(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 March 2008 (06.03.2008)

PCT

(10) International Publication Number
WO 2008/027522 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2007/019151

(22) International Filing Date: 30 August 2007 (30.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/841,689 1 September 2006 (01.09.2006) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

WO 2008/027522 A2

(54) Title: SOLID COMPOSITES OF A CALICUM RECEPTOR-ACTIVE COMPOUND

(57) Abstract: The invention encompasses solid composites of the calcium receptor-active compounds, processes for preparing the solid composites, immediate and controlled-release pharmaceutical formulations comprising the solid composites, and methods of treatment therewith.

SOLID COMPOSITES OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

Cross-Reference to Related Applications

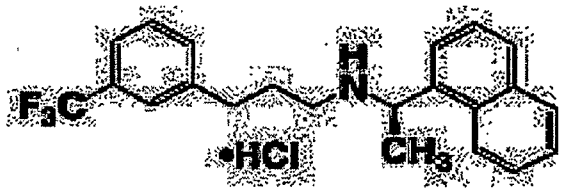
[0001] This application claims the benefit of U.S. Serial No. 60/841,689, filed September 1, 2006, which is incorporated herein by reference in its entirety.

Field of the Invention

[0002] The invention encompasses solid composites of the calcium receptor-active compounds, processes for preparing the solid composites, immediate and controlled-release pharmaceutical formulations comprising the solid composites, and methods of treatment therewith.

Background of the Invention

[0003] Cinacalcet hydrochloride has the chemical name (R)-N-[1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine hydrochloride and is reported to have the following chemical structure:



[0004] Cinacalcet hydrochloride is a calcium receptor-active compound that is currently marketed under the trade name SENSIPAR® for the treatment of hyperparathyroidism in patients with chronic kidney disease on hemodialysis. *Physicians' Desk Reference*, 60th ed. (2006), pp. 603-605. The dosing of SENSIPAR® is expressed in terms of amount of cinacalcet free base, (R)-N-[1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl) phenyl]propan-1-amine, present in the tablet, rather than in terms of the amount of the hydrochloride salt. *See id.*

[0005] Cinacalcet is a solid that is understood to be slightly soluble in water and very soluble in some organic solvents, such as methanol and ethanol. For example, U.S. Patent Application No. 10/937,870, published as U.S. Patent Application Publication No. 2005/0147669 ("the '669 publication") reports that cinacalcet has a solubility in water of less than about 1 μg/ml at neutral pH. The '669 publication, p. 1, ¶ 2. Further, the '669

publication reports that 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. *Id.*

[0006] Compounds having low water solubility typically demonstrate a low rate of dissolution and, often, low bioavailability. *See, e.g.*, Ansel, et al., *Pharmaceutical Dosage Forms and Delivery Methods* (6th ed., 1995), pp. 105, 108.

[0007] The '669 publication addresses the poor water solubility of cinacalcet by providing pharmaceutical compositions comprising cinacalcet in the form of particles with a D_{50} of less than or equal to about 50 μm. '669 publication, pp. 2-3, ¶ 26. The '669 publication discloses that these pharmaceutical compositions have a dissolution profile that results in about 50 percent to about 125 percent of a target amount of cinacalcet 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. type 2 apparatus at a temperature of 37°C±0.5°C at a rotation speed of 75 r.p.m. *Id.* at p. 5, ¶ 61.

[0008] However, this technique of increasing the solubility in water, and, thus, the bioavailability, of cinacalcet requires micronization of the cinacalcet to achieve the desired particle size distribution. Micronization poses a health risk during production on an industrial scale. Thus, there is a need for a method to reduce the health risks involved with micronized powders of active ingredients, such as cinacalcet, while maintaining an adequate dissolution profile, and, thus, bioavailability.

[0009] There is also a need for a method of releasing drugs, such as cinacalcet, at a position in the gastrointestinal tract where the pH is such that they are most soluble.

Summary of the Invention

[0010] The present invention is directed to a composition, comprising a solid composite of cinacalcet in intimate association with at least one carrier. In preferred embodiments of the invention, the composition is the solid composite. In preferred embodiments, at least about 85 percent of the cinacalcet is in intimate association with the at least one carrier, at least about 85 percent of the cinacalcet is not in particulate form, at least about 85 percent of the cinacalcet is not in crystalline form, and/or the solid composite is a solid solution. Preferably, substantially all of the cinacalcet is in solution in the solid solution.

[0011] In preferred embodiments of the invention, the carrier comprises a polymer, such as povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol,

copovidone, copolymers of methacrylate, copolymers of methacrylic acid, and mixtures thereof. Preferably, the polymer is povidone or a copolymer of methacrylic acid. In preferred embodiments the carrier comprises a sugar or sugar derivative, such as sucrose, mannitol, lactose, maltitol, sorbitol, xylitol, sucralose, and mixtures thereof.

[0012] In preferred embodiments of the invention, the solid composite is a particulate having an average particle size of more than about 100 μm, preferably, from about 100 to about 600 μm. In preferred embodiments of the invention, the composite has a drug to carrier weight ratio of from about 1:0.5 to about 1:10, preferably, from about 1:2 to about 1:6.

[0013] In preferred embodiments of the invention, the composition is a pharmaceutical formulation, comprising from about 10 percent to about 40 percent by weight of cinacalcet. In preferred embodiments of the invention, the composition further comprises about 0.5 percent to about 5 percent by weight relative to the total weight of the formulation of at least one glidant or lubricant and/or about 1 percent to about 6 percent by weight of at least one coating material.

[0014] In preferred embodiments of the invention, the composition is an immediate release composition from which at least about 80 percent of the cinacalcet is released within about 30 minutes in 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m.

[0015] In preferred embodiments of the invention, the composition is a controlled release pharmaceutical formulation, and wherein, when the formulation is exposed to a solution of 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m. for about 30 minutes, followed by addition of a buffer in an amount sufficient to neutralize the solution and continued exposure to the neutralized solution, more than about 50 percent of the cinacalcet is released from the formulation within about the first 30 minutes of exposure, and not less than about 70 percent of the calcium receptor-active compound is released from the formulation within about the first 90 minutes of exposure. Preferably, at least about 50 percent of the cinacalcet is released within about the first 60 minutes of exposure, more preferably, not less than about 80 percent of the cinacalcet is released from the formulation during about the first 90 minutes of exposure, and, most preferably, not less than about 90 percent of the cinacalcet is released from the formulation during about the first 90 minutes of exposure.

[0016] In preferred embodiments of the invention, the invention is directed to a method for preparing a solid composite, comprising combining cinacalcet, at least one carrier, and at least one liquid solvent to form a solution, and removing the solvent to obtain a

solid composite of the cinacalcet and the at least one carrier. In preferred embodiments of the invention, the solid composite is a solid solution. In preferred embodiments of the invention, the carrier is selected from the group consisting of povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol, copovidone, copolymers of methacrylate, and copolymers of methacrylic acid, preferably at least one of lower aliphatic alcohols and C3-8 ketones. In preferred embodiments of the invention, the solvent is removed by evaporation, preferably under vacuum, in a fluidized bed drier, or by spray drying. In preferred embodiments of the invention, the composition is the cinacalcet and at least one carrier are dissolved in an organic or inorganic solvent to form the solution, a supercritical fluid is added to induce precipitation of a mixture of the cinacalcet and the carrier, and the solvent and the supercritical fluid are removed by evaporation. In preferred embodiments of the invention, the solvent is a supercritical fluid, preferably, at least one of carbon dioxide, water, methane, ethane, propane, ethylene, propylene, methanol, ethanol, and acetone, and, more preferably, carbon dioxide. In preferred embodiments of the invention, the supercritical fluid is removed by evaporation.

[0017] In preferred embodiments, the invention the invention is directed to a method for preparing the solid composite, comprising combining cinacalcet and at least one carrier to form a mixture, heating the mixture to a temperature at which both the cinacalcet and the carrier melt to form a fusion product, and cooling the fusion product in a manner that does not allow crystallization of the cinacalcet out of the fusion product. In preferred embodiments of the invention, the method further comprises combining the cinacalcet and at least one carrier to form a mixture, heating the mixture to control its viscosity, and feeding the heated mixture through a hot melt extrusion system.

[0018] In preferred embodiments the invention, is directed to a method of treatment, comprising administering an effective amount of a preferred composition of the invention to a mammal, such as a human.

Brief Description of the Drawings

[0019] Figure 1 illustrates an XRD diffractogram of cinacalcet raw material.

[0020] Figure 2 illustrates an XRD diffractogram of PVP K-30.

[0021] Figure 3 illustrates an XRD diffractogram of a 1:2 solid solution of cinacalcet with PVP K-30.

[0022] Figure 4 illustrates an XRD diffractogram of EUDRAGIT® L-100-55.

[0023] Figure 5 illustrates an XRD diffractogram of a 1:2 solid solution of cinacalcet with EUDRAGIT L-100-55.

[0024] Figure 6 illustrates a DSC thermogram of cinacalcet raw material.

[0025] Figure 7 illustrates a DSC thermogram of PVP K-30.

[0026] Figure 8 illustrates a DSC thermogram of a 1:2 solid solution of cinacalcet with PVP K-30.

[0027] Figure 9 illustrates a DSC thermogram of EUDRAGIT® L-100-55.

[0028] Figure 10 illustrates a DSC thermogram of a 1:2 solid solution of cinacalcet with EUDRAGIT L-100-55.

[0029] Figure 11 illustrates a dissolution profile of a solid solution of cinacalcet with PVP (P-00709), of a physical mixture of cinacalcet with PVP (1:3), and of SENSIPAR® in 0.05 N HCl, USP apparatus 2, 37°C, 75 r.p.m.; and

[0030] Figure 12 illustrates a dissolution profile of a solid solution of cinacalcet with PVP (P-00709), of a physical mixture of cinacalcet with PVP (1:3), and of SENSIPAR® in 6 g/L NaH_2PO_4, pH 6, 0.15% SLS, USP apparatus 2, 37°C, 75 r.p.m.

[0031] Figure 13 illustrates a dissolution profile of a 1:2 solid solution of cinacalcet with EUDRAGIT® and of SENSIPAR® in 0.05 N HCl, U.S.P. type 2 apparatus, 37°C, 75 r.p.m.; and in 6 g/L NaH_2PO_4, pH 6, 0.15% SLS, USP apparatus 2, 37°C, 75 r.p.m.

[0032] Figure 14 illustrates a dissolution profile of formulations of solid solutions of cinacalcet in a simulated gastrointestinal environment.

Detailed Description of the Invention

[0033] As used herein, unless otherwise defined, "cinacalcet" means cinacalcet free base and pharmaceutically acceptable salts and solvates thereof. Preferably, "cinacalcet" means cinacalcet hydrochloride.

[0034] As used herein, unless otherwise defined, "intimate association" or "intimately associated," when used with respect to a mixture of cinacalcet and at least one carrier, means that the carrier(s) and the cinacalcet interact on the molecular level, there being no easily detectable separate cinacalcet phase. A non-intimate association is, for example, a powder blend, or a compressed powder blend, as it is possible to discern between different phases using, for example, electron microscopy. Another example of a non-intimate association is an emulsion, where separate phases co-exist in the solution, and may be visualized using, for example, a light microscope. An example for an intimate associations is a liquid solution,

where there is no way to separate between the carrier and the solute by physical means, or to observe a phase of solute within the carrier.

