 10 mg to 1800 mg, e.g., 25 mg to 1800 mg, e.g., 10 mg to 1600 mg, e.g., 10 mg to 1200 mg, e.g., 50 mg to 1200 mg, e.g., 50 mg to 1000 mg, e.g., 75 mg to 1000 mg, e.g., 75 mg to 800 mg, e.g., 75 mg to 500 mg, e.g., 100 mg to 750 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.12 Any of Compositions 1 or 1.1-1.11 comprising 75 mg to 1000 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.13 Any of Compositions 1 or 1.1-1.11 comprising 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.14 Any of Compositions 1 or 1.1-1.11 comprising 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g, 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-

(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.15 Any of Compositions 1 or 1.1-1.10 for administration of 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.16 Any of Compositions 1 or 1.1-1.15 comprising less than 50% w/w of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, e.g., less than about 40% w/w, e.g., less than about 30% w/w, less than about 20 % w/w, e.g., about 1-40% w/w, e.g., about 5-40% w/w, e.g., about 10-30% w/w, e.g., about 15-25% w/w, e.g., about 15-20% w/w, e.g., about 17% w/w, e.g., about 25% w/w.

1.17 Any of Compositions 1 or 1.1-1.16 further comprising hydroxypropyl methylcellulose (e.g., hypromellose HPMC K4M).

1.18 Composition 1.17 wherein the composition comprises at least 10% w/w of the hydroxypropyl methylcellulose, e.g., about 10-50% w/w, e.g., about 10-40% w/w, e.g., about 20-50% w/w, e.g., about 20-40% w/w, e.g., about 30-40% w/w, e.g., about 37% w/w.

1.19 Composition 1.17 or 1.18 wherein the degree of methoxy substitution of the hydroxypropyl methylcellulose is 19-24%.

1.20 Any of Compositions 1.17-1.19 wherein the degree of hydroxypropoxy substitution of the hydroxypropyl methylcellulose is 4-12%.

1.21 Any of Compositions 1.17-1.20 wherein the hydroxypropyl methylcellulose is hypromellose 2208.

1.22 Any of Compositions 1.17-1.21 wherein the hydroxypropyl methylcellulose has a nominal viscosity of 4,000 mPA•s.

1.23 Any of Compositions 1.17-1.21 wherein the hydroxypropyl methylcellulose has a viscosity of 2,000-6,000 mPA•s, e.g., about 2,600 to 5,000 mPA•s, e.g., about 2,663 to 4,970 mPA•s.

1.24 Any of Compositions 1 or 1.1-1.23 wherein the composition further comprises lactose (e.g., alpha-lactose monohydrate).

1.25 Composition 1.24 wherein the composition comprises at least 10% w/w of the alpha-lactose monohydrate, e.g., about 10-80% w/w, e.g., about 20-70% w/w, e.g., about 20-60% w/w, e.g., about 20-50% w/w, e.g., about 20-40% w/w, e.g., about 20-30% w/w, e.g., about 30-70% w/w, e.g., about 30-60% w/w, e.g., about 30-50% w/w, e.g., about 30%-40% w/w, e.g., about 37% w/w.

1.26 Composition 1.24 or 1.25 wherein the composition comprises milled alpha-lactose monohydrate.

1.27 Any of Compositions 1 or 1.1-1.26 wherein the composition comprises a co-processed mixture of hydroxpropyl methylcellulose and alpha-lactose monohydrate (e.g., Retalac®).

1.28 Composition 1.27 wherein the mixture comprises equal parts of the hydroxpropyl methylcellulose and alpha-lactose monohydrate.

1.29 Composition 1.27 or 1.28 wherein the mixture comprises particles of hydroxpropyl methylcellulose and alpha-lactose monohydrate with d_{50} (median diameter) in the range of 100 μm to 200 μm, e.g., about 125 μm.

1.30 Any of Compositions 1.27-1.29 wherein the mixture comprises particles of hydroxpropyl methylcellulose and alpha-lactose monohydrate wherein the particle size distribution is as follows:

< 63 μm $\leq 25\%$

< 100 μm: 35%

< 250 μm $\geq 80\%$.

