Formulations 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. 62/383,818, filed September 6, 2016, the entire contents of which are incorporated by reference herein.

Field of the Invention

[0002] The present invention relates to immediate release formulations of (*R*)-2-amino-3-phenylpropyl carbamate (APC) and methods of using the same to treat disorders.

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, U.S. 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 U.S. 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 by reference in their entireties for all purposes.

[0004] The present invention overcomes shortcomings in the art by providing immediate release formulations of APC suitable for treatment of disorders responsive to APC.

Summary

[0005] The present invention describes the development of immediate release formulations of APC. The invention additionally relates to the use of the formulations for the treatment of disorders responsive to APC.

[0006] In one example, the present disclosure refers to an immediate release compressed tablet for oral delivery of (*R*)-2-amino-3-phenylpropyl carbamate, the tablet comprising: (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; at least one binder in an amount of about 1-5% by

weight of the tablet; and at least one lubricant in an amount of about 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject. In another example, the present disclosure refers to an immediate release oral dosage form of (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof, the oral dosage form comprising: (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the oral dosage form; at least one binder in an amount of about 1-5% by weight of the oral dosage form; and at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form; wherein the oral dosage form releases at least 85% of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject. Accordingly, one example of the disclosure describes an immediate release compressed tablet for oral delivery of APC, the tablet comprising: APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; at least one binder in an amount of about 1-5% by weight of the tablet; and at least one lubricant in an amount of about 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

[0007] In one example, the present disclosure refers to an immediate release compressed tablet for oral delivery of (*R*)-2-amino-3-phenylpropyl carbamate, the tablet comprising (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; wherein the tablet exhibits substantially identical dissolution rates of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8. In another example, there is described an immediate release oral dosage form of APC, the oral dosage form comprising:

APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the oral dosage form;

at least one binder in an amount of about 1-5% by weight of the oral dosage form; and

at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form;

wherein the oral dosage form releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

[0008] In another example, there is described an immediate release compressed tablet for oral delivery of APC, the tablet comprising APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; wherein the tablet exhibits substantially identical dissolution rates of the APC or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

[0009] In one example, the present disclosure refers to the use of the immediate release compressed tablet 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 immediate release compressed tablet disclosed herein is to be administered to the subject. In another example, the present disclosure refers to the use of the compressed tablet or oral dosage form 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 compressed tablet or oral dosage form disclosed herein is to be administered to the subject. In another example, there is described 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 the compressed tablet of the disclosure.

[0009a] In one aspect, the present disclosure provides for an immediate release compressed tablet for oral delivery of (*R*)-2-amino-3-phenylpropyl carbamate, the tablet comprising: a pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet; at least one binder in an amount of 1-5% by weight of the tablet; and at least one lubricant in an amount of 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and wherein the tablet exhibits substantially

identical dissolution rates of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

[0009b] In another aspect, the present disclosure provides for an immediate release compressed tablet for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, the tablet comprising: a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet and a total weight of between 30 to 300 mg per tablet; hydroxypropyl cellulose in an amount of 1-3% by weight of the tablet; and magnesium stearate in an amount of 0.1% to 1.0% by weight of the tablet; wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and wherein the tablet exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8.

[0009c] In yet another aspect, the present disclosure provides for an immediate release compressed tablet for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, the tablet comprising: a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet and a total weight of between 30 to 300 mg per tablet; hydroxypropyl cellulose in an amount of 2% by weight of the tablet; and magnesium stearate in an amount of 0.5% by weight of the tablet; wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and wherein the tablet exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8.

[0009d] In yet another aspect, the present disclosure provides for use of the immediate release compressed tablet 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 immediate release compressed tablet as disclosed herein is to be administered to the subject.

[0009e] In yet another aspect, the present disclosure provides for an immediate release oral dosage form of (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof, the oral dosage form comprising: (*R*)-2-amino-3-phenylpropyl carbamate or a

pharmaceutically acceptable salt thereof in an amount of 90-98% by weight of the oral dosage form; at least one binder in an amount of 1-5% by weight of the oral dosage form; and at least one lubricant in an amount of 0.1-2% by weight of the oral dosage form; wherein the oral dosage form releases at least 85% of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject; and wherein the oral dosage form exhibits substantially identical dissolution rates of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

[0009f] In yet another aspect, the present disclosure provides for use of the compressed tablet or oral dosage form 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 oral dosage form as disclosed herein is to be administered to the subject.

[0010] The present invention is explained in greater detail in the drawings herein and the specification set forth below.

