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DESCRIPTION

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 60/502,219, filed September 12, 2003.

[0002] Calcium receptor-active compounds are known in the art. One example of a calcium receptor-active compound is cinacalcet HCl, which is described, for example, in U.S. Patent No. 6,001,884. Such calcium receptor-active compounds may be insoluble or sparingly soluble in water, particularly in their non-ionized state. For example, cinacalcet has a solubility in water of less than about 1 µg/mL at neutral pH. The solubility of cinacalcet can reach about 1.6 mg/mL when the pH ranges from about 3 to about 5. However, when the pH is about 1, the solubility decreases to about 0.1 mg/mL. Such limited solubility can reduce the number of formulation and delivery options available for these calcium receptor-active compounds. Limited water solubility can also result in low bioavailability of the compounds.

[0003] There is therefore a need to maximize the dissolution of the calcium receptor-active compound from a dosage form, and potentially during *in vivo* exposure. There is also a need to improve the bioavailability of the calcium receptor-active compound during *in vivo* exposure.

[0004] One aspect of the present invention provides a pharmaceutical composition comprising

1. a) from 10% to 40% by weight of cinacalcet HCl;
2. b) from 45% to 85% by weight of at least one diluent selected from starch, microcrystalline cellulose, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof;

wherein the percentage by weight is relative to the total weight of the composition; and wherein the composition is in granular form and the granules have a D50 ranging from 50µm to 150µm. Also disclosed herein is at least one calcium receptor active compound in combination with at least one pharmaceutically acceptable carrier. Certain examples of the present disclosure are directed to a pharmaceutical composition with a defined dissolution profile.

[0005] Also disclosed herein is a method of manufacturing the pharmaceutical composition to achieve the desired dissolution profile, as well as a method of treating a disease using the pharmaceutical composition. In addition, certain examples in the present disclosure are directed to a method for controlling dissolution rate of a formulation comprising the pharmaceutical composition.

[0006] Also disclosed herein is a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in United States Pharmacopeia (USP) - National Formulary (NF) (USP 26/NF 21), chapter 711 using a USP 2 apparatus at a temperature of 37 °C ±0.5 °C, and at a rotation speed of 75 r.p.m., which comprises from

about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

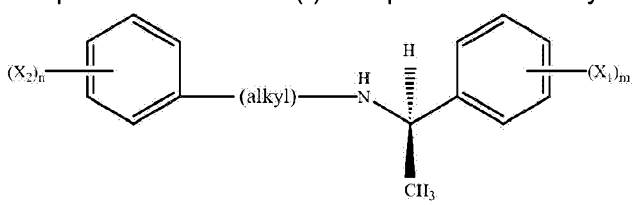
[0007] Also disclosed herein is a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

[0008] Also disclosed herein is a method of controlling the dissolution rate of a formulation comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, the method comprising producing the formulation in a granulator which has a volume ranging from about 1 L to about 2000 L, and contains water in a granulation level ranging from about 10% to about 50% relative to the weight of the dry powders in the granulator.

[0009] The calcium receptor-active compound useful in the present disclosure may be a calcimimetic compound or a calcilytic compound. As used herein, the term "calcimimetic compounds" refers to compounds that bind to a calcium receptor, and induce a conformational change that reduces the threshold for calcium receptor activation by the endogenous ligand Ca^{2+}, thereby reducing parathyroid hormone ("PTH") secretion. These calcimimetic compounds can also be considered allosteric modulators of the calcium receptor. As used herein, the term "calcilytic compounds" refers to compounds that act as calcium receptor antagonists, and stimulate PTH secretion.

[0010] The calcimimetic compounds and calcilytic compounds useful in the present disclosure include those disclosed in, for example, European Patent No. 933 354; International Publication Nos. WO 01/34562, WO 93/04373, WO 94/18959, WO 95/11221, WO 96/12697, WO 97/41090; U.S. Patent Nos. 5,981,599, 6,001,884, 6,011,068, 6,031,003, 6,172,091, 6,211,244, 6,313,146, 6,342,532, 6,363,231, 6,432,656, and U.S. Patent Application Publication No. 2002/0107406.