1.31 Any of Compositions 1.27-1.30 wherein the composition comprises at least 20% w/w of the mixture, e.g., about at least 30% w/w, e.g., at least about 40% w/w, e.g., at least about 50% w/w, e.g., at least about 60% w/w, e.g., at least about 70% w/w, e.g, at least about 80% w/w, e.g., about 20-90% w/w, e.g., about 30-80% w/w, e.g., about 40-80% w/w, e.g., about 50-80% w/w, e.g., about 60-80% w/w, e.g., about 70-80% w/w, e.g., about 75% w/w.

1.32 Any of Compositions 1 or 1.1-1.31 wherein the composition further comprises a lubricant, e.g., magnesium stearate.

1.33 Composition 1.32 wherein the lubricant is one or more of glyceryl behenate, magnesium stearate, talc, and sodium stearyl fumarate, e.g, magnesium stearate.

1.34 Composition 1.32 or 1.33 wherein the composition comprises less than 10% w/w of the lubricant, e.g., less than about 5% w/w, less than about 3% w/w, less than about 1% w/w, e.g., about 0.1 to 1% w/w, e.g., about 0.1 to 0.8% w/w, e.g., about 0.5% w/w.

1.35 Any of Compositions 1.32-1.34 wherein the composition comprises less than 10% w/w of magnesium stearate, e.g., less than about 5% w/w, less than about 3% w/w, less than about 1%, e.g., about 0.1 to 1% w/w, e.g., about 0.1 to 0.8% w/w, e.g., about 0.5% w/w.

1.36 Any of Compositions 1 or 1.1-1.35 wherein the composition further comprises one or more of a diluent, disintegrant, binder, and modified release agent.

1.37 Composition 1.36 wherein the diluent is one or more of mannitol (e.g., Pearlitol 300 DC), micro-crystalline cellulose (e.g., Avicel pH 102), and pre-gelatinized starch (e.g., Starch 1500).

1.38 Composition 1.36 wherein the disintegrant is one or both of crospovidone (e.g., Polyplasdone XL-10) and sodium starch glycolate (e.g., Explotab).

1.39 Composition 1.36 wherein the binder is polyvinylpyrrolidone (e.g., Povidone K29/32).

1.40 Composition 1.36 wherein the modified release agent is one or more of hydroxypropyl cellulose (e.g., Klucel EXF, Klucel MXF and/or Klucel HXF) and hydroxypropyl methylcellulose (e.g., Methocel K100M, Methocel K4M PREM, Methocel K15M PREM CR).

1.41 Composition 1.36 or 1.40 wherein the composition comprises at least 5% w/w of the modified release agent, e.g., about 5-60% w/w, e.g., about 10-50% w/w, e.g., about 10-40% w/w.

1.42 Composition 1.40 or 1.41 wherein the modified release agent is hydroxypropyl methylcellulose.

1.43 Composition 1.42 wherein the degree of methoxy substitution of the hydroxypropyl methylcellulose is 19-24%.

1.44 Composition 1.42 or 1.43 wherein the degree of hydroxypropoxy substitution of the hydroxypropyl methylcellulose is 4-12%.

1.45 Any of Compositions 1.42-1.44 wherein the hydroxypropyl methylcellulose is hypromellose 2208.

1.46 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 75,000-140,000 mPA•s.

1.47 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 2,000-6,000 mPA•s, e.g., about 2,600 to 5,000 mPA•s, e.g., about 2,663 to 4,970 mPA•s.

1.48 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 12,000-26,000 mPA•s, e.g., about 13,000 to 25,000 mPA•s, e.g., about 13,275 to 24,780 mPA•s.

1.49 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 100,000 cps.

1.50 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 3,600 cps.

1.51 Any of Compositions 1.42-1.45 wherein the hydroxypropyl methylcellulose has a viscosity of 18,000 cps.

1.52 Composition 1.36, 1.40, or 1.41 wherein the modified release agent is hydroxypropyl cellulose (e.g., Klucel EXF, Klucel MXF and/or Klucel HXF).

1.53 Any of Compositions 1 or 1.1-1.52 for administration once, twice, three, or four times daily.

1.54 Any of Compositions 1 or 1.1-1.53 further comprising another drug.

1.55 Any of Compositions 1 or 1.1-1.54 wherein the composition further comprises an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β-blocker, a hormone, or a combination thereof.

