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(54) Benævnelse: **FORMULERINGER AF (R)-2-AMINO-3-PHENYLPROPYLCARBAMAT**

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DESCRIPTION

Field of the Invention

[0001] The present invention is defined in the appended claims and relates to immediate release compressed tablets for oral delivery of (*R*)-2-amino-3-phenylpropyl carbamate (APC) as defined in claim 1 and the associated dependent claims. These immediate release compressed tablets can be used in methods of treating disorders.

Background of the Invention

[0002] 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. US 2015/0018414 A1 discloses a "method for promoting cessation or reduction in the smoking and/or chewing of tobacco or nicotine-containing products in a subject in need thereof, comprising administering to the subject an effective amount of certain carbamate compounds". It also discloses "a method for preventing relapse smoking and/or chewing of tobacco or nicotine-containing products in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of certain carbamate compounds."

[0003] The present invention overcomes shortcomings in the art by providing immediate release formulations of APC suitable for treatment of disorders responsive to APC.

Summary of the Invention

[0004] The present invention is defined in the appended claims and relates 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 0.1-1.4% 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, wherein the at least one binder is selected from at least one of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and povidone; and

wherein the at least one lubricant is selected from at least one of magnesium stearate, calcium stearate, and sodium stearyl fumarate;

wherein the term "about", when used to refer to an amount, encompasses variations of ± 10%, ± 5%, ± 1%, ± 0.5%, or ± 0.1% of the specified amount.

[0005] The invention also relates to this immediate release compressed tablet for use in a method of treating a disorder selected from 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 method comprises administering to the subject the immediate release compressed tablet.

[0006] In one embodiment, the invention also relates to the immediate release compressed tablet defined in claim 1 for oral delivery of APC, 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.

[0007] The invention further relates to an immediate release compressed tablet as defined above for use in 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, wherein the method comprises administering to the subject the immediate release compressed tablet of the invention.

[0008] The present invention is explained in greater detail in the drawings herein and the specification set forth below.

Brief Description of the Drawings

[0009]

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

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

Figure 3 shows the effect of tablet size on the dissolution rate of immediate release APC tablets.

Figure 4 shows the effect of disintegrant on the dissolution rate of immediate release APC tablets.

Detailed Description of the Invention

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0011] As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

[0012] Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0013] Furthermore, the term "about", as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ± 10%, ± 5%, ± 1%, ± 0.5%, or even ± 0.1% of the specified amount.

[0014] The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term "materially altered", as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

[0015] The term "therapeutically effective amount" or "effective amount", as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, *etc.*, as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, *e.g.,* at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

[0016] "Treat" or "treating" or "treatment" refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more

symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, *etc.*, as would be well known in the art.

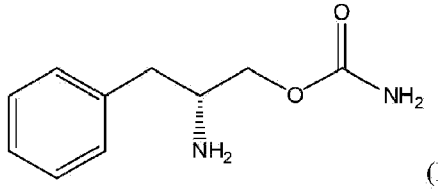
[0017] A "disorder amenable to treatment with APC" refers to any disorder in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Examples of such disorders include, without limitation, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity.

[0018] "Pharmaceutically acceptable", as used herein, means a material that is not biologically or otherwise undesirable, *i.e.*, the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, *e.g.*, Remington's Pharmaceutical Science; 21st ed. 2005).

[0019] "Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

[0020] The present invention is defined in the appended claims and provides an immediate release compressed tablet for oral delivery of APC or a pharmaceutically acceptable salt thereof according to claim 1 and its associated dependent claims. Formulations described herein are suited to the immediate release of high dose APC. In the present invention, immediate release formulations are provided as an immediate release tablet.

[0021] The immediate release APC compositions described herein comprise a therapeutically effective amount of APC or a pharmaceutically acceptable salt thereof. The structure of the free base of APC is given below as formula I.



(I)

[0022] Administration of APC in solid form presents several challenges. Patients treated with

APC may have difficulty taking solid medications by mouth because they have disease states that make handling and swallowing difficult. Accordingly, it is desirable to keep the size of the tablet as small as possible while incorporating the largest amount of active ingredient and meeting the desired dissolution profile. In addition, it is desirable to have a formulation that dissolves quickly without high levels of excipients to speed dissolution.

[0023] Accordingly, the invention relates to 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 0.1-1.4% 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 subj ect;

wherein the at least one binder is selected from at least one of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and povidone; and

wherein the at least one lubricant is selected from at least one of magnesium stearate, calcium stearate, and sodium stearyl fumarate;

wherein the term "about", when used to refer to an amount, encompasses variations of ± 10%, ± 5%, ± 1%, ± 0.5%, or ± 0.1% of the specified amount.

[0024] In one embodiment, the tablet comprises:

APC or a pharmaceutically acceptable salt thereof in an amount of about 91-95% by weight of the tablet;

the at least one binder as claimed in an amount of about 2-3% by weight of the tablet;

the at least one lubricant as claimed in an amount of about 0.1-1% by weight of the tablet; and optionally, a cosmetic film coat in an amount of about 3-4% 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.

[0025] In one embodiment, the tablet comprises:

APC or a pharmaceutically acceptable salt thereof in an amount of about 93.22% by weight of

the tablet;

the at least one binder as claimed (e.g., hydroxypropylcellulose) in an amount of about 2.87% by weight of the tablet;

the at least one lubricant as claimed (e.g., magnesium stearate) in an amount of about 0.52% by weight of the tablet; and

optionally, a cosmetic film coat (*e.g.*, Opadry® II yellow) in an amount of about 3-4% 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.

[0026] The tablets provided herein are utilized to achieve immediate release of APC or a pharmaceutically acceptable salt thereof.

[0027] Suitable salts of APC include, without limitation, acetate, adipate, alginate, aspartate, benzoate, butyrate, citrate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, hydroxynapthoate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, can be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. In certain embodiments, the salt is the hydrochloride salt.

[0028] Compounds of the formulae herein include those having quaternization of any basic nitrogen-containing group therein.

[0029] In some embodiments, the tablet releases at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of 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, e.g., less than 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 minutes. In some embodiments, the tablet releases at least 95%, 96%, 97%, 98%, or 99% of 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.