[0011] In the present disclosure, the calcium receptor-active compounds are chosen from compounds of formula (I) and pharmaceutically acceptable salts thereof



(I)

wherein:

X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5;

m ranges from 1 to 5; and

the alkyl radical is chosen from C1-C3 alkyl radicals, which are optionally substituted with at least one group chosen from saturated and unsaturated, linear, branched, and cyclic C1-C9 alkyl groups, dihydroindolyl and thiodihydroindolyl groups, and 2-, 3-, and 4-piperid(in)yl groups; and the stereoisomers thereof.

[0012] Calcium receptor-active compounds useful in the present disclosure can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methansulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. When compounds of the disclosure include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable salts for the carboxy group are well known to those skilled in the art and include, for example, alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," see infra and Berge et al., J. Pharm. Sci. 66:1 (1977). In certain examples disclosed herein salts of hydrochloride and salts of methanesulfonic acid can be used.

[0013] In some examples disclosed herein, the calcium-receptor active compound can be chosen from cinacalcet, i.e., N-(1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane, cinacalcet HCl, and cinacalcet methanesulfonate. The cinacalcet HCl and cinacalcet methanesulfonate can be in various forms, such as amorphous powders, crystalline powders, and mixtures thereof. For example, the crystalline powders can be in forms including polymorphs, psuedopolymorphs, crystal habits, micromeretics, and particle morphology.

[0014] The therapeutically effective amount of the calcium receptor-active compound in the compositions disclosed herein ranges from about 1 mg to about 360 mg, for example from about 5 mg to about 240 mg, or from about 20 mg to about 100 mg. As used herein, the "therapeutically effective amount" is an amount that changes in a desired manner at least one

of the calcium level, the phosphorus level, the PTH level, and the calcium phosphorus product in a subject. In some embodiments, the therapeutically effective amount of cinacalcet HCl in the composition disclosed herein can be chosen from about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg.

[0015] The compound administered will normally be present as an active ingredient in a pharmaceutical composition. Thus, a pharmaceutical composition of the present disclosure may comprise a therapeutically effective amount of at least one calcium receptor-active compound, or an effective dosage amount of at least one calcium receptor-active compound.

[0016] As used herein, an "effective dosage amount" is an amount that provides a therapeutically effective amount of the at least one calcium receptor active compound when provided as a single dose, in multiple doses, or as a partial dose. Thus, an effective dosage amount of the at least one calcium receptor active compound disclosed herein includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multidose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the at least one calcium receptor-active compound is administered by administering a portion of the composition.

[0017] Alternatively, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the at least one calcium receptor active compound may be administered in less than an effective amount for one or more periods of time (i.e, a once-a-day administration, and a twice-a-day administration), for example to ascertain the effective dose for an individual subject, to desensitize an individual subject to potential side effects, to permit effective dosing readjustment or depletion of one or more other therapeutics administered to an individual subject, and/or the like.

[0018] The effective dosage amount of the pharmaceutical composition disclosed herein ranges from about 1 mg to about 360 mg from a unit dosage form, for example about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg from a unit dosage form.

[0019] In some embodiments of the present invention, the compositions of the invention comprise a therapeutically effective amount of cinacalcet HCl for the treatment of hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product. In certain examples disclosed herein, the cinacalcet HCl can be present in an amount ranging from about 1% to about 70%, such as from about 5% to about 40%, from about 10% to about 30%, or from about 15% to about 20%, by weight relative to the total weight of the

composition.

[0020] The compositions disclosed herein may contain one or more active ingredients in addition to the calcium receptor-active compound. The additional active ingredient may be another calcium receptor-active compound, or it may be an active ingredient having a different therapeutic activity. Examples of such additional active ingredients include, for example, vitamins and their analogs, such as vitamin D and analogs thereof, antibiotics, and cardiovascular agents.

[0021] The cinacalcet HCl or other calcium receptor-active compound that can be used in the composition is typically present in the form of particles. These particles can have a particle D_{50} of, for example, less than or equal to about 50 μm. As used herein, the "particle D_{50}" is the particle size of the active pharmaceutical ingredient at the 50^{th} percentile of a particle size distribution. According to certain embodiments of the invention, the active pharmaceutical ingredient in the formulation has a particle D_{50} that is less than the granule D_{50} of the formulation, discussed in detail below.