1.56 Any of Compositions 1 or 1.1-1.55 wherein the composition further comprises fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluovoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate,

lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.

1.57 Any of Compositions 1 or 1.1-1.56 further comprising an mGluR5 antagonist.

1.58 Composition 1.57 further comprising fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.

1.59 Composition 1.58 further comprising RO4917523, mavoglurant (AFQ056), or a combination thereof.

1.60 Any of Compositions 1 or 1.1-1.59 further comprising a GABA-B agonist.

1.61 Composition 1.60 comprising arbaclofen.

1.62 Any of Compositions 1 or 1.1-1.61 further comprising a GABA modulator.

1.63 Composition 1.62 further comprising acamprosate.

1.64 Any of Compositions 1 or 1.1-1.63 further comprising minocycline.

1.65 Any of Compositions 1 or 1.1-1.64 wherein the C_{max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

1.66 Any of Compositions 1 or 1.1-1.65 wherein the C_{max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., about 20-50%, e.g., about 30-50%, e.g., about 30-40%, of the C_{max} obtained after

administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

1.67 Composition 1 wherein the composition comprises 25% w/w (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride, 74.5% w/w of an equal parts mixture of hydroxypropyl methylcellulose and alpha-lactose monohydrate, and 0.5% w/w magnesium stearate.

1.68 Any of Compositions 1 or 1.1-1.67 for use in indications as described in U.S. Patent No. 8,461,196, International Publication No. WO 2013/019271, and International Patent Application No. PCT/US14/69401, the contents of each of which are hereby incorporated by reference.

EXAMPLES

Example 1

[0029] Sustained release pharmaceutical compositions comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride may be made utilizing a direct blend process, with screening of the excipients and (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride through a Quadro 197S Co-Mil, and blending in a V-shell blender prior to compression on a rotary tablet press.

Example 2

[0030] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	25%	100
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	74.5%	298
Magnesium Stearate, NF (Hyqual® Vegetable source)	0.5%	2
Total	100%	400

[0031] HPLC conditions for dissolution and dissolution conditions for Examples 3-9 are set forth in Tables 1 and 2.

Table 1. HPLC Conditions Dissolution

Item	Setting			
Column	Waters XBridge C18 3.0x150mm 3.5µm			
Mobile Phase	MPA: 6mM Ammonium Formate; 95% Water, 5% CAN MPB: 5 mM Ammonium Formate; 5% Water, 95% ACN			
Flow Rate	See Gradient			
Detection	226 nm			
Column Temp.	40°C			
Run Time	42 minutes			
Injection Volume	20 µL			
Gradient	Time	%MPA	%MPB	Flow Rate (mL/min)
	0	95	5	0.8
	30	50	50	0.8
	30.1	5	95	0.8
	35	5	95	1.2
	35.1	95	5	0.8
	42	95	5	0.8

Table 2. Dissolution Testing Conditions

Item	Setting/Condition
Media	Water
Volume	900 mL
Speed	50 rpm
Apparatus	USP, App. 2, Paddle
Temp.	37° C ± 0.5

Example 3

[0032] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

[0033] Manufacture by a direct blend process. Compress on Dynamic Exim rotary tablet press using concave 3/8" tooling. Compress at a target weight of 300 mg (±15 mg) and target hardness of approximately 8kp ± 2 kp.

Ingredient	**Concentration (%W/W)**	**Tablet Unit Weight (mg)**
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	16.7%	50
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	82.8%	248.5
Magnesium Stearate, NF	0.5%	1.5
Total	100%	300

Table 3.

Dissolution Data:

12-hour dissolution profile

Numerical Data

Vessel	1hr	2hr	4hr	6hr	8hr	12hr
1	23	35	52	65	74	84
2	22	33	51	64	73	84
3	21	34	50	64	73	84
Ave	22	34	51	64	73	84
%RSD	3.0	2.3	1.8	1.0	0.6	0.2

Example 4

[0034] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

[0035] Manufacture by a direct blend process. Compress on Dynamic Exim rotary tablet press using concave 3/8" tooling. Compress at a target weight of 300 mg (±15 mg) and target hardness of approximately 8kp ± 2 kp.