[0030] In certain embodiments, the tablet does not comprise a disintegrant. The term "disintegrant," as used herein, refers to an agent added to a tablet to promote the breakup of the tablet in an aqueous environment. The tablets of the present invention are advantageous in that they dissolve rather than disintegrate. In the present invention the presence of

disintegrant in the formulation may actually slow down release of APC.

[0031] In certain embodiments, APC or a pharmaceutically acceptable salt thereof is present in an amount of about 90%, 90.5%, 91%, 91.5%, 92%, 92.5%, 93%, 93.5%, 94%, 94.5%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, or 98% by weight of the tablet or any value or range therein. In certain embodiments, APC or a pharmaceutically acceptable salt thereof is present in an amount of about 90% to about 98%, about 92% to about 98%, about 94% to about 98%, about 96% to about 98%, about 90% to about 92%, about 90% to about 94%, about 90% to about 96%, about 92% to about 94%, about 92% to about 96%, or about 94% to about 96%.

[0032] In certain embodiments, the at least one binder is present in an amount of about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the tablet or any value or range therein. In the invention, the at least one binder is present in an amount of about 1% to about 5%. In certain embodiments, the at least one binder is present in an amount of about 2% to about 5%, about 3% to about 5%, about 4% to about 5%, about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 2% to about 3%, about 2% to about 4%, or about 3% to about 4%. The tablet may comprise 1, 2 or 3 binders.

[0033] The at least one binder is selected from at least one of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and povidone or any combination thereof. In some embodiments, the at least one binder is hydroxypropyl cellulose.

[0034] In certain embodiments, the at least one lubricant is present in an amount of about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, or 1.4% by weight of the tablet or any value or range therein. In the invention, the at least one lubricant is present in an amount of about 0.1% to about 1.4%. In certain embodiments, the at least one lubricant is present in an amount of about 0.1% to about 0.5%, about 0.1% to about 1.0%, about 0.1% to about 1.4%, about 0.5% to about 1.0%, about 0.5% to about 1.4%, or about 1.0% to about 1.4%. The tablet may comprise 1, 2 or 3 lubricants. Lower lubricant levels may be achieved with use of a "puffer" system during tableting. Such systems are known in the art, commercially available and apply lubricant directly to the punch and die surfaces rather than throughout the formulation.

[0035] The at least one lubricant is selected from at least one of magnesium stearate, calcium stearate, and sodium stearyl fumarate or any combination thereof. In some embodiments, the at least one lubricant is magnesium stearate. In other embodiments, magnesium stearate may be used in combination with one or more other lubricants or a surfactant, such as sodium lauryl sulfate. In particular, if needed to overcome potential hydrophobic properties of magnesium stearate, sodium lauryl sulfate may also be included when using magnesium stearate (Remington: the Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000)).

[0036] In some embodiments, the at least one binder is hydroxypropyl cellulose. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at

least one binder is hydroxypropyl cellulose and the at least one lubricant is magnesium stearate.

[0037] In certain embodiments, the tablet is coated. The coating may be, without limitation, a color overcoat.

[0038] In some embodiments, the APC or a pharmaceutically acceptable salt thereof is APC hydrochloride.

[0039] The tablet may be of any shape that is suitable for immediate release and allows the release of 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. In some embodiments, the tablet maximizes surface area to volume ratio to promote rapid dissolution. In some embodiments, the tablet is oblong in shape.

[0040] The tablet may contain any amount of APC or a pharmaceutically acceptable salt thereof suitable for administration as a unit dosage form. In some embodiments, the tablet contains about 1 mg to about 1000 mg of the drug or any range or value therein, e.g., about 10 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

[0041] APC or a pharmaceutically acceptable salt thereof may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Patent Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532.

[0042] "Immediate release" as used herein, refers to a composition that releases APC or a pharmaceutically acceptable salt thereof substantially completely into the gastrointestinal tract of the user within a period of less than about 15 minutes, usually between about 1 minute and about 15 minutes from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to an oral solution. Such rapid absorption will typically occur for an immediate release unit dosage form, such as a tablet, caplet or capsule, if the drug included in such dosage form dissolves in the upper portion the gastrointestinal tract.

[0043] Release rates can be measured using standard dissolution test methods. For example, the standard conditions may be those described in FDA guidance (*e.g.*, 50 rpm, 37°C, USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel).

[0044] "Dissolution rate," as used herein, refers to the quantity of drug released *in vitro* from a dosage form per unit time into a release medium.

[0045] "Bioavailability," as used herein, refers to the estimated area under the curve, or AUC of the active drug in systemic circulation after oral administration with a dosage form as disclosed herein when compared with the AUC of the active drug in systemic circulation after intravenous

administration of the active drug. The AUC is affected by the extent to which the drug is absorbed in the GI tract.

[0046] Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test product to reference product is within 80% to 125%.

[0047] The term "$AUC_{(0-t)}$" means the area under the plasma concentration curve from time 0 to time t.

[0048] The term "$AUC_{(0-\infty)}$" or "AUC_{0-inf}" means the area under the plasma concentration time curve from time 0 to infinity.

[0049] "C_{max}" refers to the maximum plasma concentration of APC.

[0050] "T_{max}" refers to the time to maximum plasma concentration for a given drug.

[0051] "$t_{1/2}$" refers to the time to reduce the plasma concentration by 50% during the terminal elimination phase of the drug.

[0052] The immediate release tablets for oral administration defined in the claims can deliver a therapeutically effective dose of APC upon ingestion thereof by the patient of one or more of said tablets, each of which can provide a dosage of, for example, about 1 to about 1000 mg of APC. Additionally, the immediate release tablets can be shaped or scored to facilitate dose adjustment through tablet splitting.

[0053] The formulation and structure of an immediate release tablet as disclosed herein can be adjusted to provide immediate release performance that suits a particular dosing need. In particular, the formulation and structure of the tablets as described herein can be adjusted to provide any combination of the immediate release performance characteristics described herein. In particular embodiments, for example, an immediate release tablet as disclosed herein provides rapid onset of action, releasing more than about 85%, such as, for example, more than about 90% or 95%, of the drug contained therein within a period of time selected from less than 15 minutes, less than 12 minutes, less than 10 minutes, and less than 5 minutes after administration.