[0035] As used herein, unless otherwise defined, "free drug" means solid particles consisting essentially of cinacalcet that are not in intimate association with a carrier.

[0036] As used herein, unless otherwise defined, "non-crystalline" and "not in crystalline form" means a material comprising cinacalcet that does not produce an X-ray powder diffraction pattern having peaks characteristic of crystalline cinacalcet, and that does not exhibit a discernable endotherm in differential scanning calorimetry using heating rates of 2 to 20 degrees per minute.

[0037] As used herein, unless otherwise defined, a "solid solution" means a solid, homogenous mixture of at least two components (e.g. cinacalcet and a carrier) wherein the components are interspersed on a molecular level. In solid solutions, the individual physical properties related to the crystalline structure of the components present in lesser amounts, commonly referred to as the solutes, are lost. Presence of the solutes can be detected spectroscopically or by measure of the colligative properties of the solid solution. Even in the solid solutions, some portion of the cinacalcet may come out of solution or remain undissolved in the carrier without departing from the scope of the invention. However, in the solid solutions, at least about 85 percent of the cinacalcet is in solution in the solid solution. Preferably, substantially all, and, most preferably, all, of the cinacalcet is in solution in the solid solution.

[0038] As used herein, the term "supercritical fluid" refers to substances at a temperature and pressure above their thermodynamic critical point. A supercritical fluid solution is a solution in which a supercritical fluid is the solvent. Such a substance has unique properties, such as the ability to diffuse through a solid like a gas, and dissolve solids like a liquid. Additionally, it is possible to change the density of such a substance by subtle changes in temperature and/or pressure. Useful supercritical fluids are, for example, carbon dioxide, water, methane, ethane, propane, ethylene, propylene, methanol, ethanol, and acetone. Preferably, the supercritical fluid is selected from the group comprising carbon dioxide, water, and ethanol. More preferably, the supercritical fluid is carbon dioxide.

[0039] As used herein, unless otherwise defined, "effective" and "therapeutically effective" amount of a drug or pharmacologically active agent means an amount of the drug or agent that is nontoxic and sufficient to provide the desired effect, *e.g.*, treatment of secondary hyperparathyroidism.

[0040] As used herein, unless otherwise defined, "treating," "treated," and "treatment" means at least one of the following: reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, or improvement or remediation of damage.

[0041] The invention encompasses a solid composite comprising cinacalcet and at least one carrier, wherein at least about 85 percent of the cinacalcet is in intimate association with the carrier.

[0042] Preferably, the solid composite is a solid solution. Preferably, substantially all of the cinacalcet is in solution in the solid solution. More preferably, all of the cinacalcet is in solution in the solid solution.

[0043] Preferably, the solid composite is particulate and has an average particle size larger than about 100 μm, more preferably between 100 and 600μm.

[0044] Preferably at least about 85 percent of the cinacalcet in the solid composite is not in crystalline form. More preferably, the cinacalcet in the solid composite has no detectable crystalline cinacalcet.

[0045] The carrier may be any pharmaceutically acceptable inert solid carrier known to one of skill in the art, including, for example, sugars and polymers.

[0046] Preferably, the carrier is a hydrophilic polymer or a polymer presenting a pH dependent solubility profile in aqueous media. The hydrophilic polymer may be selected from the group consisting of povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol, copovidone, and amino alkyl methacrylate type A NF.

[0047] The polymer presenting a pH dependent solubility profile in aqueous media may be selected from copolymers of methacrylic acid. More preferably, the carrier is povidone or a copolymer of methacrylic acid. Although hydroxypropyl methyl cellulose phthalate, polymethylacrylate, and hydroxypropyl cellulose may be used in the present invention as carriers, other carriers, particularly povidone and copolymers of methacrylic acid, are more preferred in the present invention.

[0048] Preferably, the carrier is present in an amount sufficient to maintain at least about 85 percent of the cinacalcet in intimate association with, and, more preferably, in solid solution in, the carrier. One of skill in the art can easily determine by routine experimentation such an amount of carrier. Typically, the drug-to-carrier weight ratio in the solid composites is within a range of about 1:0.5 to about 1:10, preferably about 1:2 to about 1:6.

[0049] The invention further encompasses a process for preparing the solid composite comprising: combining cinacalcet, at least one carrier, and at least one liquid solvent to form a solution; and removing the liquid solvent to obtain the solid composite.

[0050] The cinacalcet may be prepared by any means known to one of skill in the art. It will be appreciated that while preferably at least about 85 percent of the cinacalcet in the solid composites of the present invention is not in crystalline form, cinacalcet in any form (e.g. crystalline or amorphous) may be used to prepare the solid composites.

[0051] Liquid solvents suitable for preparing the solid composite include organic solvents capable of dissolving at least about 85 percent of the cinacalcet and substantially all of the carrier. Preferably, the liquid solvent is capable of dissolving at least about 85 percent of the cinacalcet and at least about 85 percent of the carrier. More preferably, the liquid solvent is capable of dissolving substantially all of the cinacalcet and carrier. Most preferably, the liquid solvent is capable of dissolving all of the cinacalcet and carrier. Preferably, the liquid solvent is one in which cinacalcet has a solubility of at least about 5 mg of cinacalcet per 1 ml solvent at 25°C.

[0052] Examples of suitable liquid solvents include, but are not limited to, at least one of lower aliphatic alcohols and C_{3-8} ketones. "Lower aliphatic alcohols" as used herein means organic compounds having the general structure R-OH, wherein R is a linear or branched C_{1-6} alkyl group. Preferred lower aliphatic alcohols include methanol, ethanol, isopropyl alcohol ("IPA"), and butanol. Preferred C_{3-8} ketones include acetone, methylisobutyl ketone ("MIBK") and methylethyl ketone ("MEK"). More preferred liquid solvents are ethanol, acetone, isopropyl alcohol, and mixtures thereof. Most preferably, the liquid solvent is ethanol or mostly ethanol in combination with one or more of the above solvents.

[0053] The combining step may include mixing the liquid solvent with cinacalcet and at least one carrier in any order. The cinacalcet, carrier, and liquid solvent may be mixed using any suitable mixing method known to one of skill in the art, such as by using magnetic stirrers, mixer stirrers, shakers, or sonification.

[0054] Preferably, at least about 85 percent of the cinacalcet and a majority of the carrier are in solution in the at least one liquid solvent. More preferably, at least about 85 percent of the cinacalcet and about 85 percent of the carrier are in solution in the at least one liquid solvent. Even more preferably, substantially all of the cinacalcet and carrier are in

solution in the at least one solvent. In particularly preferred embodiments, all of the cinacalcet and carrier are in solution in the at least one solvent.

[0055] The step of removing the liquid solvent may be performed by any method known to one of skill in the art. Preferably, the liquid solvent is removed by evaporation. More preferably, the liquid solvent is removed by evaporation under vacuum, by fluidized bed drying, or by spray-drying. "Spray-drying" broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture. In a typical spray-drying apparatus, there is a strong driving force for evaporation of solvent from the droplets, which may be provided by providing a heated drying gas. Spray-drying processes and equipment are described in *Perry's Chemical Engineer's Handbook*, pp. 20-54 to 20-57 (6th ed. 1984). The obtained solid composite may optionally be further dried.

[0056] Preferably, the obtained solid composite is in the form of a solid solution, wherein substantially all, most preferably all, of the cinacalcet is in solid solution in the carrier.

[0057] Optionally, the process further comprises the addition of at least one pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, for example, surfactants such as sodium lauryl sulfate.

[0058] The pharmaceutically acceptable excipient may be combined with the cinacalcet, carrier, and liquid solvent in step a), or may be added to the obtained solid composite of step b) after removal of the liquid solvent.

[0059] Alternatively, the pharmaceutically acceptable excipient may be added during removal of the liquid solvent in step b), by, for example, spraying the solution containing the cinacaclet, carrier and solvent onto a fluidized bed of the excipient while drying. As a result, the solid composite will be formed on the excipient. In some cases, this process will prove advantageous because it provides a solid composite with greater surface area, which can aid in dissolution in aqueous media upon administration to a patient.

[0060] The invention further encompasses a process for preparing the solid composite using supercritical fluid technology. The process may comprise: dissolving cinacalcet and at least one carrier in a supercritical fluid; and removing the supercritical fluid by evaporation. Preferably, the evaporation is accomplished under reduced pressure or by adjusting the temperature of the solution to a temperature at which the supercritical fluid becomes a gas. Alternatively, the process may comprise: dissolving cinacalcet and at least one carrier in an organic or inorganic solvent to form a liquid solution; adding a supercritical fluid

(anti-solvent) to induce precipitation of a mixture of the cinacalcet and the carrier; and removing the solvent and the supercritical fluid by evaporation. Preferably, the evaporation is accomplished under reduced pressure or by adjusting the temperature of the solution.

[0061] The invention further encompasses a process for preparing the solid composite comprising: combining cinacalcet and at least one carrier to form a mixture; heating the mixture to a temperature at which both the cinacalcet and the carrier melt to form a fusion product; and cooling the fusion product in a manner that does not allow for re-crystallization of the cinacalcet out of the fusion product.

[0062] The invention further encompasses a process for preparing the solid composite comprising: combining cinacalcet and at least one carrier to form a mixture, heating the mixture to control its viscosity; and feeding the heated mixture through a hot melt extrusion system.

[0063] It would be appreciated by one of skill in the art that the above-described solid composites reduce the health risks involved in handling active pharmaceutical ingredients in particulate form, and specifically micronized particles.

[0064] In addition, because of the enhanced solubility of the solid composites relative to the active ingredient alone or in a physical mixture with the carrier, as described below, a larger particle size of the solid composite particles may be used in the formulation without having an adverse effect on the dissolution profile of the cinacalcet.

[0065] Another method to improve the safety of the products is by using a bi-modal distribution of particle sizes of the cinacalcet, wherein the population of large particle sizes, above 70μm, avoids the need for micronization of the cinacalcet, and thus reduces production of hazardous dust. The population of small particle sizes, smaller than about 5 μm, preferably less than 2 μm, and even more preferably smaller than 1μm, is prepared using a high pressure homogenizer. This method involves micronizing the particles in a liquid medium, thus avoiding production and dispersion of dust particles of the active ingredient.

[0066] The invention further encompasses pharmaceutical formulations comprising a solid composite comprising cinacalcet and at least one carrier, and at least one pharmaceutically acceptable excipient.

[0067] The pharmaceutical formulation may contain additional cinacalcet, meaning free drug cinacalcet in addition to the cinacalcet in the solid composite, thus providing the ability to manipulate the dissolution characteristics of the formulation.

[0068] The amount of the solid composite used in the pharmaceutical formulation is preferably an amount that provides a therapeutically effective amount of cinacalcet. It will be

appreciated that the amount of solid composite used will differ according to the cinacalcet: carrier ratio in the particles.