Ingredient	**Concentration (%W/W)**	**Tablet Unit Weight (mg)**
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	16.7%	50
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	42.8%	128.4
Lactose Monohydrate, 315 SD	40.0%	120.0
Magnesium Stearate, NF	0.5%	1.5
Total	100%	300

Table 4.

Vessel	1hr	2hr	4hr	6hr	8hr	12hr	24hr
1	32	48	66	78	85	94	99
2	30	45	66	79	90	84	96
3	33	48	70	79	89	84	89
Ave	32	47	67	78	88	87	95
%RSD	3.6	4.6	3.9	0.8	2.6	6.8	5.4

Example 5

[0036] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

[0037] Manufacture by a direct blend process. Compress on Dynamic Exim rotary tablet press using concave 3/8" tooling. Compress at a target weight of 300 mg (±15 mg) and target hardness of approximately 8kp ± 2 kp.

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	16.7%	50
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	52.8%	158.5
Klucel HXF HPC	30.0%	90.0
Magnesium Stearate, NF	0.5%	1.5
Total	100%	300

Table 5.

Vessel	1hr	2hr	4hr	6hr	8hr	12hr	24hr
1	29	46	67	75	92	101	105
2	29	43	65	74	91	94	106
3	30	43	65	75	87	101	105
Ave	30	44	66	75	90	99	105
%RSD	2.0	3.5	1.6	0.7	3.0	4.3	0.6

Example 6

[0038] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	16.7%	50
Lactose Monohydrate, 315 SD	41.4%	124.25
HPMC K4M	41.4%	124.25
Magnesium Stearate, NF	0.5%	1.5
Total	100%	300

Table 6.

Vessel	1hr	2hr	4hr	6hr	8hr	12hr	24hr
1	24	37	55	68	78	88	92
2	21	33	51	63	76	92	95
3	22	34	52	62	77	93	100
4	24	38	56	72	86	100	100
5	22	34	51	63	71	84	88
6	23	36	55	66	75	98	104
Ave	23	35	53	66	77	92	96
%RSD	5.2	4.9	4.2	5.7	6.4	6.4	6.1

Example 7

[0039] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	33.3%	100
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	66.2%	198.5
Magnesium Stearate, NF (Hyqual® Vegetable source)	0.5%	1.5
Total	100%	300

Table 7.

Vessel	1hr	2hr	4hr	6hr	8hr	12hr	24hr
1	21	33	53	69	84	-	-
2	21	34	54	68	81	-	-
3	23	35	57	69	80	-	-
4	22	31	54	68	83	-	-
5	22	35	56	71	83	-	-
6	23	36	57	69	87	-	-
Ave	22	34	55	69	83	-	-
%RSD	5.0	4.8	3.6	1.5	3.0	-	-

NOTE: 12 and 24 hour pulls not performed

Example 8

[0040] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	25.0%	100
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	74.5%	298.0
Magnesium Stearate, NF (Hyqual® Vegetable source)	0.5%	2.0
Total	100%	400

Table 8.

Vessel	1hr	2hr	4hr	6hr	8hr	12hr	24hr
1	20	29	47	60	73	-	-
2	22	34	53	68	79	-	-
3	22	33	47	68	79	-	-
4	20	30	47	64	74	-	-
5	19	30	43	59	69	-	-
6	21	31	49	64	76	-	-
Ave	21	31	48	64	75	-	-
%RSD	5.5	6.6	7.3	5.7	5.0	-	-

NOTE: 12 and 24 hour pulls not performed

Example 9

[0041] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	25.0%	100
Lactose Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	74.5%	298.0
Magnesium Stearate, NF (Hyqual® Vegetable source)	0.5%	2.0
Total	100%	400