[0022] The particle D_{50} of the cinacalcet HCl particles can be determined by one of ordinary skill in the art using known light scattering techniques. In one embodiment of the invention, the particle D_{50} of the cinacalcet HCl particles is determined by using a particle size analyzer, such as a Malvern Mastersizer analyzer, that uses a laser to scan a suspension of particles. The particles diffract the incoming light to detectors: smaller particles diffract light at larger angles, while larger particles diffract light at smaller angles. The light intensities observed at each detector are translated into a particle size distribution based on the diameter of a sphere that has an equivalent volume to that of the measured particles.

[0023] Specifically, the particle size distribution of the active pharmaceutical ingredient, for example, cinacalcet HCl, can be determined according to the following procedure. The following instrument conditions in a Malvern Mastersizer particle size analyzer are specified in its software:

Refractive Index Sample	1.630
Absorptive Index	0.1
Refractive Index Dispersant	1.375
Analysis model	General purpose spherical
Calculation sensitivity	Enhanced
Measurement snaps and time	20,000 snaps over 20 seconds
Background snaps and time	20,000 snaps over 20 seconds
Stir speed	1750 rpm

[0024] While stirring, about 170 mL of a dispersion of about 0.1% sorbitan trioleate (for

example Span 85®, available from Kishida Chemical) in hexane ("dispersant-B"), is added to the sampling unit, and the laser is aligned to take a background measurement of the dispersant-B.

[0025] The entire suspension containing the cinacalcet HCl is added until a suitable obscuration range ranging from about 10 to about 20% is obtained. The sample is measured after the obscuration value has stabilized. After the measurement, the system is drained and rinsed once with about 170 mL of dispersant-B, the dispersant-B is drained, and the sampling unit is refilled with about 170 mL of dispersant-B. The measurement are repeated two more times with different riffled fractions. The riffling is performed on large samples to obtain small representative particle size fractions about 15 mg in size.

[0026] The Obscuration, D(v,0.1), D(v,0.5), D(v,0.9) values are then calculated from these measurements. The average, standard deviation, and relative standard deviation (RSD) of the D(v,0.1), D(v,0.5), D(v,0.9) values is also calculated. The RSD (%) is calculated as follows:

$$RSD\ (\%) = \frac{100}{X}\left[\frac{\sum_{i=1}^{N}(X_i - \overline{X})^2}{N-1}\right]^{\frac{1}{2}}$$

where X, is an individual measurement in a set of N measurements and is the arithmetic mean of the set.

[0027] The composition disclosed herein can be in various forms, for example, in granular form. The granules that are used in the present invention have a granule D_{50} ranging from about 50 µm to about 150 µm, such as from about 80 µm to about 130 µm. As defined herein, the "granule D_{50}" is the particle size of the composition at the 50^{th} percentile of a particle size distribution. The granule D_{50} can readily be determined by one of ordinary skill in the art using sieve analysis techniques. Specifically, the granule D_{50} is determined according to the following procedure.

[0028] Approximately 100 g of sample is added to sieve shaker equipped with 40 mesh, 60 mesh, 80 mesh, 100 mesh, 140 mesh, 200 mesh, 325 mesh, and the bottom pan. The sieve shaker is then turned on for about 10 minutes to separate the sample according to particle size. Each sieve is weighed to determine the amount of sample retained on each sieve and the bottom pan. The individual sieve weight is normalized to generate sieve weight fraction. The individual sieve weight fraction is calculated by dividing each sieve weight with the sum of all sieve weights.

$$\text{Weight Fraction of each sieve} = \frac{\text{Weight of each sieve}}{\text{Sum of all sieves}}$$

[0029] Before the particle size calculation, the mean size range must be determined for each sieve and the bottom pan. This mean size of each sieve screen represents the mean particle

size retained on the screen. The mean size of each sieve screen is determined by the hole size of the screen (lower limit) and one sieve size larger (upper limit). In the case of the 40 mesh sieve screen, the hole size of about 1410 µm is used as an upper limit. Table 1 set forth below shows the particle size range of any retained material on each screen and the mean of the particle size range.