[0054] Moreover, the rate of drug release from an immediate release tablet as disclosed herein may be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. In one embodiment, the immediate release tablet may be formulated to deliver as much as 1,000 mg of APC. In particular embodiments, the total amount of drug contained within an immediate release tablet according to the present description may be between about 10 mg and about 500 mg. For example, in certain such embodiments, the total amount of drug may be selected from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675,

700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, or 1000 mg or any range or value therein. In certain such embodiments, the total amount of drug may be about 10 mg to about 1000 mg, about 10 mg to about 500 mg, about 10 mg to about 300 mg, about 30 mg to about 1000 mg, about 30 mg to about 500 mg, about 30 mg to about 300 mg, about 100 mg to about 1000 mg, about 10 mg to about 500 mg, about 100 mg to about 300 mg, about 150 mg to about 1000 mg, about 150 mg to about 500 mg, or about 150 mg to about 300 mg.

[0055] The immediate release formulations provided herein include APC and some level of lubricant to facilitate processing of the formulations into a tablet. The formulations described herein include a combination of APC and lubricant, as described herein. The immediate release formulations described herein include a combination of APC, lubricant, and binder, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. Though the immediate release formulations described herein may be formulated using a combination of drug and a lubricant and binder, in certain embodiments, the compositions described herein may include one or more additional excipients selected from, for example, fillers, compression aids, diluents, disintegrants, colorants, flavorants, buffering agents, coatings, glidants, or other suitable excipients.

[0056] The immediate release formulations described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and dry powder blending. Suitable methods for the manufacture of the immediate release tablets described herein are provided, for example, in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms). It has been found that, even without the aid of binders or non-lubricating excipients, such as compression aids, wet granulation techniques can afford flowable granules with compression characteristics suitable for forming unit dosage forms as described herein. Therefore, in certain embodiments, where a drug content greater than about 90% or 95% by weight is desired for the immediate release formulation, wet granulation techniques may be used to prepare the immediate release formulations as described herein. In such embodiments, as illustrated in the Examples provided herein, conventional organic or aqueous solvents may be used in the wet granulation process. Suitable wet granulation processes can be performed as fluidized bed, high shear, or low shear (wet massing) granulation techniques, as are known in the art.

[0057] In addition to APC, lubricant, and binder, where desired, the immediate release formulations described herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. Where a filler or compression aid is used, in certain embodiments, it may be included in the immediate release formulation in an amount ranging from about 1%-15% by weight.

[0058] Immediate release formulations as described herein are processed into compressed tablets suitable for oral administration using conventional techniques. Immediate release tablets prepared as described are adapted for oral administration, so as to attain and maintain

a therapeutic level of APC over a preselected interval. In certain embodiments, an immediate release tablet as described herein may comprise a tablet of any desired shape and size including round, oval, oblong, cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release tablet may be flat, round, concave, or convex. In some embodiments, the shape may be selected to maximize surface area, *e.g.*, to increase the rate of dissolution of the tablet.

[0059] In particular, the immediate release tablets contain a relatively large percentage and absolute amount of APC and so are expected to improve patient compliance and convenience, by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, *e.g.*, closely spaced, in order to provide a therapeutically effective dose of APC to the subject in a relatively short period of time. For example, dissolution of a 10 mg-1000 mg tablet prepared according to the present description can provide about 80-100% of the APC to the subject in about 10-15 minutes.

[0060] Where desired or necessary, the outer surface of an immediate release tablet as disclosed herein may be coated with a moisture barrier layer using materials and methods known in the art. For example, where the APC delivered by the tablet is highly hygroscopic, providing a moisture barrier layer over the immediate release tablet as disclosed herein may be desirable. For example, protection of an immediate release tablet as disclosed herein from water during storage may be provided or enhanced by coating the tablet with a coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

[0061] Where desired or necessary, the outer surface of the immediate release tablet as disclosed herein may be coated with a color overcoat or other aesthetic or functional layer using materials and methods known in the art.

[0062] APC is a highly water soluble compound but in a pH dependent manner. The solubility decreases about 20-fold around pH 7 as shown in **Table 1**. The skilled artisan might expect that such a large drop in solubility would result in a change in dissolution as solubility drives the gradient which typically determines dissolution. Surprisingly, APC exhibits a consistent dissolution rate at different pHs above and below the solubility turning point. Further, the lack of a media pH effect has been consistently observed across doses ranging from 37.5 mg to 300 mg.

[0063] Thus, one embodiment of the invention relates to an immediate release compressed tablet for oral delivery of APC as defined in claim 1, wherein the tablet exhibits substantially identical dissolution rates of the APC or a pharmaceutically acceptable salt thereof at an acidic pH and a neutral pH, e.g., about pH 1.2, pH 4.5, and about pH 6.8. As used herein, the term

"substantially identical dissolution rates" is defined as a ratio of the time for a percentage of APC to be released from a dosage form in one condition to the time for the same percentage of APC to be released from a dosage form in another condition in the range of about 1.3 to about 0.7.

[0064] The tablet releases at least 85%, *e.g.*, at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, 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.

[0065] In certain embodiments, the tablet comprises, consists essentially of, or consists of the components described above and has one or more of the characteristics described above.

[0066] Immediate release compressed tablets of the invention can be used in methods of treating conditions amenable to treatment by APC. These methods comprise administering an effective amount of one or more immediate release compressed tablets of the invention as described herein. The present immediate release compressed tablets can be used in methods of treating a subject in need of treatment for narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity, or to promoting smoking cessation in a subject in need thereof. *See*, *e.g.*, 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.

[0067] The tablets disclosed herein can also be provided as a kit comprising, separately packaged, a container comprising a plurality of immediate release tablets, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, *e.g.*, sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC *in vivo* for preselected periods of time, to treat a preselected condition.