[0069] Preferably, the pharmaceutical formulation comprises: (a) from about 10 percent to about 40 percent by weight of a calcium receptor-active compound, such as cinacalcet; (b) from about 10 percent to about 50 percent of at least one binder, which may serve as the carrier or "solid solvent" of the solid composite; (c) from about 15 percent to about 45 percent by weight of at least one diluent; and (e) from about 10 percent to about 40 percent of at least one disintegrant; wherein the percentage by weight is relative to the total weight of the formulation.

[0070] The formulation may further comprise about 0.5 percent to about 5 percent by weight relative to the total weight of the formulation of at least one glidant or lubricant and about 1 percent to 6 percent by weight of at least one coating material. It is understood by one of skill in the art that one or more inactive ingredients can act in more than one capacity for example; the same material may function as both a diluent and a disintegrant. The formulation may further comprise a surfactant.

[0071] The pharmaceutical formulation can be processed into, for example, a unit dosage form. In particular, the pharmaceutical formulation can be formulated into oral solid dosage forms such as capsules, tablets, or gel-caps.

[0072] The solid composites and pharmaceutical formulation including them preferably allow for the rapid absorption and onset of the calcium receptor-active compound cinacalcet in a mammal.

[0073] The invention further encompasses an immediate release formulation of a calcium receptor-active compound, such as cinacalcet, wherein at least about 80 percent of the calcium receptor-active compound is released from the formulation within about 30 minutes in 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m.

[0074] The invention further encompasses a controlled release formulation of a calcium receptor-active compound, such as cinacalcet, wherein the majority of the calcium receptor-active compound is released in the intestine, where the pH is slightly acidic to neutral, rather than in the stomach, where the pH is acidic.

[0075] When the controlled release formulation is exposed to a simulated gastric environment for a period of about 30 minutes, followed by exposure to a simulated intestinal environment, more than about 50 percent of the calcium receptor-active compound is released from the formulation during about the first 30 minutes of exposure and not less than

about 70 percent of the calcium receptor-active compound is released from the formulation during about the first 90 minutes of exposure.

[0076] Preferably, at least about 50 percent of the calcium receptor-active compound is released within about the first 60 minutes of exposure, i.e., 30 minutes after the change in environment.

[0077] Preferably, not less than about 80 percent of the calcium receptor-active compound is released from the formulation during about the first 90 minutes of exposure. More preferably, not less than about 90 percent of the calcium receptor-active compound is released from the formulation during about the first 90 minutes of exposure.

[0078] The simulated gastric environment is 800 ml of 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m. The simulated intestinal environment is 6 g/L NaH_2PO_4, pH 6, 0.15% sodium lauryl sulfate in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m. These environments simulate the passage of the dosage forms through the gastrointestinal pathway.

[0079] The invention further encompasses a method of treatment comprising administering the pharmaceutical formulation to a mammal. Preferably, the mammal is a human. Preferably, the pharmaceutical formulation comprises cinacalcet and is administered to treat secondary hyperparathyroidism, which is the approved use for SENSIPAR®. As discussed above, the method of "treating" secondary hyperparathyroidism described herein encompasses both prevention of the disorder in a predisposed individual and treatment of the disorder in a clinically symptomatic individual.

[0080] The amount of calcium receptor-active compound administered and the dosing regimen used, will depend on the particular drug selected, the age and general condition of the subject being treated, the severity of the subject's condition, and the judgment of the prescribing physician.

[0081] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Examples

[0082] In the following examples, a rotary evaporator equipped with a vacuum pump, was used to remove the solvent from the liquid solutions. The liquid solutions were heated to about 50°C using a water bath during rotary evaporation.

[0083] In the following examples, dissolution profiles were determined in a dissolution vessel using a U.S.P. type 2 apparatus (paddles) in a simulated gastrointestinal environment under conditions described in Table 1. *See U.S. Pharamcopeia*, pp. 2155-2156 (26th ed. 2003). Samples were analyzed on-line by a UV detector.

Table 1. Dissolution conditions.

Medium 1	0.05 N HCl, pH=1.3
Medium 2	0.15% aqueous solution sodium lauryl sulfate and 6g/L NaH_2PO_4, pH=~6.0
Volume	900 ml
Temperature	75°C
Speed	50 RPM
Sampling points:	5,10, 30, 50, 80, 120 and (optionally) 160 minutes

Example 1: Cinacalcet Solid Solutions with Povidone

a) Cinacalcet HCl: povidone in 1:2 weight ratio

[0084] 1 g of cinacalcet HCl per 2 g of povidone (PVP K-30) were ground together using a mortar and pestle. The resulting mixture was completely dissolved in ethanol in a round-bottom flask. The ethanol was then removed from the solution using a rotary evaporator under vacuum, and heating the solution to 50°C, until dry solid flakes formed on the flask. The dry solid was then collected.

[0085] X-ray diffraction ("XRD") and differential scanning calorimetry ("DSC") were performed on the dry solid and compared to the XRD and DSC for the cinacalcet and povidone alone. The XRD and DSC for the dry solid are illustrated in Figures 3 and 8, respectively. The XRD and DSC for the cinacalcet are illustrated in Figures 1 and 6, respectively. The XRD and DSC for the povidone are illustrated in Figures 2 and 7, respectively.

b) Cinacalcet HCl: povidone in 1:3 weight ratio

[0086] 1 g of cinacalcet HCl per 3 g of povidone (PVP K-30) were ground together using a mortar and pestle. The resulting mixture was completely dissolved in ethanol in a round-bottom flask. The ethanol was then removed from the solution using a rotary

evaporator under vacuum, and heating the solution to 50°C, until dry solid flakes formed on the flask.

[0087] A sample of the dry solid was collected and its dissolution profile determined according to the conditions in Table 1. The dissolution profile of the solid was compared with the dissolution profile of a commercial version of cinacalcet HCl tablets (SENSIPAR®, 30 mg) and with a simple mixture of cinacalcet HCl (average length of the needle-shaped crystals was ~20 micron) with povidone. The results of dissolution testing are illustrated in Figures 11 and 12.

[0088] The amount of cinacalcet dissolved at the 30 minute time point demonstrates that cinacalcet in a solid solution form has a solubility greater than cinacalcet raw material in a physical mixture with lactose or starch. The percent of cinacalcet dissolved after 5 minutes demonstrates the greater dissolution rate of cinacalcet in a solid solution form, as compared with both SENSIPAR® and a physical mixture of particles with an average length of 20 μm with starch.

Example 2: Cinacalcet Solid Solution with EUDRAGIT® L-100-55 in 1:2 Weight Ratio

[0089] 1g of cinacalcet was dissolved in 10 ml of ethanol to form a first solution. 2 g of EUDRAGIT® L-100-55 was dissolved in about 15 ml of ethanol to form a second solution. The two solutions were then combined, and ethanol was evaporated from the combined solution using a rotary evaporator to obtain dry solid flakes. The dry solid was then collected.

[0090] XRD and DSC were performed on the dry solid and compared to the XRD and DSC for the cinacalcet and EUDRAGIT® L-100-55 alone. The XRD and DSC for the dry solid are illustrated in Figures 5 and 10, respectively. The XRD and DSC for the cinacalcet are illustrated in Figures 1 and 6, respectively. The XRD and DSC for the EUDRAGIT® L-100-55 are illustrated in Figures 4 and 9, respectively.

[0091] A sample of the dry solid was collected and its dissolution profile determined according to the conditions in Table 1. The dissolution profile of the solid was compared with the dissolution profile of a commercial version of cinacalcet HCl tablets (SENSIPAR®, 30 mg) in a simulated gastrointestinal environment. The results of dissolution testing are shown in Figure 13.

[0092] As illustrated in Figure 13, in the simulated gastric environment of 0.05N HCl, cinacalcet was released more quickly from the SENSIPAR® tablets than from the solid solution of cinacalcet and EUDRAGIT® L-100-55. For example, about 95 percent of the

cinacalcet was released from the SENSIPAR® tablets during about the first 30 minutes of exposure to the 0.05N HCl, while only about 15 percent of the cinacalcet was released from the solid solution of cinacalcet and EUDRAGIT® L-100-55 the under the same conditions. In the more neutral simulated intestinal environment of buffer at pH 6, however, about 95 percent of the cinacalcet was released from both the SENSIPAR® tablets and from the solid solution of cinacalcet and EUDRAGIT® L-100-55 during about the first 30 minutes of exposure.

Example 3: Formulation including cinacalcet solid solution with povidone

[0093] Prepare a formulation of cinacalcet, with a target amount of 90 mg of cinacalcet per tablet, having the following composition:

Table 2. Cinacalcet formulation prepared in Example 3.

Ingredient	Weight % (w/w)	Amount (mg/tablet)
Cinacalcet HCl	15.88	99.18
Povidone (PVP K-30)	31.76	198.36
Microcrystalline cellulose (AVICEL® PH102)	32.02	200.0
Crospovidone	9.61	60.0
Sodium Carboxymethylcellulose (AC-DI-SOL®)	9.61	60.0
Magnesium stearate	1.12	7.0
Core Tablet	100.00	624.54

[0094] Combine and mix cinacalcet HCl, povidone, microcrystalline cellulose, crospovidone, and sodium carboxymethylcellulose. Then, add magnesium stearate to the mixture and press the mixture into tablets. Measure the dissolution profile of the tablets according to the procedure described in Example 6.

Example 4: Formulation including cinacalcet solid solution with povidone

[0095] A solid solution of cinacalcet with povidone (1:2 weight ratio) prepared according to Example 1a was passed through a sieve equipped with a 30 mesh (~600 micron aperture) screen on top of a 50 mesh screen (300 micron aperture).

[0096] The sample, which passed the 50 mesh screen, is estimated to have a particle size distribution wherein approximately 100 percent of the particles are less than 300 microns

in size and an average particle size around 100 μm. This sample was used to prepare a pharmaceutical formulation of cinacalcet, with a target amount of 90 mg of cinacalcet per tablet, having the following composition:

Table 3. Cinacalcet formulation prepared in Example 4.

Ingredient	Weight % (w/w)	Amount (mg/tablet)
Cinacalcet HCl	16.68	99.18
Povidone (PVP K-30)	33.36	198.36
Microcrystalline cellulose (AVICEL® PH102)	25.24	150.0
Crospovidone	10.09	60.0
Sodium Carboxymethylcellulose (AC-DI-SOL®)	10.09	60.0
EUDRAGIT® L-100-55	3.36	20.0
Magnesium stearate	1.18	7.0
Core Tablet	100.00	594.54

[0097] The solid solution of cinacalcet with povidone was dry-mixed with microcrystalline cellulose, crospovidone, and sodium carboxymethylcellulose, followed by granulation with a 20 percent to 40 percent ethanolic solution of EUDRAGIT® L-100-55. The resulting granulate was then dried in a vacuum oven at 50°C. The granulate was then passed through an 8 mesh sieve (~2.4mm), followed by an 18 mesh sieve (~1mm). Magnesium stearate was then added to the granulate to form a lubricated blend, and the final lubricated blend was compressed into tablets using a manual press.