Table 1

Screens	Hole size of each screen (µm)	Particle size range of retained material on each screen (µm)	Median particle size of the screen (µm)
40 mesh	425	425 - 1410	918
60 mesh	250	250 - 424	337
80 mesh	180	180 - 249	215
100 mesh	150	150 - 179	165
140 mesh	106	106 - 149	128
200 mesh	75	75 - 105	90
325 mesh	45	45 - 74	60
Bottom pan	0	1 - 44	23

[0030] The weight fraction of each sieve is added to generate cumulative frequency distribution starting from the bottom pan to 40 mesh screen. Once the cumulative frequency distribution is generated, the corresponding particle size at 10 percentile (D_{10}), 50-percentile (D_{50}), and 90-percentile (D_{90}) are determined. The particle size of the corresponding percentile is determined by linear interpolation between two consecutive data from the cumulative frequency distribution. For example, particle size of 50-percentile (D_{50}) is interpolated by,

$$D_{50}(\mu m) = \frac{\left[(50 - X_n) * d_{n+1} + (X_{n+1} - 50) * d_n\right]}{(X_{n+1} - X_n)}$$

where,

X_n = cumulative quantity of sample that is just below 50-percentile (in %);

d_n = mean of the particle size range from the sieve screen where X_n occurs (in mm);

X_{n+1} = next cumulative quantity of sample that is above 50-percentile (in %).

d_{n+1} = mean of the particle size range from the sieve screen where X_{n+1} occurs (in mm).

[0031] According to all embodiments of the present invention, the particle size of active pharmaceutical ingredient is measured according to light scattering techniques, and the particle size of the granules of composition is measured according to sieve analysis.

[0032] The compositions disclosed herein can be in a form chosen from, for example, tablets, capsules, and powders. The tablets can be made by pressing the granules into the form of tablets. The capsules can also be made using the granules.

[0033] The at least one pharmaceutically acceptable excipient can be chosen from, for example, diluents such as starch, microcrystalline cellulose, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins; binders such as povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, and sodium carboxyl methylcellulose; and disintegrants such as crospovidone, sodium starch glycolate, croscarmellose sodium, and mixtures of any of the foregoing. The at least one pharmaceutically acceptable excipient can further be chosen from lubricants such as magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hygrogenated vegetable oil, glycerine fumerate and glidants such as colloidal silicon dioxide, and mixtures thereof. In some examples disclosed herein, the at least one pharmaceutically acceptable excipient is chosen from microcrystalline cellulose, starch, talc, povidone, crospovidone, magnesium stearate, colloidal silicon dioxide, sodium dodecyl sulfate, and mixtures of any of the foregoing. The excipients of the present invention, can be intragranular, intergranular, or mixtures thereof.

[0034] In some embodiments of the present invention, the composition and/or the granules within the composition can comprise microcrystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 15:1. For example, in the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 15:1, such as about 10:1, and in the granules within the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 10:1, such as about 5:1.

[0035] The microcrystalline cellulose can be present in an amount ranging from about 25% to about 85%, for example from about 50% to about 80%, or from about 60% to about 75% by weight relative to the total weight of the composition. The starch can be present in an amount ranging from about 5% to about 35%, for example, from about 5% to about 25%, or from about 5% to about 10% by weight relative to the total weight of the composition.

[0036] The compositions disclosed herein can further comprise at least one ingredient chosen from coating materials that are known in the art such as, for example, hydroxypropyl methylcellulose.

[0037] Certain compositions disclosed herein can comprise:

1. (a) from about 10% to about 40% by weight of a calcium receptor-active compound chosen from cinacalcet HCl and cinacalcet methanesulfonate;
2. (b) from about 45% to about 85% by weight of at least one diluent;

3. (c) from about 1 % to about 5% by weight of at least one binder; and
4. (d) from about 1 % to about 10% by weight of at least one disintegrant;

wherein the percentage by weight is relative to the total weight of the composition. The compositions can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from glidants, lubricants, and adherents. The composition can additionally comprise from about 1 % to about 6% by weight of at least one coating material, relative to the total weight of the composition.

[0038] In another embodiment, the composition disclosed herein comprises:

1. (a) from about 10% to about 40% by weight of cinacalcet HCl;
2. (b) from about 5% to about 10% by weight of starch;
3. (c) from about 40% to about 75% by weight of microcrystalline cellulose;
4. (d) from about 1 % to about 5% by weight of povidone; and
5. (e) from about 1 % to about 10% by weight of crospovidone;

wherein the percentage by weight is relative to the total weight of the composition.

[0039] The povidone can be present in an amount ranging from about 1% to about 5%, for example, from about 1% to about 3% by weight relative to the total weight of the composition. The crospovidone can be present in an amount ranging from about 1% to about 10%, for example from about 3% to about 6%, by weight relative to the total weight of the composition.