[0068] A daily dose of about 1 to about 2000 mg of APC or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 10-1000 mg, *e.g.*, about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about 0.01 to about 150 mg/kg body weight, *e.g.*, about 0.2 to about 18 mg/kg body weight.

[0069] In one embodiment of the invention, the immediate release compressed tablet comprising APC is administered to the subject as needed to treat a disorder. The immediate release compressed tablet can be administered continuously or intermittently. In one embodiment, the immediate release compressed tablet is administered to the subject more than once a day, *e.g.,* 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In

another embodiment, the immediate release compressed tablet is administered to the subject no more than once a week, *e.g.*, no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further embodiment, the immediate release compressed tablet is administered using two or more different schedules, *e.g.*, more frequently initially (for example to build up to a certain level, *e.g.,* once a day or more) and then less frequently (*e.g.*, once a week or less). In other embodiments, the immediate release compressed tablet can be administered by any discontinuous administration regimen. In one example, the immediate release compressed tablet can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the immediate release compressed tablet can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment the immediate release compressed tablet can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

[0070] In one aspect of the invention, the immediate release compressed tablet comprising APC is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same immediate release compressed tablet comprising APC or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the immediate release oral dosage form comprising APC. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Patent Nos. 8,952,062 and 9,050,302.

[0071] The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (*e.g.*, rats or mice), *etc.* Human subjects include neonates, infants, juveniles, adults and geriatric subjects.

[0072] In particular embodiments, the subject is a human subject that has a disorder amenable to treatment with APC. In other embodiments, the subject treated with the tablets of the invention is an animal model of a disorder amenable to treatment with APC.

[0073] The subject can be a subject "in need of" the tablets of the present invention, *e.g.*, in need of the therapeutic effects of the inventive tablets. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with APC, is suspected of having a disorder amenable to treatment with APC, and/or is anticipated to experience a disorder

amenable to treatment with APC, and the tablets of the invention are used for therapeutic and/or prophylactic treatment.

[0074] The present invention is explained in greater detail in the following non-limiting Examples.

EXAMPLE 1

Immediate release formulation of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride

[0075] Immediate release tablet formulations of APC were developed with the goal of achieving 85% dissolution in under 15 minutes. Dosage strengths of 75 mg, 150 mg, and 300 mg were targeted. The amount of APC per tablet was maximized to increase the release rate. A formulation of APC with binder and lubricant was found to maximize dissolution.

[0076] Tablets were prepared by first dry-blending screened hydroxypropylcellulose (HPC ExF, Ashland, 1.00 g)) and APC (unmilled, 19.00 g) and then wet granulating them in a bullet-type blender while adding 4 g water in 0.5 g increments. Sufficient granules were formed at 3 g, and at 4 g it was slightly over-wetted. The granules were wet sieved, dried partially to remove 0.7 g of moisture, and wet sieved again prior to drying at 60°C for about 1 hour. Magnesium stearate (0.75% of formulation) was added with blending 24 turns in a plastic container.

[0077] The active granulation was compressed with 10.31 mm (13/32") standard round tooling, 380 mg, 1000 Kg (1 ton) force applied by a Carver press to produce the 300 mg strength. The remaining tablets were compressed using 1000 Kg (1 ton) force and various size tooling.

[0078] Tablets were coated with a color overcoat (Aquarius Cool Vanilla BI-1800, Ashland/Aqualon; hydroxypropylmethylcellulose, titanium dioxide, triacetin, polysorbate) using a Caleva air-suspension coater to 2-4% by weight.

[0079] Dissolution testing was carried per FDA guidance under standard conditions (50 rpm, 37°C, USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel, sinkers for capsules). Samples were taken at 0, 2, 5, 10, 15, 20, 25, and 30 minutes with a tolerance of 2 seconds. After 30 minutes, the stirring speed was increased to 150 rpm for at least 1 minute or until all material had visibly dissolved or dispersed. The speed was then returned to 50 rpm and a sample indicating the total dissolved dose was taken. Samples were diluted 1.00 ml in 8.00 ml DI Water and then analyzed by UV (Shimadzu UV-1200).

[0080] The dissolution testing was shown to be reproducible (**FIG. 1**). The reference 150 mg tablets (uncoated) were tested on separate days, with different media preparation of the same kind and in different sequence of media recycle.

[0081] The color overcoat did not meaningfully retard dissolution (**FIG. 2**), although a slight trend was observed at 2 minutes (higher weight caused some delay, lower dissolution). The profile appears to be faster beyond 2 minutes, relative to the reference uncoated tablets. However, this could be an effect of the process (spraying water and drying in air suspension coater) rather than the coating itself. Using the 3% target coating as a reference, all profiles are similar (F2 > 50) and nearly completely dissolve in 15 minutes.

[0082] The three doses achieved by varying tablet size of a common granulation are represented in **FIG. 3**. The dissolution slows as the tablet size is increased, reflecting lower values of surface area/volume as expected. All strengths dissolve > 85% in 15 minutes, but the highest strength is marginal (86%). An increase in surface area/volume by using an oblong tablet resulted in a statistically significant increase in dissolution rate.

[0083] A substantial concern was the effect of media pH. Although APC will be developed as an immediate release product, FDA guidances require comparison of profiles in three media including pH 6.8 (representing intestinal pH). APC is highly soluble in water or acidic media (530 mg/ml) but its solubility is much less at pH 6.8 (26 mg/ml) (see **Table 1**). Remarkably, the 20-fold drop in solubility does not seem to affect the dissolution behavior, as shown in **Table 2**. The media used were 0.1 N HCl pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. The dissolution study was carried using 12 tablets per dose, apparatus 1 (basket), 900 ml media volume, 37°C, 100 rpm. The tablets were coated with Opadry white polymer system.