Example 5: Formulation including cinacalcet solid solution with EUDRAGIT L-100-55

[0098] A solid solution of cinacalcet in EUDRAGIT® L-100-55 (1:2 weight ratio) prepared according to Example 2 was passed through a sieve equipped with a 30 mesh screen on top of a 50 mesh screen.

a) Cinacalcet HCl:EUDRAGIT® L-100-55 with Average Particle Size of ~400 μm

[0099] The solid composite collected on top of the 50 mesh screen (having a particle size between 300μm and 600μm) was used in a pharmaceutical formulation (average particle size estimated to be ~400 μm).

b) Cinacalcet HCl:EUDRAGIT® L-100-55 with Average Particle Size of ~100 μm

[00100] The solid composite which passed through the 50 mesh screen (having a particle size distribution wherein 100 percent of the particles are less than 300μm in size) was used in another pharmaceutical formulation (average particle size estimated to be ~100μm).

[00101] Each solid composite (5a and 5b) was used to prepare a pharmaceutical formulation of cinacalcet, with a target amount of 90 mg of cinacalcet per tablet, having the following composition:

Table 4. Cinacalcet formulation prepared in Example 5.

Ingredient	Weight % (w/w)	Amount (mg/tablet)
Cinacalcet HCl	15.88	99.18
EUDRAGIT® L-100-55	31.76	198.36
Microcrystalline cellulose (AVICEL® PH102)	32.02	200.0
Crospovidone	9.61	60.0
Sodium Carboxymethylcellulose (AC-DI-SOL®)	9.61	60.0
Magnesium stearate	1.12	7.0
Core Tablet	100.00	624.54

[00102] The solid solution of cinacalcet with EUDRAGIT® L-100-55 was mixed with microcrystalline cellulose, crospovidone, and sodium carboxymethylcellulose, followed by granulation. Magnesium stearate was then added to the granulate to form a lubricated blend, and the final lubricated blend was compressed into tablets using a manual press.

Example 6: Dissolution profile of tablet formulations of cinacalcet

[00103] The dissolution profiles of the formulations prepared in Examples 4 and 5 were measured with a U.S.P. type 2 apparatus at a temperature of about 37°C, and at a rotation speed of about 75 r.p.m. The dissolution profiles are described in Table 5 and illustrated in Figure 14. Percentage of dissolution was adjusted to change in medium volume.

[00104] The dissolution profile was measured in a complex medium designed to imitate physiological conditions in the gastrointestinal tract. During the first 30 minutes of dissolution the medium was 800 ml 0.05N HCl, which was then neutralized with 120 ml of a

neutralizing buffer (50 g/l NaH_2PO_4 adjusted to pH 6, to which were added 35 ml/l 10 N NaOH, and 11.25 g/l SLS) for a final volume of 920 ml.

Table 5. Dissolution profiles for the formulations prepared in Examples 4, 5a, and 5b.

Time (min)	% Dissolution			
	Example 4	Example 5a	Example 5b	SENSIPAR® (90mg)
5	0.8	0.9	4.9	41.5
10	1.5	2.1	9.6	66.3
30	3.5	5.7	19.8	91.3
35	4.5	12.3	47.3	90.7
45	10.0	30.7	86.2	94.3
60	25.1	50.4	96.4	95.6
80	42.1	65.9	97.3	96.2
110	69.7	79.5	97.5	96.7
150	90.0	89.9	97.7	96.9

[00105] As illustrated in Table 5, in the simulated gastric environment of 0.05N HCl, cinacalcet was released more quickly from the SENSIPAR® tablets than from the solid solution of cinacalcet and EUDRAGIT® L-100-55. 91.3 percent of the cinacalcet was released from the SENSIPAR® tablets during the first 30 minutes of exposure to the 0.05N HCl, while only 3.5 to 19.8 percent of the cinacalcet was released from the solid solution of cinacalcet and povidone the under the same conditions. In the more neutral simulated intestinal environment of buffer at pH 6, however, 90 percent to 97.7 percent of the cinacalcet was released from both the SENSIPAR® tablets and the solid solution of cinacalcet and povidone during the first 150 minutes. Thus, the solid solution allows for the controlled release of cinacalcet in an environment more neutral than the gastric environment.

Example 7: Method for improving the safety of cinacalcet production - Preparation of sub-micron scale population of particles

[00106] A suspension of cinacalcet hydrochloride in water is placed in a Microfluidics M-110Y Laboratory Microfluidizer Processor, and processed until the D_{50} particle size is less

than about 1 μm. This population is mixed with a population of particles having a D_{50} of more than about 100 μm, so that the overall particle size D_{50} is larger than about 70 μm. This mixture is then used in a formulation, and the dissolution profile is examined.

Example 8: Preparation of cinacalcet solid solutions using supercritical fluid technology

[00107] A solution of cinacalcet in absolute ethanol, also containing PVP K-30, is introduced in the particle formation vessel of a supercritical apparatus containing supercritical carbon dioxide at an appropriate flow through the inner nozzle passage. Supercritical carbon dioxide is introduced at an appropriate flow through the outer nozzle passage. A solid fluffy substance is formed, and the pressure lowered to remove the carbon dioxide and ethanol.

What is Claimed is:

1. A composition, comprising a solid composite of cinacalcet in intimate association with at least one carrier.

2. The composition of claim 1, wherein the composition is the solid composite.

3. The composition of either of claims 1 and 2, wherein at least about 85 percent of the cinacalcet is in intimate association with the at least one carrier.

4. The composition of any of claims 1 to 3, wherein at least about 85 percent of the cinacalcet is not in particulate form.

5. The composition of any of claims 1 to 4, wherein at least about 85 percent of the cinacalcet is not in crystalline form.

6. The composition of any of claims 1 to 5, wherein the solid composite is a solid solution.

7. The composition of claim 6, wherein substantially all of the cinacalcet is in solution in the solid solution.

8. The composition of any of claims 1 to 7, wherein the carrier comprises a polymer.

9. The composition of claim 8, wherein the polymer is selected from the group consisting of povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol, copovidone, copolymers of methacrylate, copolymers of methacrylic acid, and mixtures thereof.

10. The composition of claim 8, wherein the polymer is povidone or a copolymer of methacrylic acid.

11. The composition of any of claims 1 to 7, wherein the carrier comprises a sugar or a sugar derivative.

12. The composition of claim 11, wherein the sugar or sugar derivative is selected from the group consisting of sucrose, mannitol, lactose, maltitol, sorbitol, xylitol, sucralose, and mixtures thereof.

13. The composition of any of claims 1 to 12, wherein the solid composite is a particulate having an average particle size of more than about 100 μm.

14. The composition of any of claims 1 to 12, wherein the average particle size is from about 100 to about 600 μm.

15. The composition of any of claims 1 to 14, wherein composite has a drug-to-carrier weight ratio of from about 1:0.5 to about 1:10.

16. The composition of any of claims 1 to 14, wherein composite has a drug-to-carrier weight ratio of from about 1:2 to about 1:6.

17. The composition of any of claims 1 to 16, wherein the composition is a pharmaceutical formulation, comprising from about 10 percent to about 40 percent by weight of cinacalcet.

18. The composition of claim 17, further comprising about 0.5 percent to about 5 percent by weight relative to the total weight of the formulation of at least one glidant or lubricant and/or about 1 percent to about 6 percent by weight of at least one coating material.

19. A method of treatment, comprising administering an effective amount of the pharmaceutical formulation of either of claims 17 and 18 to a mammal.

20. The composition of either of claims 17 and 18, wherein the composition is an immediate release composition from which at least about 80 percent of the cinacalcet is released within about 30 minutes in 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m.

21. A method of treatment, comprising administering an effective amount of the pharmaceutical formulation of claim 20 to a mammal.

22. The composition of either of claims 17 and 18, wherein the composition is a controlled release pharmaceutical formulation, and wherein, when the formulation is exposed to a solution of 0.05 N HCl in a U.S.P. type 2 apparatus at a temperature of about 37°C and at a rotation speed of about 75 r.p.m. for about 30 minutes, followed by addition of a buffer in an amount sufficient to neutralize the solution and continued exposure to the neutralized solution, more than about 50 percent of the cinacalcet is released from the formulation within

about the first 30 minutes of exposure, and not less than about 70 percent of the calcium receptor-active compound is released from the formulation within about the first 90 minutes of exposure.

23. The composition of claim 22, wherein at least about 50 percent of the cinacalcet is released within about the first 60 minutes of exposure.

24. The composition of claim 22, wherein not less than about 80 percent of the cinacalcet is released from the formulation during about the first 90 minutes of exposure.

25. The composition of claim 22, wherein not less than about 90 percent of the cinacalcet is released from the formulation during about the first 90 minutes of exposure.

26. A method of treatment, comprising administering an effective amount of the pharmaceutical formulation of any of claims 22 to 25 to a mammal.

27. A method for preparing a solid composite, comprising:

combining cinacalcet, at least one carrier, and at least one liquid solvent to form a solution; and

removing the solvent to obtain a solid composite of the cinacalcet and the at least one carrier.

28. The method of claim 27, wherein the solid composite is a solid solution.

29. The method of either of claims 27 and 28, wherein the carrier is selected from the group consisting of povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol, copovidone, copolymers of methacrylate, and copolymers of methacrylic acid.

30. The method of any of claims 27 to 29, wherein the solvent is selected from at least one of lower aliphatic alcohols and C_{3-8} ketones.

31. The method of any of claims 27 to 30, further comprising removing solvent by evaporation.

32. The method of claim 31, wherein the solvent is evaporated under vacuum, in a fluidized bed drier, or by spray drying.

33. The method of any of claims 27 to 32, further comprising dissolving the cinacalcet and at least one carrier in an organic or inorganic solvent to form the solution;

adding a supercritical fluid to induce precipitation of a mixture of the cinacalcet and the carrier; and

removing the solvent and the supercritical fluid by evaporation.

34. The method of claim 27, wherein the solvent is a supercritical fluid.

35. The method of either of claims 33 and 34, wherein the supercritical fluid is selected from the group consisting of carbon dioxide, water, methane, ethane, propane, ethylene, propylene, methanol, ethanol, and acetone.

36. The method of claim 35, wherein the supercritical fluid is carbon dioxide.

37. The method of either of claims 33 and 34, further comprising removing the supercritical fluid by reducing pressure.

38. A method for preparing a solid composite comprising:

combining cinacalcet and at least one carrier to form a mixture;

heating the mixture to a temperature at which both the cinacalcet and the carrier melt to form a fusion product; and

cooling the fusion product in a manner that does not allow crystallization of the cinacalcet out of the fusion product.

39. The method of claim 38, further comprising combining the cinacalcet and at least one carrier to form a mixture;

heating the mixture to control its viscosity; and

feeding the heated mixture through a hot melt extrusion system.

