NEUROACTIVE STEROID SOLUTIONS AND THEIR METHODS OF USE

RELATED APPLICATIONS

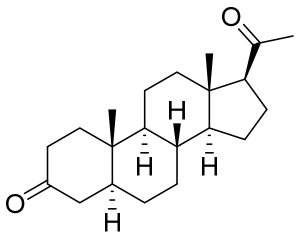
This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/181,550 filed June 18, 2015, the entire contents of which are incorporated herein by reference.

BACKGROUND

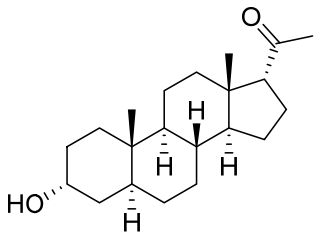
Homogeneous solutions (e.g., aqueous solutions) comprising a therapeutic agent, e.g., a neuroactive steroid described herein, enable administration to a human subject in need by various modes of administration (e.g., oral, parenteral (e.g., intravenous, intramuscular, subcutaneous) delivery). Neuroactive steroids are typically highly lipophilic compounds with low intrinsic water solubility. Particularly for intravenous administration, solutions are generally pH stable or chemically stable, preferably for an extended period of time.

SUMMARY

In one aspect of the present disclosure, there is provided a method of evaluating an aqueous composition comprising allopregnanolone and sulfo butyl ether beta cyclodextrin, the method comprising assaying the composition for the presence of a compound selected from the group consisting of:



and



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Provided herein is also a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a neuroactive steroid (e.g., allopregnanolone), a sulfobutyl ether beta cyclodextrin and a buffer; wherein: the solution is a stable solution between a pH of about 3 and about 9 (e.g., between about 5 and about 7, between about 5.5 and about 6.5), for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more.

In some embodiments, the solution is a stable solution between a pH of about 3 and about 9 (e.g., between about 5 and about 7, between about 5.5 and about 6.5), for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more at a temperature from about 2 °C to about 8 °C.

In some embodiments, the solution is a stable solution between a pH of about 3 and about 9 (e.g., between about 5 and about 7, between about 5.5 and about 6.5), for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more at a temperature from about 0 °C to about 45 °C (e.g., between about 0 °C to about 30 °C, between about 15 °C to about 25 °C).

Also provided herein is a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a neuroactive steroid (e.g., allopregnanolone), a sulfobutyl ether beta cyclodextrin and a buffer; wherein: the buffer is present at a concentration of at least 0.1 mM (e.g., at least 0.5 mM, 1 mM, 2 mM, 5 mM, or 10 mM).

Also provided herein is a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a neuroactive steroid (e.g., allopregnanolone), a sulfobutyl ether beta cyclodextrin and a buffer; wherein: the solution remains substantially free (e.g., meets product specifications of less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities (e.g., the solution is substantially free (e.g., meets product specifications of less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities at room temperature for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more). In some embodiments, the solution has at least 97% purity for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more). For example, the solution has 90-110 assay value for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more).

In some embodiments, the solution remains substantially free (e.g., less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more at a temperature from about 2 °C to about 8 °C.

In some embodiments, the solution remains substantially free (e.g., less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more at a temperature from about 0 °C to about 45 °C (e.g., between about 0 °C to about 30 °C, between about 15 °C to about 25 °C).

In some embodiments, the buffer in the solution is present at a concentration of from about 5 to 10 mM. In some embodiments, the buffer in the solution is present at a concentration of from about 0.1 to about 4 mM. In some embodiments, the buffer in the solution is present at a concentration of about 0.1, about 0.5, about 1.67, or about 3.3 mM.

In some embodiments, the solution further comprises a diluent.

In some embodiments, the solution is suitable for parenteral use.

In some embodiments, the solution is homogeneous.

In some embodiments, the neuroactive steroid is selected from pregnanolone, ganaxolone, alphadalone, alphaxalone, and allopregnanolone. In some embodiments, the neuroactive steroid is ganaxolone. In some embodiments, the neuroactive steroid is allopregnanolone.

In some embodiments, the neuroactive steroid is an estrol.

1:1 to about 1:60 (e.g., about 1:1 to about 1:20, about 1:1 to about 1:15). In some embodiments, the molar ratio of allopregnanolone to sulfoalkylether-βcyclodextrin is about 1:3 to about 1:20 (e.g., about 1:5 to about 1:10). In some embodiments, the solution additionally comprises a surfactant.