Table 1. Solubility of APC in 0.2 M phosphate buffers

pH of buffer	pH after equilibration	Solubility (mg/ml)
N/A (water)	4.22	533.74
5.33	4.25	542.49
5.95	4.78	525.46
6.97	6.76	26.60
8.02	7.47	22.53
8.99	7.55	22.38

Table 2. Dissolution of APC

		Percent release, time (min)		
Dose	Media	5	10	15
37.5 mg	pH 1.2	71.9	99.3	99.7
	pH 4.5	76.8	101.8	102.1
	pH 6.8	69.6	100.2	100.7
75 mg	pH 1.2	62.9	98.7	99.4
	pH 4.5	53.9	100.8	102.5
	pH 6.8	57.6	99.4	100.2
150 mg	pH 1.2	46.8	96.9	98.4
	pH 4.5	42.6	97.7	100.4

		Percent release, time (min)		
Dose	Media	5	10	15
	pH 6.8	42.4	97.4	100.7
300 mg	pH 1.2	35.0	91.2	99.5
	pH 4.5	30.0	89.1	99.8
	pH 6.8	31.6	89.9	100.2

[0084] As mitigation of expected poorer dissolution at pH 6.8 (which was not seen as described above), one dissolution set was performed on tablets made from a formulation containing 3% superdisintegrant (PVP-XL10). These tablets are produced for comparative purposes. The results shown in **FIG. 4** confirm that a superdisintegrant will not speed release of the tablet, which dissolves rather than disintegrates. In fact, it may retard dissolution in the later stages, by the slight swelling it may cause.

EXAMPLE 2

Formulation ranges for immediate release tablet

[0085] Materials included binder, drug, optional diluent, and lubricant. Binder was selected from hydroxypropyl cellulose (Klucel ExF PH, Ashland), hydroxypropyl methylcellulose (HPMC E5 premium LV, Dow), povidone (PVP K30, or Kollidon 30, BASF), and Starch 1500 (Colorcon). Tablets comprising Starch 1500 as the binder are not according to the invention. Lubricants were selected from magnesium stearate (Sigma Aldrich/Riedel-de-Haen), calcium stearate (Strem chemicals), and sodium stearyl fumarate (Spectrum). The optional diluent was mannitol (EMD).

[0086] Unless otherwise noted, all experiments were done in the following manner. The binder, drug, and optional diluent were admixed vigorously in a plastic container and then wet massed by hand stirring with addition of water amounting to approximately 13% of the dry mass. The wet granulation was then passed through a 1.19 mm (16 mesh) screen, dried in a 60°C oven for no less than 1 h, and then passed through a 1.19 mm (16 mesh) screen a second time. Based on the dry granulation yield, the formula amount of lubricant was weighed and added to the cylindrical plastic container, closed, and then gently blended by hand for 24 revolutions at about a 45 degree angle. Granulation and blending involving 5 g or more material was performed in a 50.8x50.8 mm (2x2 inch) (diameter x length) cylindrical polypropylene container, and lesser quantities employed a 25.4×50.8 mm (1x2 inch) container.

[0087] The blended granulation was weighed into four 375 ± 2 mg aliquots, each in turn added to 10.31 mm (13/32") standard round convex tooling, and compressed with application of 1000

Kg (1 metric ton) force and about 5 seconds dwell. Two tablets were each characterized for weight, hardness using a Scheuniger 6D hardness tester, and thickness using calipers. The other two tablets were dissolution tested using a USP Type 2 apparatus (paddles), 900 mL of 0.1 N HCl media at 37°C, 50 rpm, and two tablets per vessel. 0.5 mL samples of each vessel were taken at 0, 5, 10, 15, and 30 minutes. After 30 minutes, the stirring speed was increased to 150-200 rpm and maintained until the remainder of the tablets dissolved. The vessels were then sampled again for a total sample, indicating the total amount dissolved as a basis for normalizing. Each sample was then diluted with 8.50 mL DI water and scanned by UV spectrophotometer at 215 nm (Shimadzu UV-1200) using a 1.0 cm quartz flow cell. A calibration curve spanning the range of absorbance achieved was constructed based on a quadratic fit to standards, from which concentrations were derived. Dissolution results were normalized to the total concentration for each vessel at the end of dissolution testing.

[0088] To examine the effect of binder level, five individual granulations of 5 g each were made corresponding to binder levels ranging from 0 to 10% by blending binder (HPC ExF 0-0.50 g) and drug (APC 4.5-5.0 g) using the standard procedure. The dried granulations (4.8-5.0 g) were blended with 37 mg lubricant (0.75%) and compressed. The tablet properties and dissolution profile are shown in **Table 3**. The results show that increasing binder improves hardness but also causes a reduction in dissolution rate. Only an amount of binder of about 1-5% by weight of the tablet is according to the invention. Amounts outside of this range are only disclosed for comparative purposes.

Table 3. Effect of binder (HPC-ExF) level from 0-1,0%

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Binder	Mass	Thickness	Hardness	5	10	15	30
1	A1	0%	374	4.79	59	66%	86%	98%	99%
2	A2	1%	374	4.73	105	68%	95%	102%	101%
3	A3	2%	373	4.70	99	58%	90%	101%	103%
4	A4	5%	375	4.69	150	43%	75%	92%	102%
5	A5	10%	375	4.65	165	32%	57%	77%	98%

[0089] To examine the effect of lubricant (magnesium stearate) level, a 15 g granulation was first made according to the standard procedure. This was then subdivided into 2.0 g portions, and each portion was individually blended with varying amounts of magnesium stearate. The binder level was 3%. The results are shown in **Table 4**. The results show that lubricant had little effect on hardness as the level is increased, but caused a substantial reduction in dissolution. Only an amount of lubricant of about 0.1-1.4% by weight of the tablet is according to the invention. Amounts outside of this range are only disclosed for comparative purposes.