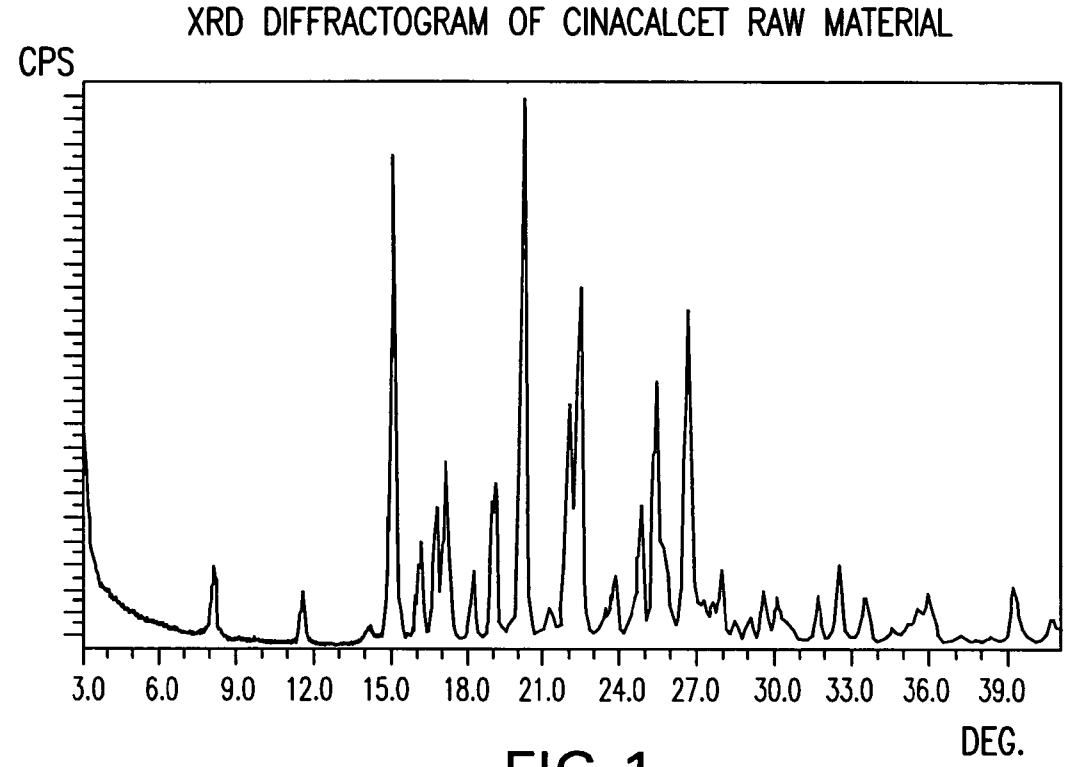


FIG. 1

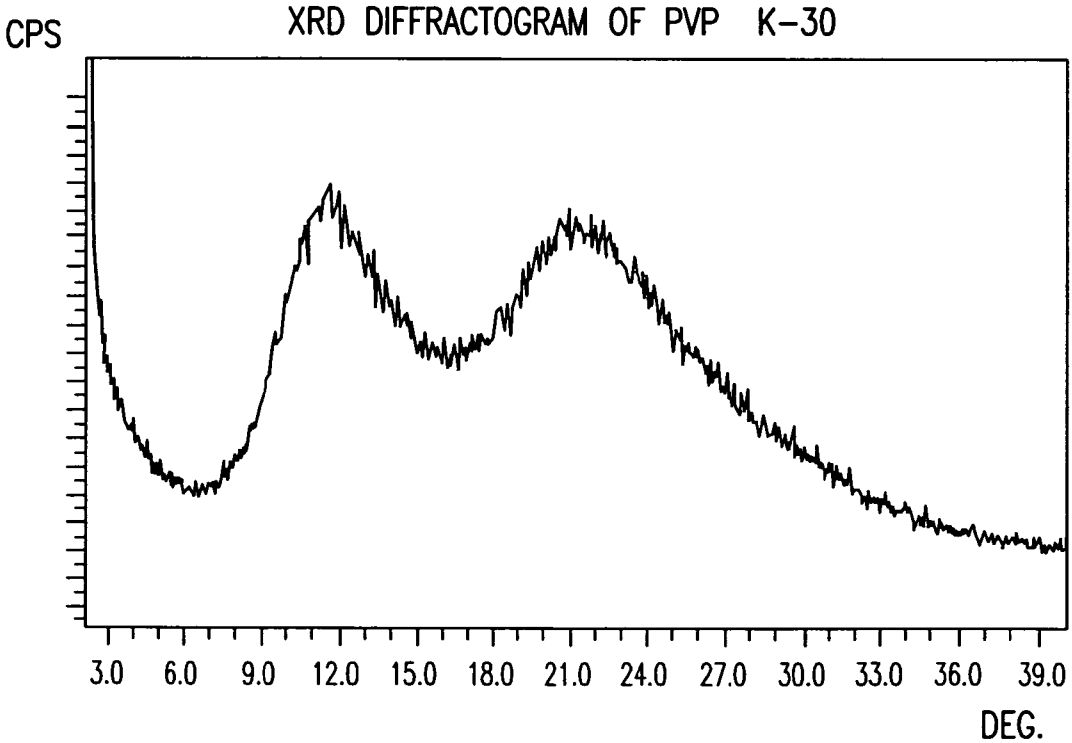
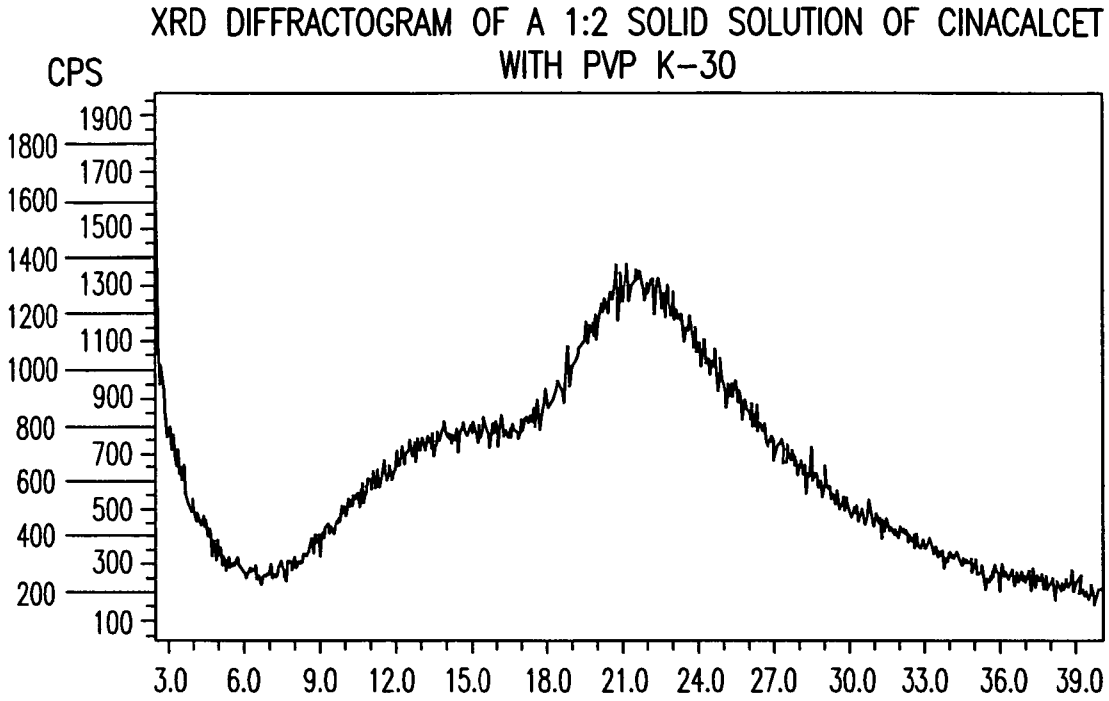


FIG. 2

SUBSTITUTE SHEET


XRD DIFFRACTOGRAM OF A 1:2 SOLID SOLUTION OF CINACALCET WITH PVP K-30
CPS
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
3.0
6.0
9.0
12.0
15.0
18.0
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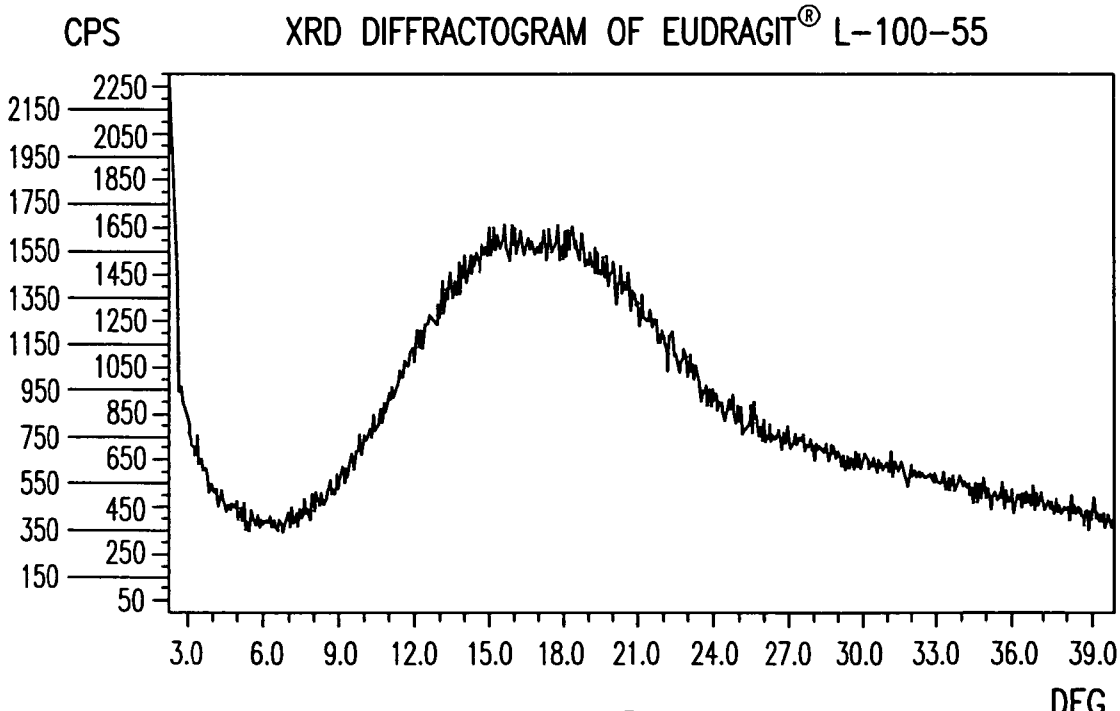
27.0
30.0
33.0
36.0
39.0
DEG.