[0040] The composition can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from colloidal silicon dioxide, magnesium stearate, talc, and the like, and mixtures of any of the foregoing. In certain embodiments of the invention, the composition comprises from about 0.05% to about 1.5% of colloidal silicon dioxide, from about 0.05% to about 1.5% of magnesium stearate, from about 0.05% to about 1.5% of talc, or mixtures of any of the foregoing. The composition can even further comprise from about 1% to about 6% by weight of at least one coating material, relative to the total weight of the composition.

[0041] As mentioned above, the compositions of certain examples disclosed herein have a dissolution profile that results in about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of a dissolution test that is conducted in 0.05 N HCl in a U.S.P. 2 apparatus at a temperature of 37°C ± 0.5°C at a rotation speed of 75 r.p.m. The dissolution test is conducted using a USP 2 apparatus, and according to the dissolution protocol described in USP 26/NF 21, chapter 711. According to this example using this dissolution protocol, a stated volume of the dissolution medium (±1%) is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to 37°C ± 0.5°C, the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

[0042] According to another embodiment of the invention, a stated volume of the dissolution medium is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to about 37°C, the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

[0043] The dissolution profile represents the percentage of the active pharmaceutical ingredient released based on a target amount of the active pharmaceutical ingredient in the formulation. As used herein "target amount" refers to the amount of active pharmaceutical ingredient in each formulation. In certain embodiments, the target amount refers to the label amount and/or label claim.

[0044] USP 26/NF 21, chapter 905, defines a protocol used to determine the dosage-unit conformity according to the present invention. According to this protocol, the content uniformity is determined by measuring the amount of active pharmaceutical ingredient in 10 dosage unit samples, and calculating whether the amount of active pharmaceutical ingredient in all the dosage unit samples falls within a range of 85% to 115% of the target amount. If one dosage unit sample is outside the range of 85% to 115% of the target amount and no unit is outside a range of 75% to 125% of the target amount, or if the Relative Standard Deviation (RSD), which is the sample standard deviation expressed as a percentage of the mean, is not greater than 6%, then 20 additional dosage unit samples are tested. After treating at least 30 dosage units, the content uniformity requirement is met if not more than one dosage unit sample is outside the range of 85% to 115% of the target amount, and no unit is outside a range of 75% to 125% of the target amount, and the RSD of the at least 30 dosage units does not exceed 7.8%.

[0045] In certain examples, the dissolution profile of the compositions disclosed herein can result in, for example, at least about 50%, at least about 70%, at least about 75%, or at least about 85%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In certain examples, the dissolution profile of the compositions disclosed herein can comprise at most about 125%, for example at most about 115%, at most about 110%, or at most about 100% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In additional examples, the dissolution profile of the compositions disclosed herein can comprise from about 50% to about 125%, for example from about 70% to about 110%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

[0046] The present disclosure is also directed to a method of
making a pharmaceutical composition comprising:

1. (a) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and
2. (b) controlling the particle size of the granule such that from about 50% to about 125% of

a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37 °C ±0.5 °C, and a rotation speed of 75 r.p.m.

[0047] The present disclosure is also directed to a method of
making a pharmaceutical composition comprising:

(b) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37 °C, and a rotation speed of about 75 r.p.m.

[0048] The granule can be formed by any known process, such as high wet shear granulation, low wet shear granulation, fluid bed granulation, rotary granulation, extrusion-spheronization, dry granulation, roller compaction, and the like.

[0049] The particle size of the granule of the composition can be controlled by various factors. In certain embodiments of the present invention, the particle size of the granule of the composition can be controlled by the amount of water added to the materials present in a granulator. For example, a desired particle size of the granule can be achieved when the granulator has a volume ranging from about 1 L to about 1200 L, such as from about 65 L to about 1200 L, or from about 300 L to about 800 L, and the amount of water added ranges from about 20% to about 40%, such as from about 30% to about 36%, relative to the amount of dry powders present in the granulator to form the granules.

[0050] The granulator's impeller tip speed can also affect the particle size of the granules. In some embodiments, the impeller tip speed, measured in meters per second (m/s), can range from about 5 m/s to about 10 m/s, such as from about 7 m/s to about 9 m/s.

[0051] The present disclosure is also directed to a method of making a pharmaceutical composition comprising

1. (a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and
2. (b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is

released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37 °C ±0.5 °C, and a rotation speed of 75 r.p.m.