Table 4. Effect of lubricant (magnesium stearate) level, binder fixed at 3% HPC

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Lubricant	Mass	Thickness	Hardness	5	10	15	30
6	B1	0.00%	374	4.77	140	78%	97%	101%	101%
7	B2	0.32%	375	4.76	130	71%	93%	101%	99%
8	B3	0.52%	374	4.71	124	63%	87%	99%	100%
9	B4	0.83%	374	4.72	126	57%	83%	96%	100%
10	B5	0.99%	375	4.71	138	50%	77%	93%	101%
11	B6	1.45%	373	4.67	125	41%	69%	85%	99%
12	B7	2.51%	373	4.68	120	33%	53%	68%	99%

[0090] To examine the effect of APC level, with lubricant and binder held constant, two 6-gram granulations were first prepared using 3% HPC ExF as binder. One granulation was produced without diluent, thus 97% APC, and the other had mannitol sufficient to reduce the APC loading to 86%. The two granulations were then blended in proportions to make five 2 g granulations ranging from 86% to 97% before blending. The proportions were 2.0/0 g, 0/2.0 g, 1.5/0.5 g, 1.0/1.0 g, and 0.5/1.5 g blending of the high and low granulations, respectively. Each was then blended with 15 mg magnesium stearate (0.75% level). The results are shown in **Table 5**. The data show that dissolution is not substantially impacted over the tested range of APC. Only an amount of APC of about 90-98% by weight of the tablet is according to the invention. Amounts outside of this range are only disclosed for comparative purposes.

Table 5. Effect of API loading (binder HPC ExF at 3% and lubricant magnesium stearate at 0.75%)

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	API	Mass	Thickness	Hardness	5	10	15	30
14	C2	85.7%	376	4.71	128	50%	79%	93%	96%
17	C5	88.7%	376	4.69	127	47%	80%	94%	99%
16	C4	91.1%	376	4.73	118	50%	85%	98%	103%
15	C3	93.3%	375	4.72	112	49%	81%	95%	100%
13	C1	96.3%	375	4.74	120	51%	85%	101%	103%

[0091] To examine the effect of binder type, four binders (HPMC E5, PVP K30, HPC ExF, and Starch 1500), were evaluated at two levels each (2% and 5%) by making individual 5 g granulations. Tablets comprising Starch 1500 as the binder are not according to the invention. The results are shown in **Table 6**.

Table 6. Effect of binder type and level (2% or 5%), magnesium stearate fixed at 0.75%

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Binder	Mass	Thickness	Hardness	5	10	15	30
18	D1	2% HPMC-E5	375	4.76	92	61%	91%	95%	98%
19	D2	2% PVP-K30	375	4.76	108	66%	95%	98%	101%
20	A3	2% HPC-ExF	375	4.69	128	56%	87%	97%	99%
21	D4	2% Starch 1500	374	4.76	66	41%	68%	82%	97%
22	D5	5% HPMC-E5	376	4.77	127	49%	81%	97%	99%
23	D6	5% PVP-K30	377	4.76	120	62%	94%	99%	99%
4	A4	5% HPC-ExF	375	4.69	150	43%	75%	92%	102%
24	D7	5% Starch 1500	374	4.76	66	29%	51%	64%	90%

[0092] To evaluate the effect of lubricant type, a single 15-gram granulation was made with 3% HPC ExF and no diluent. The dried granulation was then subdivided into 5 g aliquots. Each aliquot was then blended with one of three lubricants (magnesium stearate, calcium stearate, or sodium stearyl fumarate -"SSF") using the standard 24 turns. After the initial set of tablets was made, the remaining portion of each granulation was then vigorously shaken for 1 minute to evaluate the consequences of overblending. The standard and overblended results are shown in **Table 7**. Overblending had no substantial effect on tablet properties, but affected dissolution for all lubricants.

Table 7. Effect of lubricant type and overblending

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Lube & blending	Mass	Thickness	Hardness	5	10	15	30
25	E1	Mg Stearate - standard	374	4.70	103	53%	86%	100%	100%
26	E2	Ca stearate - standard	375	4.70	113	51%	84%	97%	100%
27	E3	SSF - standard	374	4.68	129	57%	87%	99%	99%
28	E1a	Mg stearate - overblend	375	4.70	102	35%	60%	75%	97%
29	E2a	Ca stearate - overblend	374	4.68	91	40%	69%	86%	100%
30	E3a	SSF - overblend	377	4.70	138	44%	72%	89%	98%

[0093] The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims. Any subject-matter falling

outside the scope of the claims has been provided for information purposes only.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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Patentkrav

1. Komprimeret tablet med øjeblikkelig frigivelse til oral levering af (*R*)-2-amino-3-phenylpropylcarbamat, hvilken tablet omfatter:

(*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf i en mængde på omtrent 90-98 vægtprocent af tabletten;

mindst et bindemiddel i en mængde på omtrent 1-5 vægtprocent af tabletten; og

mindst et smøremiddel i en mængde på omtrent 0,1-1,4 vægtprocent af tabletten;

hvor tabletten frigiver mindst 85% af (*R*)-2-amino-3-phenylpropyl-carbamatet eller et farmaceutisk acceptabelt salt deraf indeholdt deri inden for en periode på mindre end 15 minutter efter indgivelse af tabletten til et individ;

hvor det mindst ene bindemiddel er valgt fra mindst en af hydroxypropyl-cellulose, hydroxypropylmethylcellulose og povidon; og

hvor det mindst ene smøremiddel er valgt fra mindst en af magnesium-stearat, calciumstearat og natriumstearylfumarat;

hvor udtrykket "omtrent", når det anvendes til at henvise til en mængde, omfatter variationer på ± 10%, ± 5%, ± 1%, ± 0,5% eller ± 0,1% af den angivne mængde.

2. Den komprimerede tablet med øjeblikkelig frigivelse ifølge krav 1, hvor tabletten ikke omfatter et desintegreringsmiddel.

3. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-2, omfattende:

(*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf i en mængde på omtrent 90-98 vægtprocent af tabletten;

hydroxypropylcellulose i en mængde på omtrent 1-5 vægtprocent af tabletten; og

magnesiumstearat i en mængde på omtrent 0,1-1,4 vægtprocent af tabletten.

4. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-3, yderligere omfattende et overtræk.

5. Den komprimerede tablet med øjeblikkelig frigivelse ifølge krav 4, hvor overtrækket er et farveovertræk.

6. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-5, hvor (R)-2-amino-3-phenylpropylcarbamatet eller et farmaceutisk acceptabelt salt deraf er (*R*)-2-amino-3-phenylpropylcarbamathydrochlorid.

7. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-6, hvor tabletten har en aflang form.

8. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-7, hvor tabletten omfatter omtrent 300 mg (*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf.

9. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-7, hvor tabletten omfatter omtrent 150 mg (*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf.

10. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-7, hvor tabletten omfatter omtrent 75 mg (*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf.

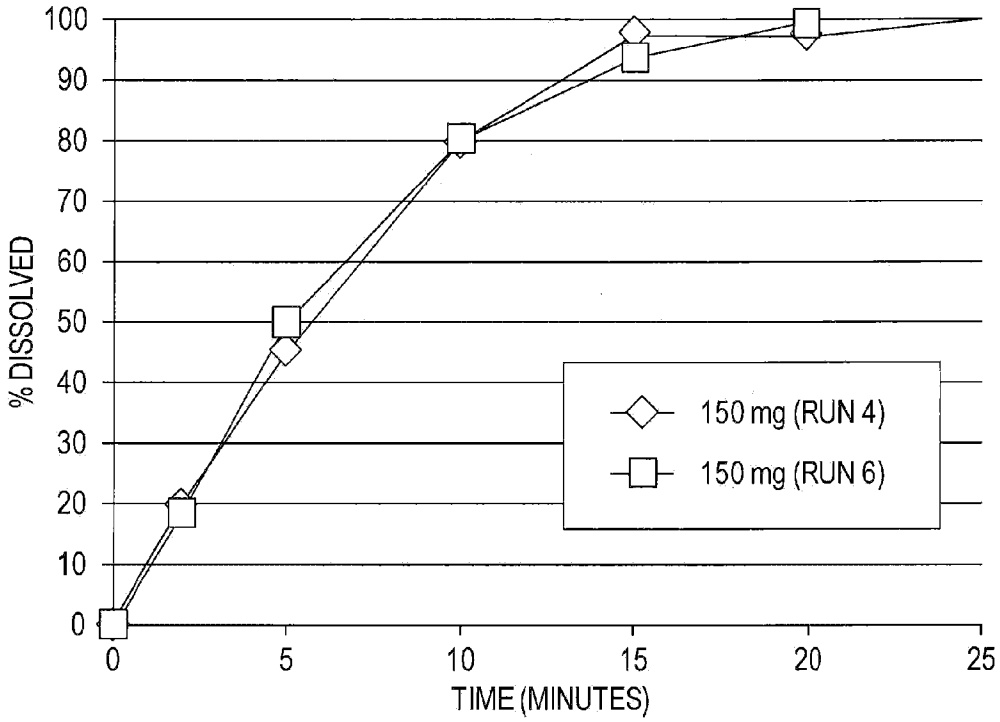
11. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-7, hvor tabletten omfatter omtrent 37,5 mg (*R*)-2-amino-3-phenylpropylcarbamat eller et farmaceutisk acceptabelt salt deraf.

12. Komprimeret tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-11 til anvendelse i en fremgangsmåde til at behandle en lidelse valgt fra narkolepsi, kataplekси, overdreven søvnighed i dagtiden, stofmisbrug, seksuel dysfunktion, træthed, fibromyalgi, ADHD (attention deficit hyperactivity disorder), uro i benene, depression, bipolar lidelse eller fedme hos et individ, som har behov

derfor, eller til at fremme rygestop hos et individ, som har behov derfor, hvor fremgangsmåden omfatter indgivelse til individet af den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-11.

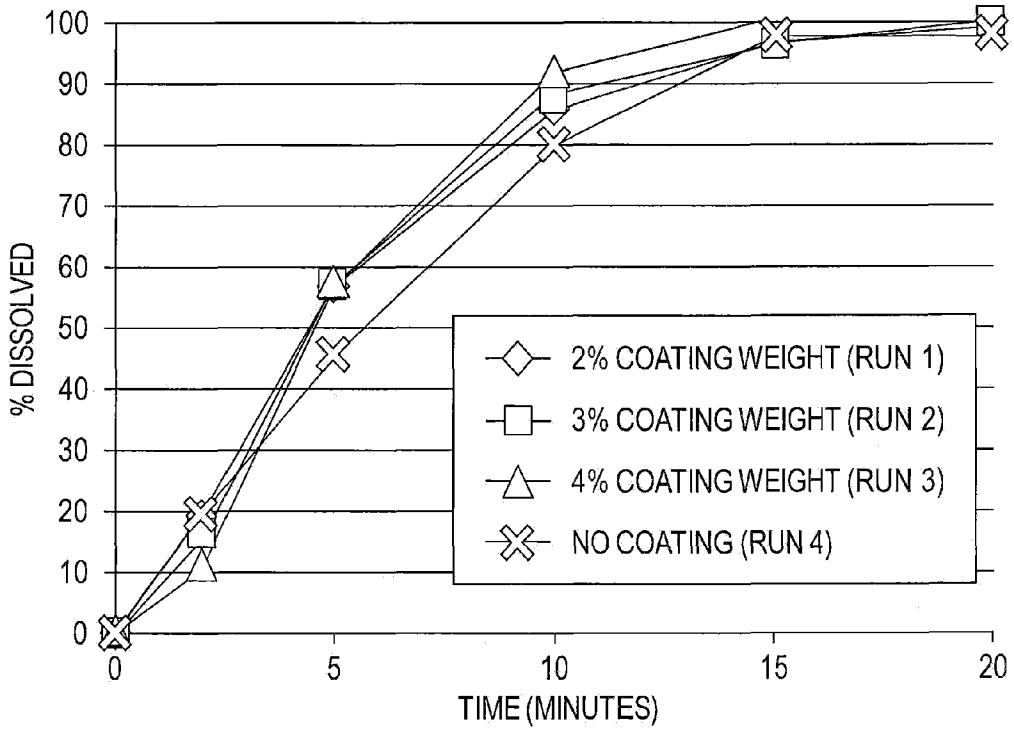
13. Den komprimerede tablet med øjeblikkelig frigivelse ifølge et hvilket som helst af kravene 1-11, hvor tabletten udviser i alt væsentligt identiske opløsningshastigheder for (*R*)-2-amino-3-phenylpropylcarbamatet eller et farmaceutisk acceptabelt salt deraf ved pH 1,2, pH 4,5 og pH 6,8.