FIG.3


CPS
XRD DIFFRACTOGRAM OF EUDRAGIT® L-100-55
2250
2150
2050
1950
1850
1750
1650
1550
1450
1350
1250
1150
1050
950
850
750
650
550
450
350
250
150
50
3.0
6.0
9.0
12.0
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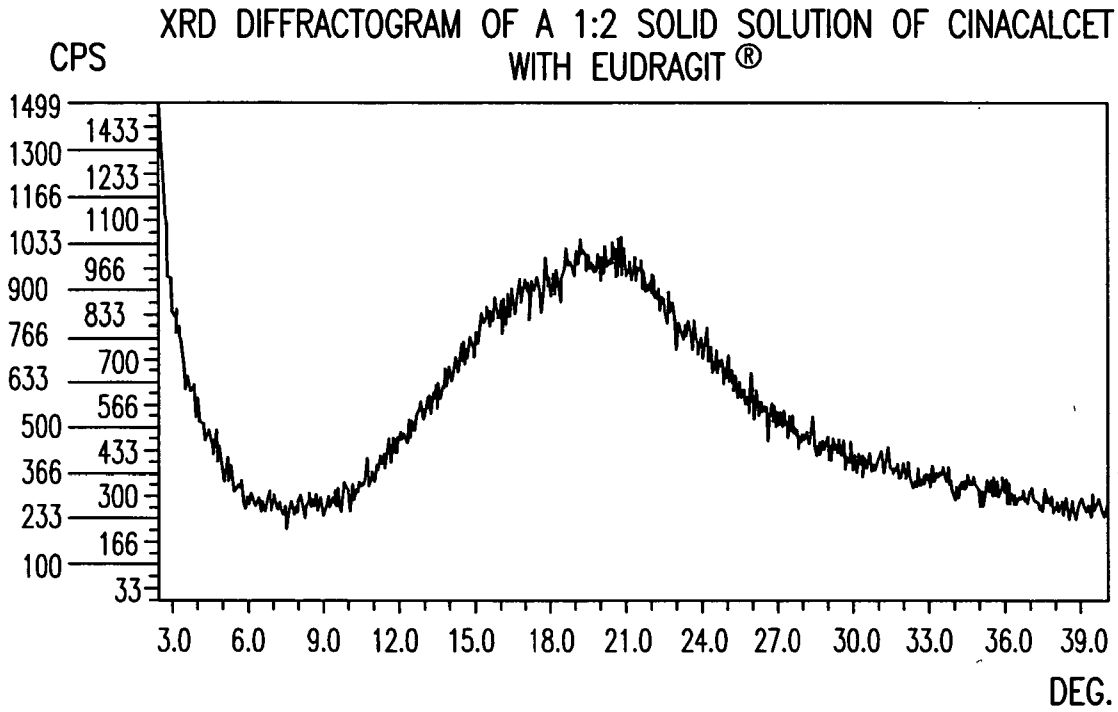
27.0
30.0
33.0
36.0
39.0
DEG.

FIG.4


XRD DIFFRACTOGRAM OF A 1:2 SOLID SOLUTION OF CINACALCET WITH EUDRAGIT ®
CPS
1499
1300
1166
1033
900
766
633
500
366
233
100
1433
1233
1100
966
833
700
566
433
300
166
33
3.0
6.0
9.0
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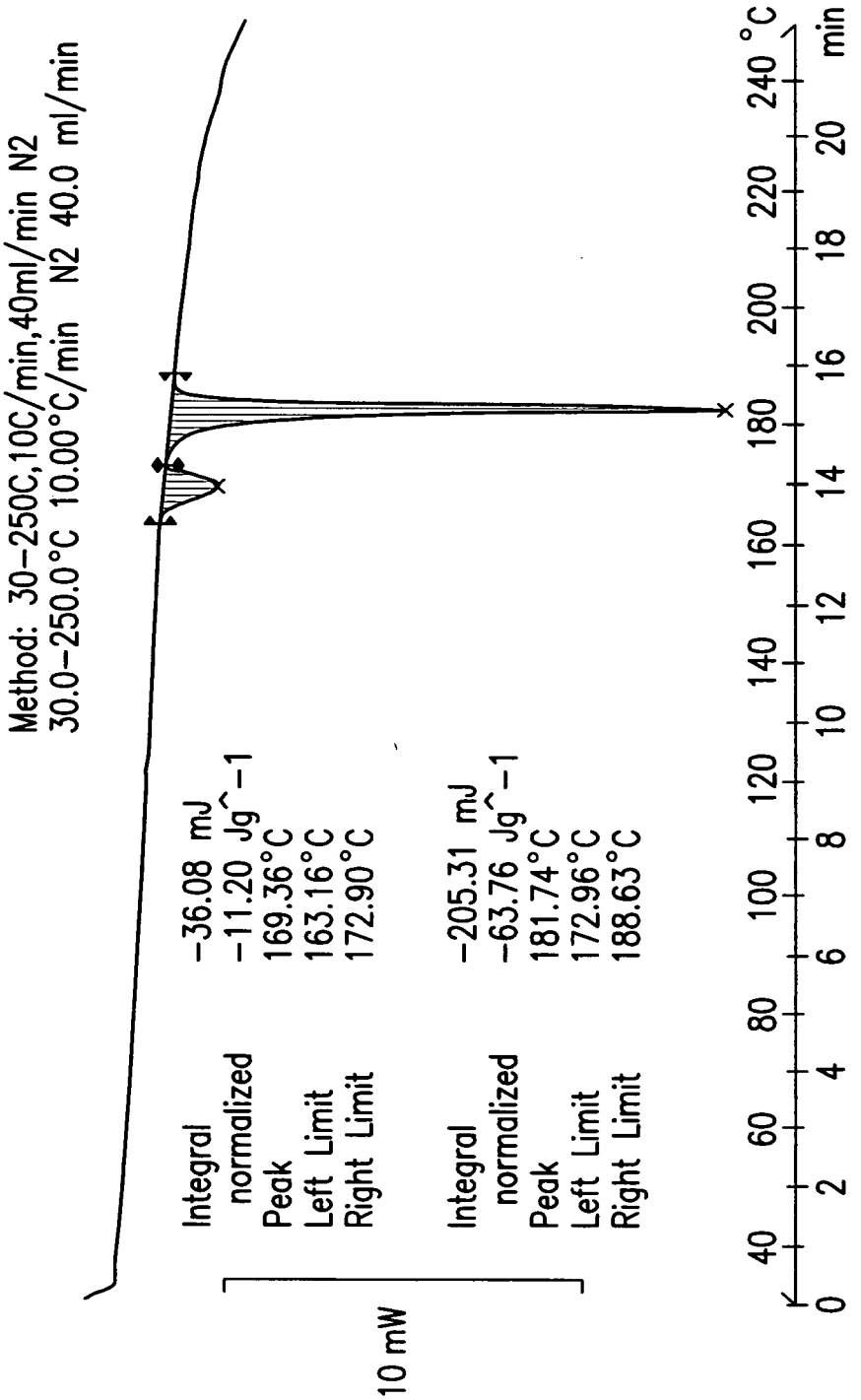
30.0
33.0
36.0
39.0
DEG.

FIG.5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30.0-250.0°C 10.00°C/min N2 40.0 ml/min
10 mW
Integral -36.08 mJ
normalized -11.20 Jg^-1
Peak 169.36°C
Left Limit 163.16°C
Right Limit 172.90°C
Integral -205.31 mJ
normalized -63.76 Jg^-1
Peak 181.74°C
Left Limit 172.96°C
Right Limit 188.63°C
0 2 4 6 8 10 12 14 16 18 20 min
40 60 80 100 120 140 160 180 200 220 240 °C

FIG.6

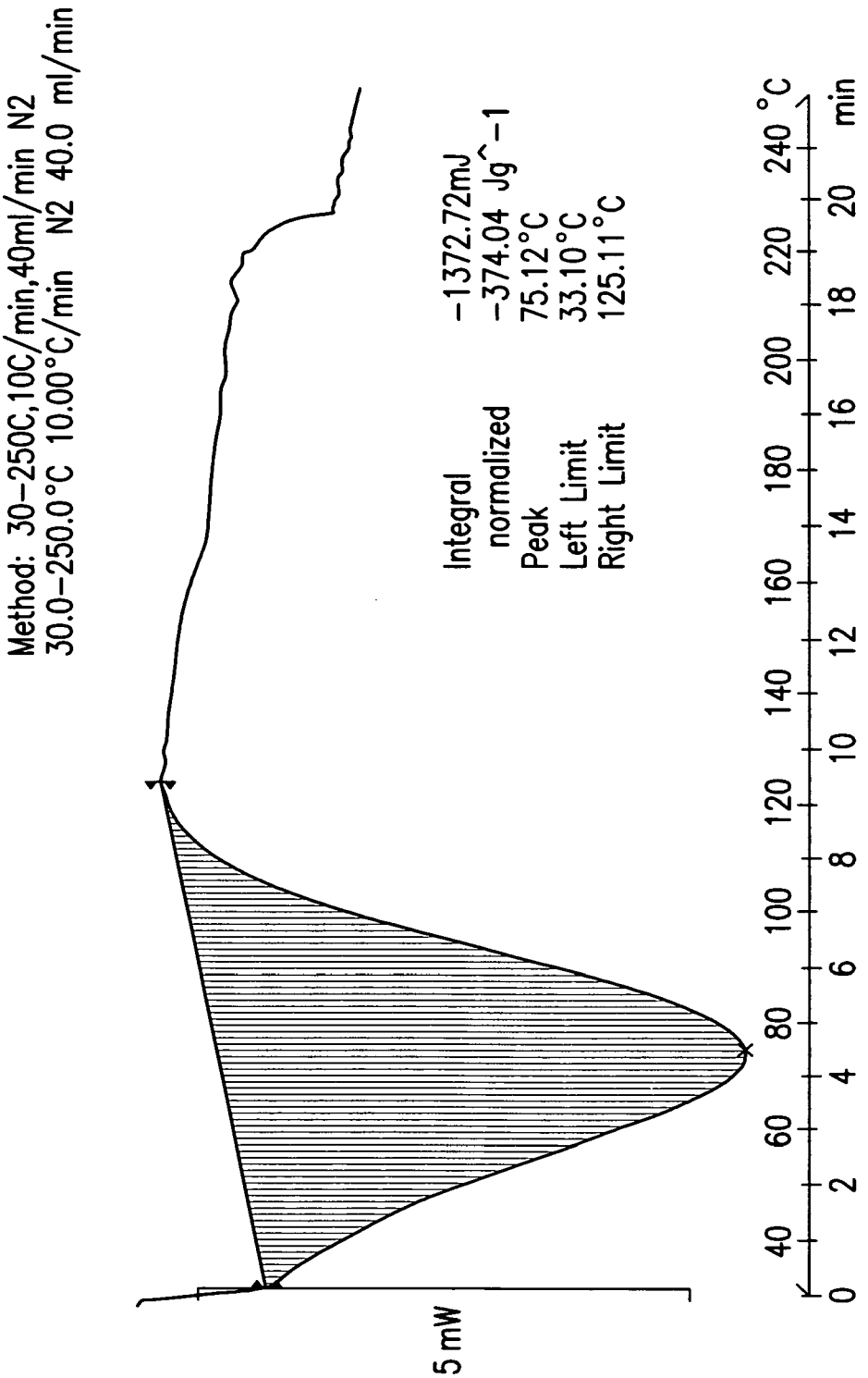
Method: 30-250C,10C/min,40ml/min N2
30.0-250.0°C 10.00°C/min N2 40.0 ml/min
Integral -1372.72mJ
normalized -374.04 Jg^-1
Peak 75.12°C
Left Limit 33.10°C
Right Limit 125.11°C
5 mW
0 2 4 6 8 10 12 14 16 18 20 min
40 60 80 100 120 140 160 180 200 220 240 °C

