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 invention 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 invention describes the identification of a novel solvate form of APC which is a hemihydrate form. The invention further describes a method of preparing

APC with minimal contaminants. The invention 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 invention 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 aspect, the present invention 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. The invention 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 invention 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 invention 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 aspect, the present invention 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 aspect, the present invention refers to a composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, the composition comprising less than about 5 ppm 2-chloropropane. The invention further describes a composition comprising APC, wherein less than about 10% of the APC in the composition is the solvate form of the invention.

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

[0010] In one aspect, the present invention 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. The invention 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 invention.

[0011] The invention 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 invention further describes a composition comprising APC with increased purity as prepared by the method of the invention.

[0013] The invention 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 APC with increased purity as prepared by the method of the invention.

[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.

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

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

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

13. Use of the composition of any one of claims 8-11 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 of any one of claims 8-11 is to be administered to the subject.

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

15. The use of claim 13, wherein the tablet is to be administered more than once per day.

16. 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.

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

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

19. The method of any one of claims 16-18, wherein the amount of 2-chloropropane in the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is less than about 5 ppm.

20. A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, the composition comprising less than about 5 ppm 2-chloropropane.

21. The composition of claim 20, wherein the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is prepared by the method of any one of claims 16-19.

22. The composition of claim 20 or 21, wherein the composition is a dosage form.

23. The composition of claim 22, wherein the composition is an immediate release oral dosage form.

24. The composition of claim 23, wherein the composition is a tablet or a capsule.

25. Use of the composition of any one of claims 20-24 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 of any one of claims 20-24 is to be administered to the subject.

26. The use of claim 25, wherein the tablet is to be administered once per day.

27. The use of claim 25, wherein the tablet is to be administered more than once per day.