Solvate Form of (*R*)-2-amino-3-phenylpropyl carbamate

Statement Of Priority

[0001] The present invention claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 62/383,822, filed September 6, 2016, the entire contents of which are incorporated by reference herein.

Field of the Invention

[0002] The present invention relates to a newly identified solvate form of (*R*)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride, a method of preparing APC hydrochloride, and methods of using the same to treat disorders. The invention further relates to methods of producing APC hydrochloride with increased purity.

Background of the Invention

[0003] APC is a phenylalanine analog that has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others. See, for example, US Patent Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414. Methods for producing APC (which also has other names) and related compounds can be found in US Patent Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated herein by reference in their entireties for all purposes.

[0004] The present invention overcomes shortcomings in the art by providing a new solvate form of APC and a method of preparing APC with minimal contaminants.

Summary

[0005] In one aspect, the present disclosure refers to a solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 Form B and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and 27.3 ± 0.2 °2θ. The present disclosure describes the identification of a novel solvate form of APC which is a hemihydrate form. The disclosure further describes a method of preparing

APC with minimal contaminants. The disclosure additionally describes the use of the new solvate form and/or the APC with increased purity for the treatment of disorders responsive to APC.

[0006] Accordingly, the disclosure describes a solvate form of APC hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and 27.3 ± 0.2 °2θ.

[0007] In another example, the present disclosure refers to a process of preparing a solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, comprising slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration. In another aspect, the present disclosure refers to a process of preparing the solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride as disclosed herein, comprising slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration. The disclosure further describes a process of preparing a solvate form of APC hydrochloride, comprising slurrying APC hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration. In yet another aspect, the present disclosure refers to a method of preparing (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing (*R*)-2-amino-3-phenylpropyl carbamate in the presence of aqueous HCl, thereby producing crystals of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride.

[0008] In a further aspect, the present disclosure refers to a composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, wherein at least 30% of the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is the solvate form as disclosed herein. In yet another example, the present disclosure refers to a composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, wherein less than 10% of the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is the solvate form as disclosed herein. In one example, the present disclosure refers to a composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, the composition comprising less than about 5 ppm 2-chloropropane. The disclosure further describes a composition comprising APC, wherein less than about 10% of the APC in the composition is the solvate form of the disclosure.

[0009] The disclosure also relates to a composition comprising APC, wherein at least about 30% of the APC in the composition is the solvate form of the disclosure.

[0010] In one example, the present disclosure refers to the use of the composition disclosed herein in the manufacture of a medicament for treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, wherein the composition disclosed herein is to be administered to the subject. In yet another aspect, the present disclosure refers to use of the composition as disclosed herein in the manufacture of a medicament for treating narcolepsy, cataplexy, excessive daytime sleepiness, cocaine addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, wherein the composition as disclosed herein is to be administered to the subject. The disclosure additionally describes a method of treating a disorder amenable to treatment with APC, *e.g.*, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject a dosage form comprising the solvate form of the disclosure.

[0011] The disclosure also describes a method of preparing APC hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing APC in the presence of aqueous HCl, thereby producing crystals of APC hydrochloride.

[0012] The disclosure further describes a composition comprising APC with increased purity as prepared by the method of the disclosure.

[0013] The disclosureadditionally describes a method of treating a disorder amenable to treatment with APC, *e.g.*, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject a dosage form comprising APC with increased purity as prepared by the method of the disclosure.

[0014] The present invention is explained in greater detail in the drawings herein and the specification set forth below.

Brief Description of the Drawings

[0015] Figure 1 shows the X-ray pattern diffraction (XRPD) of crystalline forms of APC.

What is Claimed is:

1. A solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 Form B and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and 27.3 ± 0.2 °2θ.

2. The solvate form of claim 1, further characterized by differential scanning calorimetry as having a broad endotherm with onset at 69.1°C and peak at 71.7°C and a sharp endotherm with onset at 182.5°C and peak at 183.6°C.

3. The solvate form of claim 1 or 2, wherein the solvate form is a hemihydrate.

4. The solvate form of any one of claims 1-3, further characterized as being produced by slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v).

5. A process of preparing the solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride of any one of claims 1-4, comprising slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration.

6. The process of claim 5, wherein the slurrying is performed at about room temperature.

7. The process of claim 5 or 6, wherein the slurrying is performed at for at least about 20 hours.

8. A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, wherein at least 30% of the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is the solvate form of any one of claims 1-4.

9. The composition of claim 8, wherein the composition is a dosage form.

10. The composition of claim 9, wherein the composition is an immediate release oral dosage form.

11. The composition of claim 10, wherein the composition is a tablet or a capsule.

12. Use of the composition of any one of claims 8-11 in the manufacture of a medicament for treating narcolepsy, cataplexy, excessive daytime sleepiness, cocaine addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, wherein the composition of any one of claims 8-11 is to be administered to the subject.

13. The use of claim 12, wherein the composition is to be administered once per day.

14. The use of claim 12, wherein the composition is to be administered more than once per day.

15. A method of preparing (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing (*R*)-2-amino-3-phenylpropyl carbamate in the presence of aqueous HCl, thereby producing crystals of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride.

16. The method of claim 15, wherein the crystallizing is performed at a temperature of about 25°C to about 30°C.

17. The method of claim 15 or 16, further comprising drying the crystals of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride at a temperature of about 35°C or less.

18. The method of any one of claims 15-17, wherein the amount of 2-chloropropane in the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is less than about 5 ppm.