FIG. 7

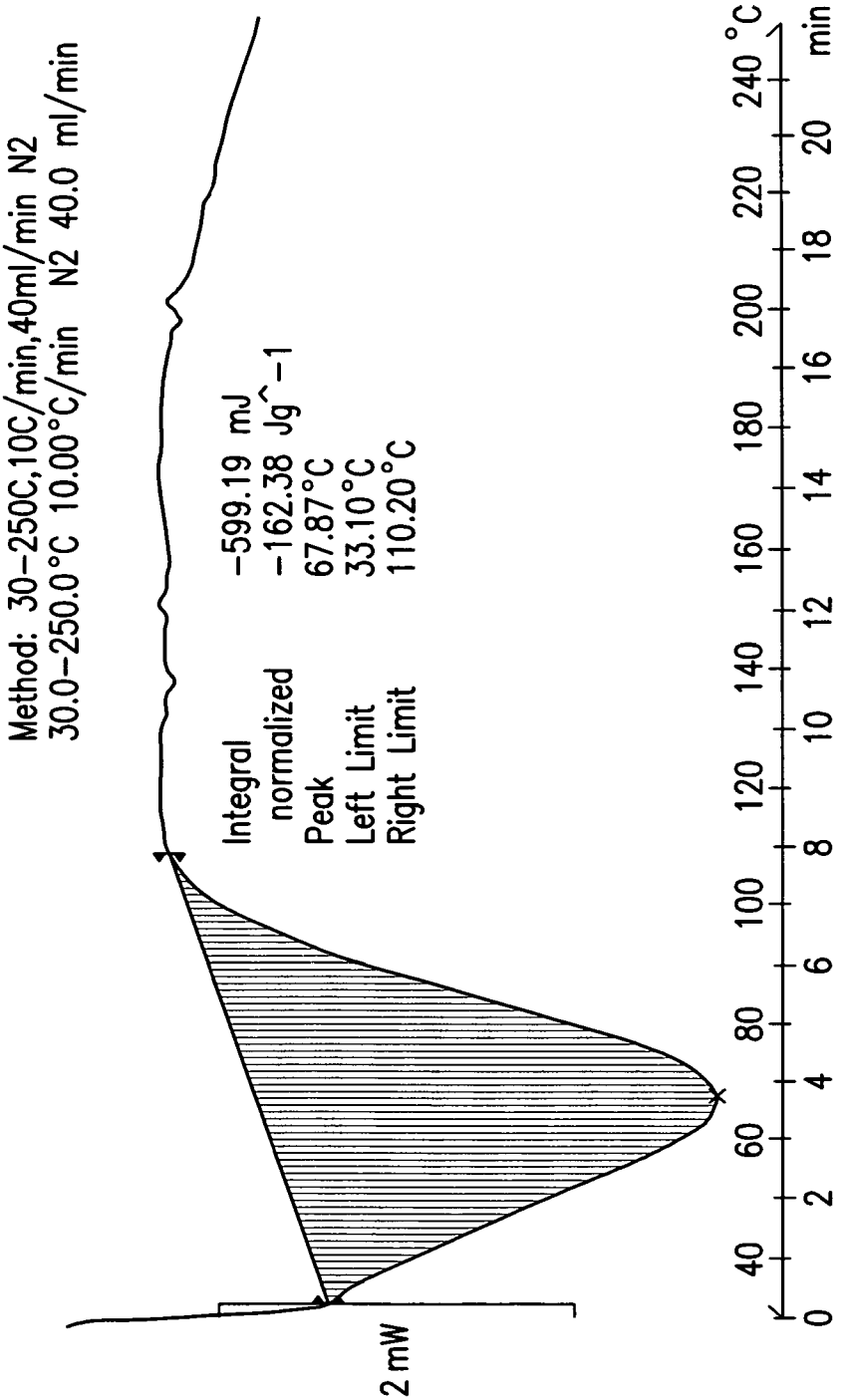
Method: 30-250C,10C/min,40ml/min N2
30.0-250.0°C 10.00°C/min N2 40.0 ml/min
Integral -599.19 mJ
normalized -162.38 Jg^-1
Peak 67.87°C
Left Limit 33.10°C
Right Limit 110.20°C
2 mW
0 40 2 60 4 80 6 100 8 120 10 140 12 160 14 180 16 200 18 220 20 240 °C
min

FIG.8

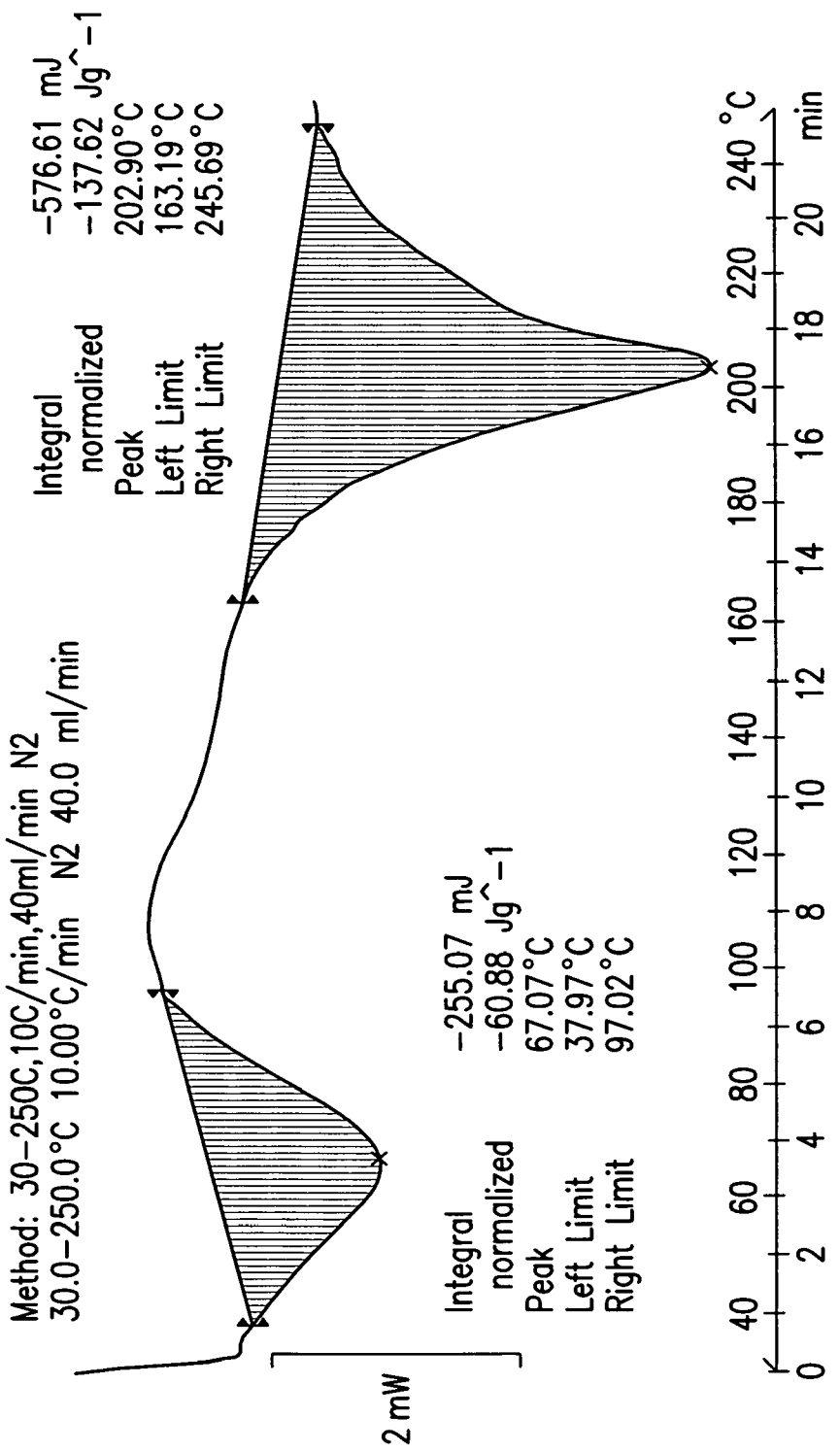
Method: 30-250C,10C/min,40ml/min N2
30.0-250.0°C 10.00°C/min N2 40.0 ml/min
Integral -576.61 mJ
normalized -137.62 Jg^-1
Peak 202.90°C
Left Limit 163.19°C
Right Limit 245.69°C
Integral -255.07 mJ
normalized -60.88 Jg^-1
Peak 67.07°C
Left Limit 37.97°C
Right Limit 97.02°C
2 mW
0 2 4 6 8 10 12 14 16 18 20 min
40 60 80 100 120 140 160 180 200 220 240 °C

FIG.9

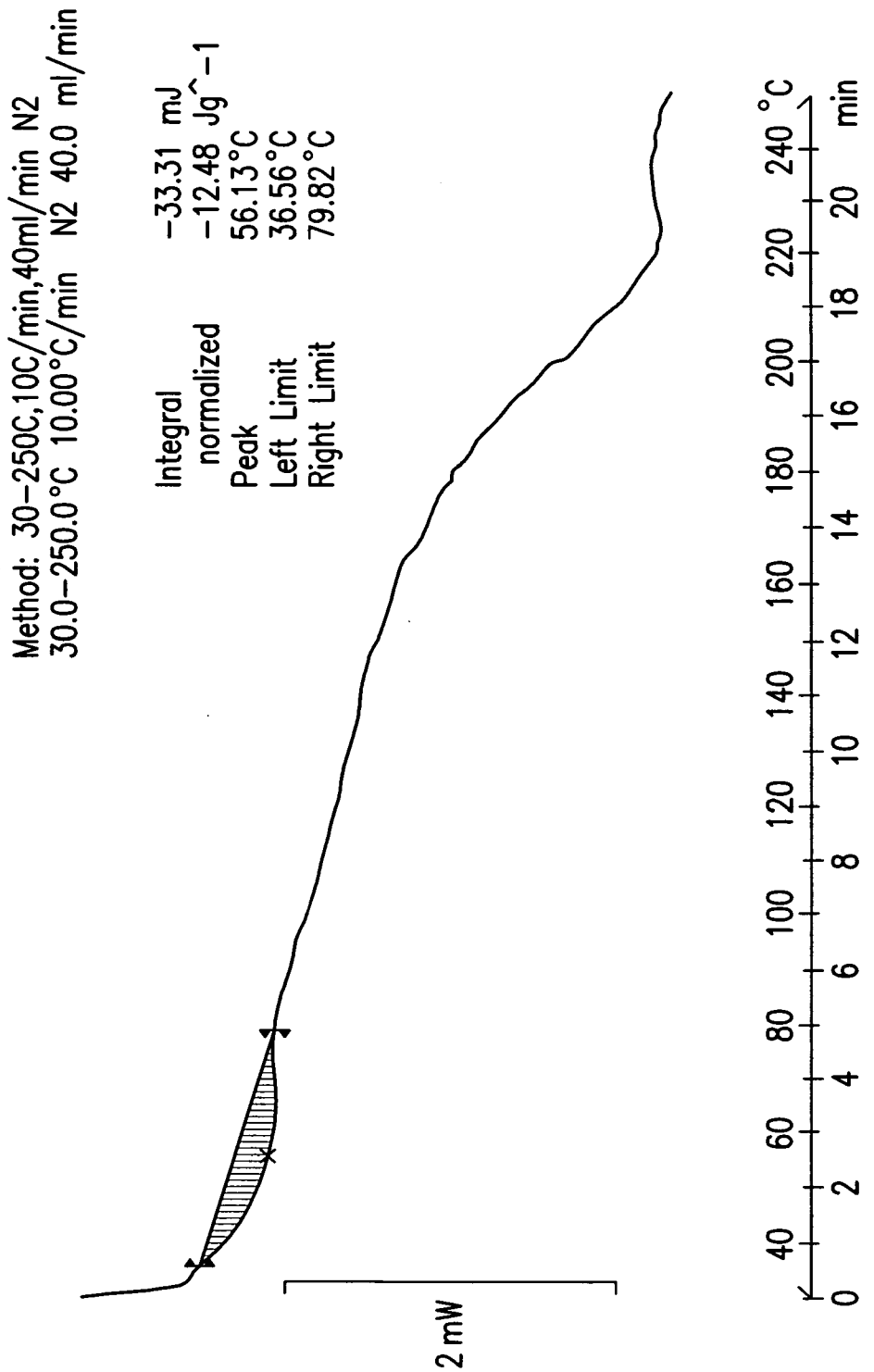
Method: 30-250C,10C/min,40ml/min N2
30.0-250.0°C 10.00°C/min N2 40.0 ml/min
Integral -33.31 mJ
normalized -12.48 Jg^-1
Peak 56.13°C
Left Limit 36.56°C
Right Limit 79.82°C
2 mW
°C
min
0 2 4 6 8 10 12 14 16 18 20
40 60 80 100 120 140 160 180 200 220 240