[0042] Batch has an approximate 50% dissolution release at 4 hours and approximate 80% release at 8 hours.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition (Composition 1), e.g., a sustained release pharmaceutical composition, comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
2. The composition of claim 1, wherein the composition is sustained release.
3. The composition of claim 1 or 2 wherein the pharmaceutical composition is substantially free of the corresponding (-) enantiomer.
4. The composition of claim 1, 2, or 3, wherein the composition comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
5. The composition of any one of claims 1-4, wherein the composition comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
6. The composition of any one of claims 1-5, wherein the composition comprises less than or equal to 5% w/w of the corresponding (-) enantiomer.
7. The composition of any one of claims 1-6, wherein the composition comprises less than or equal to 2% w/w of the corresponding (-) enantiomer.
8. The composition of any one of claims 1-7, wherein the composition comprises less than or equal to 1% w/w of the corresponding (-) enantiomer.
9. The composition of any one of claims 1-8, wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
10. The composition of claim 9, wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt
11. The composition of claim 10, wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
12. The composition of any one of claims 1-11 comprising 1 mg to 1800 mg, e.g., 10 mg to 1800 mg, e.g., 25 mg to 1800 mg, e.g., 10 mg to 1600 mg, e.g., 10 mg to 1200 mg, e.g., 50 mg to 1200 mg, e.g., 50 mg to 1000 mg, e.g., 75 mg to 1000 mg, e.g., 75 mg to 800 mg, e.g., 75 mg to 500 mg, e.g., 100 mg to 750 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

13. The composition of any one of claims 1-12 comprising 75 mg to 1000 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
14. The composition of any one of claims 1-12 comprising 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
15. The composition of any one of claims 1-12 comprising 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g, 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
16. The composition of any one of claims 1-11 for administration of 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
17. The composition of any one of claims 1-16 comprising less than 50% w/w of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, e.g., less than about 40% w/w, e.g., less than about 30% w/w, less than about 20 % w/w, e.g., about 1-40% w/w, e.g., about 5-40% w/w, e.g., about 10-30% w/w, e.g., about 15-25% w/w, e.g., about 15-20% w/w, e.g., about 17% w/w, e.g., about 25% w/w.
18. The composition of any one of claims 1-17 further comprising hydroxypropyl methylcellulose.
19. The composition of claim 18, wherein the composition comprises at least 10% w/w of the hydroxypropyl methylcellulose, e.g., about 10-50% w/w, e.g., about 10-40% w/w, e.g., about 20-50% w/w, e.g., about 20-40% w/w, e.g., about 30-40% w/w, e.g., about 37% w/w.
20. The composition of claim 18 or 19, wherein the degree of methoxy substitution of the hydroxypropyl methylcellulose is 19-24%.
21. The composition of any one of claims 18-20, wherein the degree of hydroxypropoxy substitution of the hydroxypropyl methylcellulose is 4-12%.

22. The composition of any one of claims 18-21, wherein the hydroxypropyl methylcellulose is hypromellose 2208.
23. The composition of any one of claims 18-22, wherein the hydroxypropyl methylcellulose has a nominal viscosity of 4,000 mPA•s.
24. The composition of any one of claims 18-22, wherein the hydroxypropyl methylcellulose has a viscosity of 2,000-6,000 mPA•s, e.g., about 2,600 to 5,000 mPA•s, e.g., about 2,663 to 4,970 mPA•s.
25. The composition of any one of claims 1-24, wherein the composition further comprises alpha-lactose monohydrate.
26. The composition of claim 25, wherein the composition comprises at least 10% w/w of the alpha-lactose monohydrate, e.g., about 10-80% w/w, e.g., about 20-70% w/w, e.g., about 20-60% w/w, e.g., about 20-50% w/w, e.g., about 20-40% w/w, e.g., about 20-30% w/w, e.g., about 30-70% w/w, e.g., about 30-60% w/w, e.g., about 30-50% w/w, e.g., about 30%-40% w/w, e.g., about 37% w/w.
27. The composition of claim 25 or 26, wherein the composition comprises milled alpha-lactose monohydrate.
28. The composition of any one of claims 1-27, wherein the composition comprises a co-processed mixture of hydroxpropyl methylcellulose and alpha-lactose monohydrate (e.g., Retalac®).
29. The composition of claim 28, wherein the mixture comprises equal parts of the hydroxpropyl methylcellulose and alpha-lactose monohydrate.
30. The composition of claim 28 or 29, wherein the mixture comprises particles of hydroxpropyl methylcellulose and alpha-lactose monohydrate with d_{50} (median diameter) in the range of 100 μm to 200 μm, e.g., about 125 μm.
31. The composition of any one of claims 28-30, wherein the mixture comprises particles of hydroxpropyl methylcellulose and alpha-lactose monohydrate wherein the particle size distribution is as follows:

    < 63 μm ≤ 25%

    < 100 μm: 35%

    < 250 μm ≥ 80%.