DRAWINGS



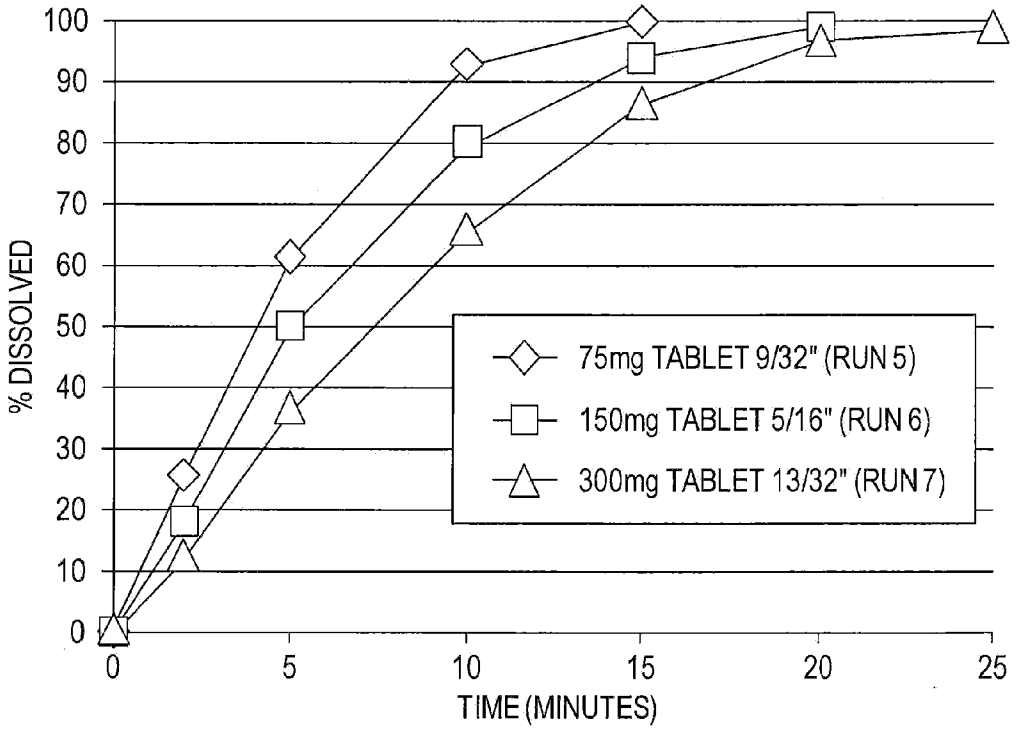
SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
4	0%	20%	45%	80%	98%	97%	100%	103%	163.5	182.7	74.5
6	0%	18%	50%	80%	94%	99%			151.4	163.3	*

FIG. 1



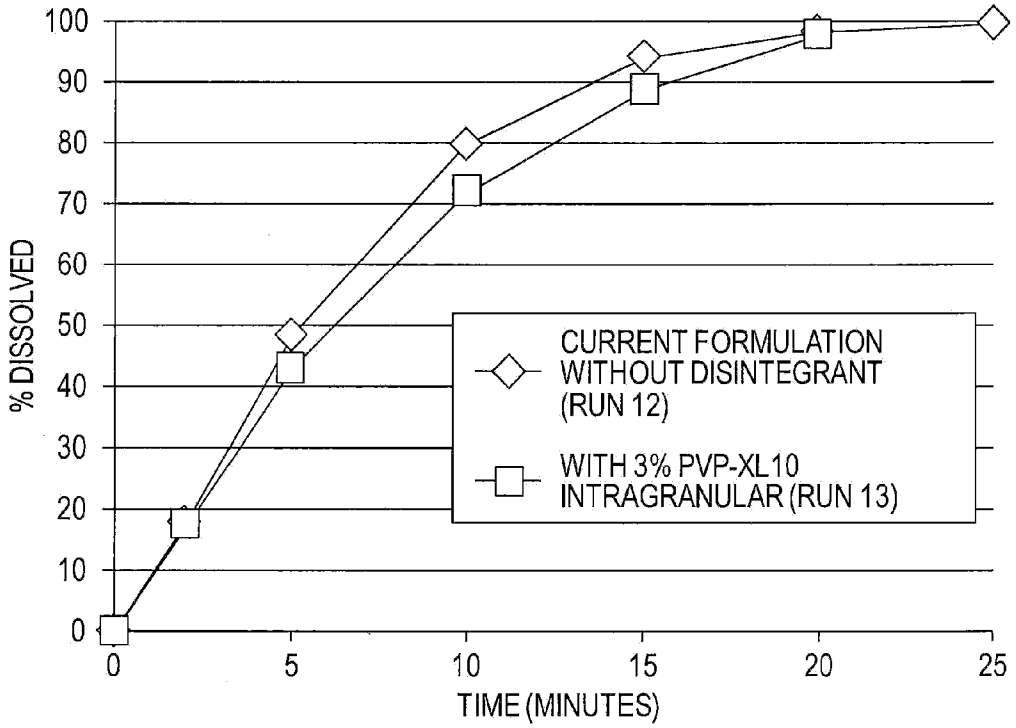
SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
1	0%	20%	57%	85%	97%	99%	98%	100%	148.6	164.4	75.9
2	0%	16%	57%	89%	96%	100%	100%	100%	150.8	166.4	*
3	0%	11%	57%	92%	100%	101%			154.4	172.6	71.5
4	0%	20%	45%	80%	98%	97%	100%	103%	163.5	182.7	52.8

FIG. 2



SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
5	0%	26%	61%	93%	100%				149.2	78.77	48.5
6	0%	18%	50%	80%	94%	99%			151.4	163.3	*
7	0%	13%	37%	66%	86%	96%	99%		153.7	345.7	48.3

FIG. 3



SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
12	0%	17%	48%	80%	94%	98%	100%	100%	153.0	162.3	*
13	0%	17%	43%	72%	89%	98%			153.9	166.8	63.3

FIG. 4