Brief Description of the Drawings

[0011] Figure 1 shows the dissolution rate of immediate release APC tablets.

[0012] Figure 2 shows the effect of coating on the dissolution rate of immediate release APC tablets.

What is claimed is:

1. An immediate release compressed tablet for oral delivery of (*R*)-2-amino-3-phenylpropyl carbamate, the tablet comprising:
a pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet;
at least one binder in an amount of 1-5% by weight of the tablet; and
at least one lubricant in an amount of 0.1-2% by weight of the tablet;
wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and
wherein the tablet exhibits substantially identical dissolution rates of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

2. The immediate release compressed tablet of claim 1, wherein the tablet releases at least 95% of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

3. The immediate release compressed tablet of claim 1 or 2, wherein the at least one binder is selected from at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, sodium carboxymethylcellulose, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate.

4. The immediate release compressed tablet of any one of claims 1-3, wherein the at least one lubricant is selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

5. The immediate release compressed tablet of any one of claims 1-4, comprising:
a pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet;
hydroxypropyl cellulose in an amount of 1-5% by weight of the tablet; and
magnesium stearate in an amount of 0.1-2% by weight of the tablet.

6. The immediate release compressed tablet of any one of claims 1-5, further comprising a coating.

7. The immediate release compressed tablet of claim 6, wherein the coating is a color overcoat.

8. The immediate release compressed tablet of any one of claims 1-7, wherein the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate is (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride.

9. The immediate release compressed tablet of any one of claims 1-8, wherein the tablet is oblong in shape.

10. The immediate release compressed tablet of any one of claims 1-9, wherein the tablet comprises about 300 mg of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate.

11. The immediate release compressed tablet of any one of claims 1-9, wherein the tablet comprises about 150 mg of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate.

12. The immediate release compressed tablet of any one of claims 1-9, wherein the tablet comprises about 75 mg of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate.

13. The immediate release compressed tablet of any one of claims 1-9, wherein the tablet comprises about 37.5 mg of the pharmaceutically acceptable salt of (*R*)-2-amino-3-phenylpropyl carbamate.

14. The immediate release compressed tablet of any one of claims 1-13, wherein the tablet is free of other excipients.

15. The immediate release compressed tablet of any one of claims 1-14, comprising a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof in an amount of 90-98% by weight of the tablet and a total weight of between 30 to 300 mg per tablet.

16. The immediate release compressed tablet of any one of claims 1-15, comprising hydroxypropyl cellulose in an amount of 1-3% by weight of the tablet.

17. The immediate release compressed tablet of any one of claims 1-16, comprising magnesium stearate in an amount of 0.1% to 1.0% by weight of the tablet.

18. An immediate release compressed tablet for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, the tablet comprising:
a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet and a total weight of between 30 to 300 mg per tablet;
hydroxypropyl cellulose in an amount of 1-3% by weight of the tablet; and
magnesium stearate in an amount of 0.1% to 1.0% by weight of the tablet;
wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and
wherein the tablet exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8.

19. An immediate release compressed tablet for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, the tablet comprising:
a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of 90-98% by weight of the tablet and a total weight of between 30 to 300 mg per tablet;

hydroxypropyl cellulose in an amount of 2% by weight of the tablet; and
magnesium stearate in an amount of 0.5% by weight of the tablet;
wherein the tablet releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the tablet to a subject; and
wherein the tablet exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8.

20. Use of the immediate release compressed tablet of any one of claims 1-19 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 immediate release compressed tablet of any one of claims 1-19 is to be administered to the subject.

21. The use of claim 20, wherein the tablet is to be administered once per day.

22. The use of claim 20, wherein the tablet is to be administered more than once per day.

23. An immediate release oral dosage form of (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof, the oral dosage form comprising:
(*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof in an amount of 90-98% by weight of the oral dosage form;
at least one binder in an amount of 1-5% by weight of the oral dosage form; and
at least one lubricant in an amount of 0.1-2% by weight of the oral dosage form;
wherein the oral dosage form releases at least 85% of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject; and
wherein the oral dosage form exhibits substantially identical dissolution rates of the (*R*)-2-amino-3-phenylpropyl carbamate or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

24. Use of the compressed tablet or oral dosage form of claim 23 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 oral dosage form of claim 23 is to be administered to the subject.

25. The use of claim 24, wherein the oral dosage form is to be administered once per day.

26. The use of claim 24, wherein the oral dosage form is to be administered more than once per day.