[0052] Additional examples in the present disclosure are directed to a method of making a pharmaceutical composition comprising

1. (a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and
2. (b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37 °C, and a rotation speed of about 75 r.p.m.

[0053] The size of the particles is controlled during the production of the active pharmaceutical ingredient, for example, by use of a milling step, or a controlled crystallization process. For example, the active pharmaceutical ingredient can be milled using a stainless steel hammer mill with 5 mm screen and 12 hammers forward at a mill speed of 8100 ± 100 rpm, with the feed speed is set at 90 ± 10 rpm.

[0054] The present disclosure also provides a method for the treatment of a disease or disorder that can be treated by altering a subject's calcium receptor activity. In some examples, a method for the treatment of a disease chosen from hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37 °C ±0.5 °C, and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

[0055] A further example in the present disclosure is directed to a method for the treatment of a disease chosen from hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution

test conducted in a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

[0056] Reference will now be made to the following examples.

Examples

[0057] Three pharmaceutical formulations with target amounts of 30mg, 60mg, and 90 mg active pharmaceutical ingredient with the following components were prepared:

	Weight % (w/w)	30 mg Tablet	60 mg Tablet	90 mg Tablet
		Amount (mg)	Amount (mg)	Amount (mg)
Cinacalcet HCl	18.367	33.06	66.12	99.18
Pregelatinized starch (Starch 1500)	33.378	60.08	120.16	180.24
Microcrystalline cellulose (Avicel PH102)	6.678	12.02	24.04	36.06
Povidone (Plasdone K29/32)	2.044	3.68	7.36	11.04
Crospovidone (Polyplasdone XL)	1.233	2.22	4.44	6.66
Purified Water[1]	----	----	----	----
Microcrystalline cellulose (Avicel PH102)	34.300	61.74	123.48	185.22
Magnesium stearate	0.500	0.90	1.80	2.70
Colloidal silicon dioxide (Colloidal anhydrous silica) (Cab-O-Sil M5P)	0.500	0.90	1.80	2.70
Crospovidone (Polyplasdone XL)	3.000	5.40	10.80	16.20
Core Tablet	**100.000**	**180.00**	**360.00**	**540.00**
Purified Water[1]	----	----	----	----
Opadry® II (colored film former)	4.000	7.20	14.40	21.60
Purified Water[1]	----	----	----	----
Opadry® Clear (clear film former)	1.500	2.70	5.40	8.10
Carnauba Wax Powder	0.010	0.018	0.036	0.054
Opacode® Ink (Black)[2]	----	----	----	----

[1] The purified Water was removed during processing.
[2] Trace quantities of ink were applied to the coated tablet.

[0058] The 30-, 60- and 90-mg tablets were made according to the process flow diagram depicted below.

Equipment	Components	Unit Operation	Critical Process Controls
PMA 800L granulator	purified water and intra-granular components[a]	granulation[b]	water level, impeller speed, water spray rate
		↓	
Comil (In-line)		wet mill	
		↓	
Aeromatic MP6		fluid bed dry	
		↓	
Quadro Mill 196S (Comil)		dry mill	
		↓	
Gallay tote blender (650 L)	extra-granular components[c]	pre-blend	
		↓	
Gallay tote blender (1000 L)	combine granulation mix A and B and extra-granular mix	final blend	blend time
		↓	
Gallay tote blender (1000 L)	magnesium stearate	lubrication	
		↓	
Unipress 27		compression[d]	tablet press speed, tablet weight, thickness, hardness, friability, disintegration time
		↓	
3 X Vector Hi-Coater pan (3 spray guns) delivery (peristaltic pump)	color coat (Opadry® II), clear coat (Opadry® Clear), carnauba Wax	film coating and wax	spray rate, exhaust temperature
		↓	
Ackley ink-based offset printer	Opacode® black	print	

[a] cinacalcet HCl, pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone

[b] The granulation step to dry milling step is repeated to generate 2 bowls of wet granulation (Mix A and B).