In some embodiments, the solution additionally comprises a chelating agent.

In some embodiments, the solution additionally comprises a preservative.

In some embodiments, the solution additionally comprises a isotonizing agent. In some embodiments, the isotonizing agent is present in an amount to obtain isotonicity.

In some embodiments, the solution is sterilized by heat treatment.

There is also provided a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a neuroactive steroid, a sulfobutyl ether beta cyclodextrin and a buffer; the composition comprising less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities (e.g., the solution is substantially free (e.g., less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities for at least 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months; 1, 2, 3 years or more).

There is further provided a method for preparing a stable solution comprising allopregnanolone, the method comprising contacting allopregnanolone with a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a sulfobutyl ether beta cyclodextrin and a buffer.

In some embodiments, the solution is at between about 0 °C to about 60 °C (e.g., between about 20 °C to about 50 °C, between about 35 °C to about 45 °C). In some embodiments, the solution is at room temperature (e.g., 35-45 ºC).

In some embodiments, the solution is chemically stable.

In some embodiments, the solution is autoclaved (e.g., subjected to cycles of heat sterilization, e.g., subjected to at least 10 (e.g., at least 15, 20, 30, 40 minutes) of heat (e.g., from 110 to 150 ºC (e.g., 121 to 123 ºC)). In some embodiments, the solution is at from 110 to 150 ºC (e.g., 121 to 123 ºC).

In some embodiments, the amount of degradant of the neuroactive steroid present in the solution is less than 0.1% w/w for 1, 2, 3, 4, 5, 6, 7 days or more; 1, 2, 3, 4 weeks or more; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or more; 1, 2, 3 years or more.

Provided herein is also a pharmaceutically acceptable aqueous solution comprising (e.g., consisting essentially of, consisting of) a neuroactive steroid (e.g., allopregnanolone), a sulfobutyl ether beta cyclodextrin and a buffer; wherein: the solution is a stable solution between a pH of about 3 and about 9 (e.g., between about 5 and about 7, between about 5.5 and about 6.5), for at least 5 minutes, e.g., at least10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60 minutes or more at a temperature from about 120°C to about 124°C ; or the buffer is present at a concentration of at least 0.1 mM; or the solution remains substantially free (e.g., meets product specifications of less than 3, 2, 1, 0.5, 0.3, 0.2, 0.1% w/w) of impurities for at least 5 minutes, e.g., at least10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60 minutes or more at a temperature from about 120°C to about 124°C.

Provided herein is also a method of parenteral administration, the method comprising mixing a first solution comprising allopregnanolone (e.g., a solution described herein) with a diluent (e.g., water or injection or saline solution) to provide a diluted solution; and parenterally administering the diluted solution to a subject. In some embodiments, the first solution is diluted with two parts diluent to one part first solution. In some embodiments, the first solution is diluted with nine parts diluent to one part first solution.

Provided herein is also a method of preparing an aqueous solution comprising a neuroactive steroid, a sulfoalkyl ether beta cyclodextrin (e.g., sulfobutyl ether beta cyclodextrin or sulfobutylether-β-cyclodextrin), and a buffer, wherein the solution is mixed (e.g., by high-shear homogenization) to provide a solution substantially free (e.g., less than about 1, 0.5, 0.2, 0.1% w/v) of solids (e.g., free of any solid with a particle size of 0.22, 0.45, 1 micron or greater in diameter).

In some embodiments, the solution is mixed with a suitable mixing device or method. In some embodiments, the mixing device is a high shear impeller mixer, rotor stator mixer, homogenizer, ultrasonic device, or microfluidizer.

In some embodiments, the rotor stator mixer spins at 2,000 to 18,000 rpm. In some embodiments, the homogenizer functions at 1000 to 5000 psi.

In some embodiments, the solution is mixed by suitable high-shear mixing device such as rotor/stator device, a homogenizer, microfluidizer or sonication device. In some embodiments, the high shear mixing device (e.g., a rotor/stator, homogenizer, microfluidizer or sonication device uses inline high shear assemblies).

In some embodiments, the method is used for a suitable period of time to achieve solubilization (e.g., at least 15, 30, 60 or more minutes).

In some embodiments, the solution is diluted with a diluent, e.g., to produce an admixture.

Provided herein is also a closed container comprising a neuroactive steroid, a sulfoalkyl ether beta cyclodextrin (e.g., sulfobutyl ether beta cyclodextrin or sulfobutylether-β-cyclodextrin), and a buffer; additionally comprising a gaseous layer substantially comprising (e.g., comprising more than 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.5, 99.98, 99.99% of an inert gas (e.g., nitrogen, argon).