32. The composition of any one of claims 28-31, wherein the composition comprises at least 20% w/w of the mixture, e.g., about at least 30% w/w, e.g., at least about 40% w/w, e.g., at least about 50% w/w, e.g., at least about 60% w/w, e.g., at least about 70% w/w, e.g, at least about 80% w/w, e.g., about 20-90% w/w, e.g., about 30-80% w/w, e.g., about 40-80% w/w, e.g., about 50-80% w/w, e.g., about 60-80% w/w, e.g., about 70-80% w/w, e.g., about 75% w/w.
33. The composition of any one of claims 1-32, wherein the composition further comprises a lubricant, e.g., magnesium stearate.
34. The composition of claim 33, wherein the lubricant is one or more of glyceryl behenate, magnesium stearate, talc, and sodium stearyl fumarate, e.g, magnesium stearate.
35. The composition of claim 33 or 34, wherein the composition comprises less than 10% w/w of the lubricant, e.g., less than about 5% w/w, less than about 3% w/w, less than about 1% w/w, e.g., about 0.1 to 1% w/w, e.g., about 0.1 to 0.8% w/w, e.g., about 0.5% w/w.
36. The composition of any one of claims 33-35, wherein the composition comprises less than 10% w/w of magnesium stearate, e.g., less than about 5% w/w, less than about 3% w/w, less than about 1%, e.g., about 0.1 to 1% w/w, e.g., about 0.1 to 0.8% w/w, e.g., about 0.5% w/w.
37. The composition of any one of claims 1-36, wherein the composition further comprises one or more of a diluent, disintegrant, binder, and modified release agent.
38. The composition of claim 37, wherein the diluent is one or more of mannitol (e.g., Pearlitol 300 DC), micro-crystalline cellulose (e.g., Avicel pH 102), and pre-gelatinized starch (e.g., Starch 1500).
39. The composition of claim 37, wherein the disintegrant is one or both of crospovidone (e.g., Polyplasdone XL-10) and sodium starch glycolate (e.g., Explotab).
40. The composition of claim 37, wherein the binder is polyvinylpyrrolidone (e.g., Povidone K29/32).
41. The composition of claim 37, wherein the modified release agent is one or more of hydroxypropyl cellulose (e.g., Klucel EXF, Klucel MXF and/or Klucel HXF) and hydroxypropyl methylcellulose (e.g., Methocel K100M, Methocel K4M PREM, Methocel K15M PREM CR).

42. The composition of claim 37 or 41, wherein the composition comprises at least 5% w/w of the modified release agent, e.g., about 5-60% w/w, e.g., about 10-50% w/w, e.g., about 10-40% w/w.

43. The composition of claim 41 or 42, wherein the modified release agent is hydroxypropyl methylcellulose.

44. Any of Compositions 1, e.g., 1.1-1.67, for use in indications as described in U.S. Patent No. 8,461,196, International Publication No. WO 2013/019271, and International Patent Application No. PCT/US14/69401, the contents of each of which are hereby incorporated by reference.

45. Any of the compositions of the preceding claims for use in indications as described in U.S. Patent No. 8,461,196, International Publication No. WO 2013/019271, and International Patent Application No. PCT/US14/69401, the contents of each of which are hereby incorporated by reference.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/69416

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 209/02; A61K 31/403 (2015.01)
CPC - C07D 209/52
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07D 209/02; A61K 31/403 (2015.01)
CPC: C07D 209/52

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/412; 548/515

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST
"(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo [3.1.0]hexane", composition, formulation, dosage form, sustained release

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/019271 A1 (MCKINNEY et al.) 07 February 2013 (07.02.2013) para [0008]-[0010], [0028], [0069]	1-3
A	US 2008/0058535 A1 (CHEN et al.) 06 March 2008 (06.03.2008) Entire Document	1-3

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2015 (26.01.2015)	26 FEB 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/69416

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 44
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
because it is not drafted in accordance with PCT Rule 6.2 and 6.3.

3. ☒ Claims Nos.: 4-43 and 45
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.