[c] Extra-granular components are microcrystalline cellulose, crospovidone, and

colloidal silicon dioxide
[d] Tooling dimension is dependent on tablet size and strength, (30 mg; 0.2372" x 0.3800" oval shape plain, 60 mg; 0.3000" x 0.4800" modified oval (double radius) plain, 90 mg; 0.3420" x 0.5480" modified oval (double radius) plain)

[0059] The wet granulation process was conducted in a PMA 800L high-shear granulator with water serving as the granulation fluid. The cinacalcet HCl and the intra-granulation excipients (pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone) were dry-mixed for 1 to 2 minutes with an impeller speed set point at 116 ± 10 rpm, followed by granulation with 30.0% to 36.0% w/w water (based on intra-granular lot size; target was 34.9% w/w) with an impeller speed set point at 116 ± 10 rpm and at a slow or fast chopper speed (target was slow speed). During the granulation process water was delivered at 9.8 ± 0.5 kg/min.

[0060] Following granulation, the mixture was wet-milled using an in-line Comil equipped with a 0.375" (0.953 cm) opening screen and an impeller speed set point at 1400 ± 50 rpm. The mixture was then discharged into a fluid-bed dryer.

[0061] After completion of the wet-milling process, the granulation mixture was dried in an Aeromatic MP6 fluid bed dryer with an inlet temperature set point at 70° ± 5°C. When the outlet temperature reached 37°C to 41°C, samples were taken to determine moisture levels by loss on drying (LOD). The granules were dried until the average moisture levels reached 1.0% to 2.5%.

[0062] The dried granulation mixture was milled through a Quadro Mill 196S (Comil) equipped with a 0.055" (0.140 cm) opening screen at an impeller speed of 1650 ± 50 rpm into a 1000L Gallay tote.

[0063] Except for magnesium stearate, the extra-granular excipients were blended in a 650 L Gallay tote blender for 7 ± 1 minutes at 12 ± 1 rpm. This mixture was further blended with the dry-milled granulation in a 1000 L Gallay tote blender for 15 ± 5 minutes at 12 ± 1 rpm, and then for 6 ± 1 minutes at 12 ± 1 rpm after magnesium stearate was added for lubrication.

[0064] The final lubricated blend was compressed into tablets containing 30-, 60-, or 90 mg of the free base equivalent of active cinacalcet HCl using a Unipress 27 tablet press set to a speed of 2000 ± 300 tablets per minute and equipped with a force feeder. Throughout the compression operation, individual tablet weights (target weights of 180, 360, and 540 mg for 30-, 60-, and 90-mg tablets, respectively), the average weight of 10 tablets, tablet hardness and thickness were monitored at pre-determined intervals.

[0065] The color-coating suspension and clear-coating solution were prepared by slowly adding either the Opadry® II (green) or Opadry® Clear into purified water while mixing until uniform (≥ 45 minutes). The color suspension and clear solution deaerated for ≥ 45 minutes before the spraying process began, and were used within a pre-determined time limit.

[0066] Each lot was film-coated with color and clear coats in a Vector Hi-Coater 48" pan. The color-coating suspension was applied onto a moving core tablet bed (pan speed = 4 to 7 rpm) and a spray rate of 250 ± 50 grams per minute per 3 guns. The distance between the spray guns and the tablet bed was approximately 8" (20 cm) to 11" (28 cm), and the air volume was 600 ± 200 ft^3 per minute (17.1 ± 5.7 m^3 per minute) with a pan pressure differential maintained between -0.1" (-0.25 cm) to -0.3" (-0.76 cm) of water. Supply air temperature was adjusted to 80 ± 10°C to maintain an exhaust temperature of 41 ± 3°C.

[0067] When the clear-coating application was completed, the heater and the air supply was turned off and the wax was spread evenly over the moving tablet bed (after it reached ≤ 37°C) with a pan speed of 4 to 7 rpm. The tablets were rotated for 5 ± 1 minutes, and after the supply air and exhaust fan were turned on, the tablets were rotated for an additional 5 ± 1 minutes with a pan speed of 4 to 7 rpm and supply air of 600 ± 200 ft^3 per minute (17.1 ± 5.7 m^3 per minute). The pan was jogged until the tablet bed temperature reached ≤ 30°C.

[0068] An Ackley ink-based offset printer was used to produce 2-sided printed tablets.

[0069] The dissolution profile of the three formulations were measured according the dissolution protocol described in the USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m. The dissolution profile of the formulations in which at least about 75% of the cinacalcet HCl was released from the composition in no later than about 30 minutes from the start of the test is set forth in Table 2.