In some embodiments, the gaseous layer comprises less than 21, 20, 17, 15, 12, 10, 8, 5, 3, 1, 0.5, 0.2, 0.1, 0.05% oxygen gas (e.g., free of oxygen gas).

In some embodiments, the container comprises a vial, stopper, or an overseal.

In some embodiments, the container is a prefilled syringe. In some embodiments, the container is a glass container. In some embodiments, the container is a plastic container. In some embodiments, the plastic container and low oxygen levels are provided by an overwrap (e.g aluminum laminate pouch).

Provided herein is also a method of treating a subject (e.g., a subject suffering from a disease or disorder described herein (e.g., depression (e.g., postpartum depression), the method comprising administering an aqueous solution or admixture described herein, thereby treating a subject.

Provided herein is also a method of treating a subject (e.g., a subject suffering from a disease or disorder described herein (e.g., depression (e.g., postpartum depression), the method comprising administering one part of an aqueous solution described herein, per two parts of a diluents described herein (e.g., WFI), thereby treating a subject.

Provided herein is also a method of treating a subject (e.g., a subject suffering from a disease or disorder described herein (e.g., depression (e.g., postpartum depression), the method comprising administering one part of an aqueous solution described herein, per nine parts of a diluents described herein (e.g., WFI), thereby treating a subject.

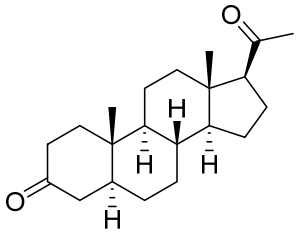
DETAILED DESCRIPTION OF FIGURES

Figure 1. Depiction of Allopregnanolone Degradation Processes

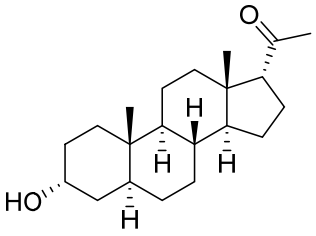
Figure 2. Depiction of Allopregnanolone Solubility in SBECD

CLAIMS

1. A method of evaluating an aqueous composition comprising allopregnanolone and sulfo butyl ether beta cyclodextrin, the method comprising assaying the composition for the presence of a compound selected from the group consisting of:



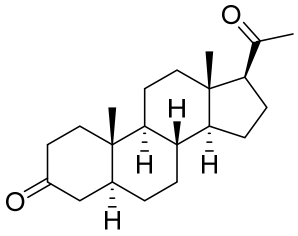
and



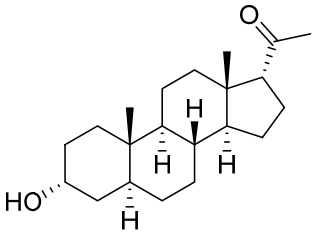
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2. The method of claim 1, wherein the assaying comprises analysis using HPLC.

3. The method of claim 1, the method further comprising assaying for the amount of a compound selected from the group consisting of:



and



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4. The method of claim 1, wherein the composition further comprises a buffer.

5. The method of claim 4, wherein the buffer is a citrate buffer.

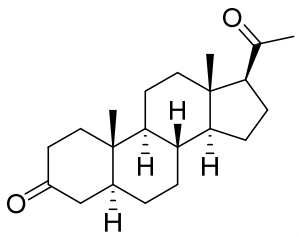
6. The method of claim 4, wherein the buffer in the composition is present at a concentration of from about 0.1 to about 20 mM.

7. The method of claim 1, wherein the composition comprises about 5 mg/mL of allopregnanolone.

8. The method of claim 1, wherein the composition comprises about 250 mg/mL of sulfo butyl ether beta cyclodextrin.

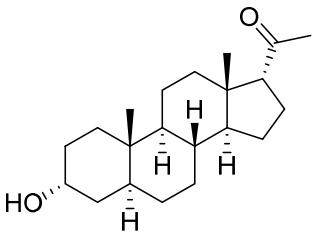
9. The method of claim 1, wherein the composition comprises about 5 mg/mL of allopregnanolone and about 250 mg/mL of sulfo butyl ether beta cyclodextrin.

10. The method of claim 1, wherein the composition is assayed for the presence of a compound having the following structure:



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11. The method of claim 1, wherein the composition is assayed for the presence of a compound having the following structure:



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