Table 2

Time (min)	30 mg Tablet	60 mg Tablet	90 mg Tablet
15	85.3	81.9	80.8
30	95.2	93.8	93.4
45	97.7	97.7	97.9
60	98.7	98.8	99.8

[0070] The content uniformity of the three formulations were measured in accordance with USP 26/NF 21, chapter 905, described in detail above. The content uniformity and for each of the three formulations is set forth in Table 3.

Table 3

Container	30 mg Tablet		60 mg Tablet		90 mg Tablet	
	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD
1 (beg.)	98.5	0.8	96.7	1.6	99.7	1.2
5	98.8	0.8	98.5	0.8	100.7	0.9
11	98.5	0.6	98.3	1.0	99.9	0.7

Container	30 mg Tablet		60 mg Tablet		90 mg Tablet	
	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD
16	98.3	0.8	97.6	1.3	99.9	0.5
22	98.3	1.0	96.3	1.8	100.7	0.9
end	98.0	0.6	95.8	1.9	99.3	0.8

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. a) fra 10 til 40 vægtprocent cinacalcet-HCl; b) fra 45 til 85 vægtprocent af mindst ét fortyndingsmiddel valgt blandt stivelse, mikrokrystallinsk cellulose, dicalciumphosphat, lactose, sorbitol, mannitol, saccharose, methyldextriner og blandinger deraf; hvor vægtprocenten er i forhold til den samlede vægt af sammensætningen; og hvor sammensætningen er i granulær form, og granulerne har et D_{50}-interval fra 50 µm til 150 µm.

2. Sammensætning ifølge krav 1, hvor mindst én dosisenhed af sammensætningen har en opløsningsprofil i 0,05 N HCl målt ved anvendelse af en opløsningstest udført i et USP 2-apparat ved en temperatur på 37 °C ± 0,5 °C og ved en en rotationshastighed på 75 rpm, som omfatter fra 50 til 125 % af en målmængde af cinacalcet, der frigives fra sammensætningen højst ca. 30 minutter fra testens start.

3. Sammensætning ifølge krav 1, der yderligere omfatter fra 1 til 10 % af mindst ét disintegreringsmiddel.

4. Sammensætning ifølge krav 1, der yderligere omfatter fra 1 til 10 % af mindst ét disintegreringsmiddel valgt blandt crospovidon, natriumstivelsesglycolat, croscarmellosenatrium og blandinger deraf.

5. Sammensætning ifølge krav 3, hvor det mindst ene disintegreringsmiddel er crospovidon.

6. Sammensætning ifølge krav 5, hvor crospovidon er til stede intergranulært, intragranulært eller en kombination deraf.

7. Sammensætning ifølge krav 1, der yderligere omfatter fra 0,05 til 5 % af mindst ét additiv valgt blandt glidemidler, smøremidler og klæbemidler, hvor vægtprocenten er i forhold til den samlede vægt af sammensætningen.

8. Sammensætning ifølge krav 1, der yderligere omfatter mindst én bestanddel valgt blandt smøremidler og klare og farvede belægningsmaterialer.

9. Sammensætning ifølge krav 1, der yderligere omfatter fra 1 til 6 vægtprocent af mindst ét belægningsmateriale valgt blandt klare og farvede belægningsmaterialer i forhold til den samlede vægt af sammensætningen.

10. Sammensætning ifølge krav 1, hvor cinacalcet-HCl-partiklernes partikel-D_{50} er mindre end eller lig med 50 µm.

11. Sammensætning ifølge krav 1, hvor sammensætningen er i en form valgt blandt granulat, tabletter, kapsler og pulvere.

12. Sammensætning ifølge krav 1, hvor granulatet er presset i form som en tablet, eller hvor der er dannet kapsler ved anvendelse af granulatet.

13. Sammensætning ifølge krav 1, der yderligere omfatter fra 0,05 til 1,5 vægtprocent kolloid siliciumdioxid i forhold til den samlede vægt af sammensætningen.

14. Sammensætning ifølge krav 1, der yderligere omfatter fra 0,05 til 1,5 vægtprocent magnesiumstearat i forhold til den samlede vægt af sammensætningen.

15. Sammensætning ifølge krav 1, hvor cinacalcet-HCl er til stede i en effektiv dosismængde til behandling af mindst én af hyperparathyreoidisme, hyperphosphoni, hypercalcæmi og forhøjet calciumphosphorprodukt.