FIG.1O

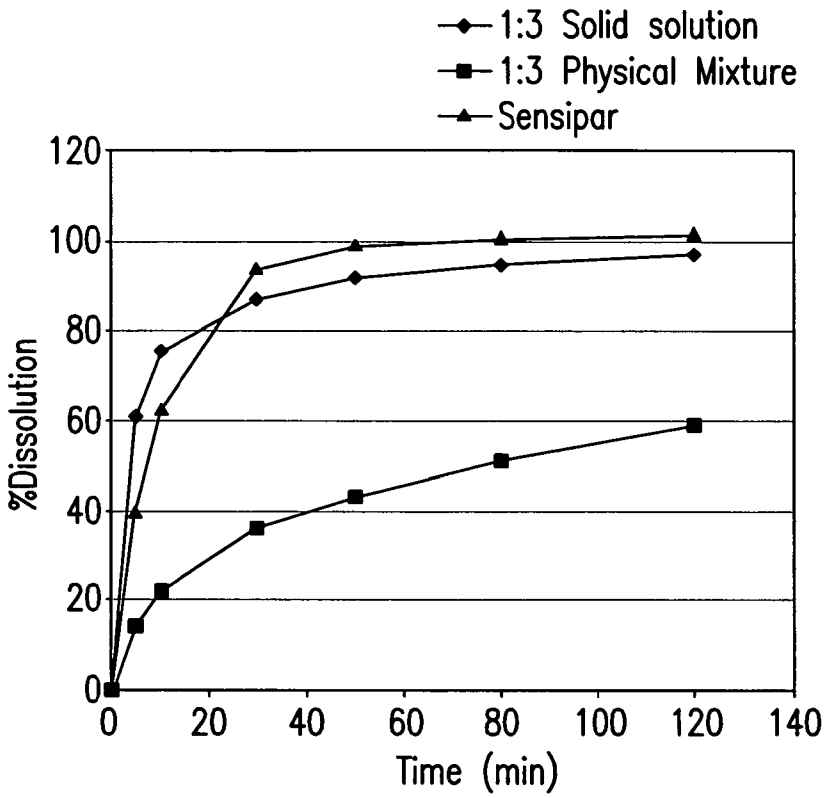
1:3 Solid solution
1:3 Physical Mixture
Sensipar
%Dissolution
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min)

FIG.11

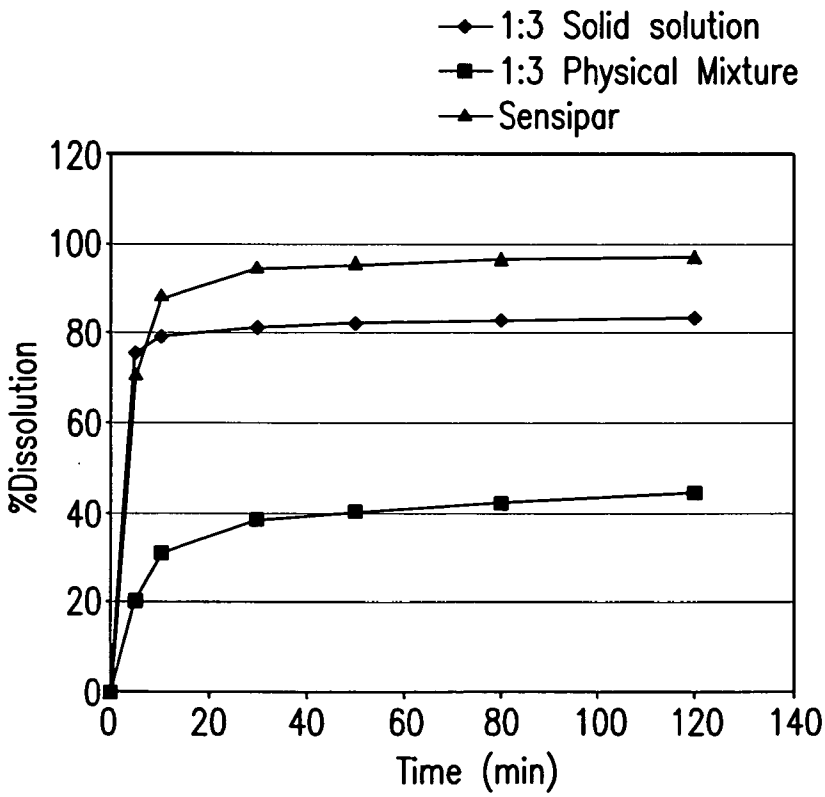
1:3 Solid solution
1:3 Physical Mixture
Sensipar
%Dissolution
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min)

FIG.12

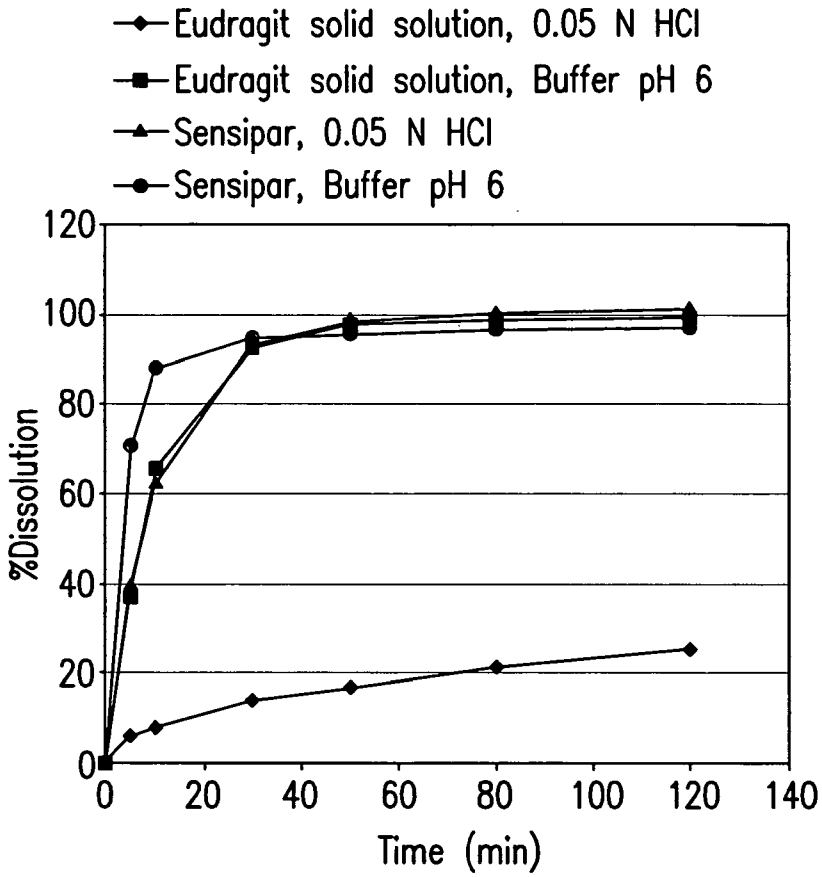
Eudragit solid solution, 0.05 N HCl
Eudragit solid solution, Buffer pH 6
Sensipar, 0.05 N HCl
Sensipar, Buffer pH 6
%Dissolution
Time (min)
0
20
40
60
80
100
120
140

FIG.13

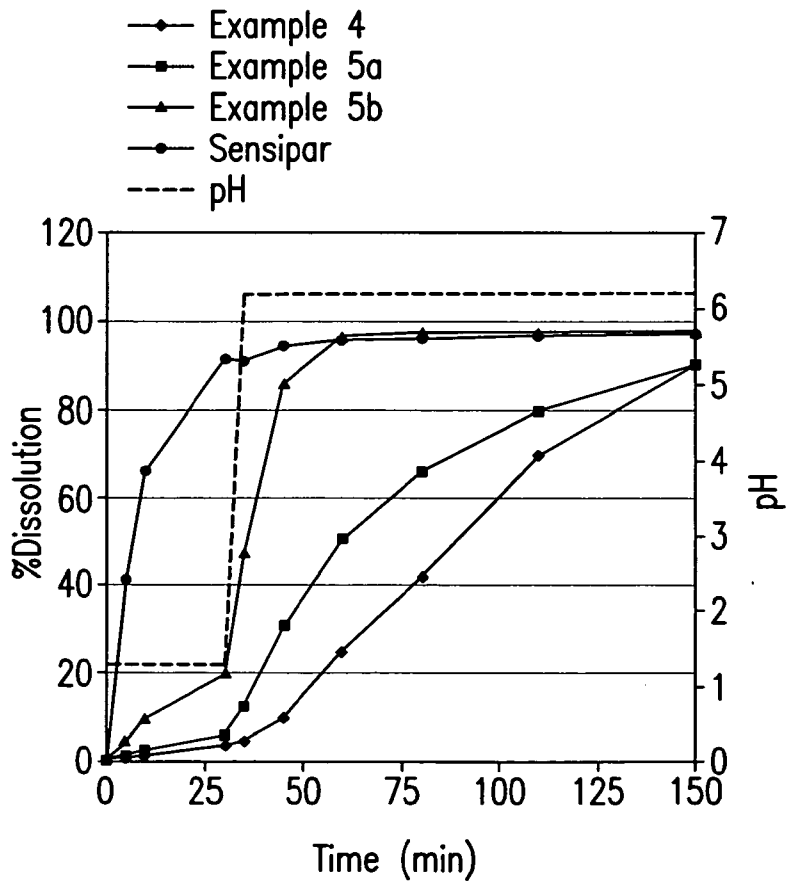
Example 4
Example 5a
Example 5b
Sensipar
pH
%Dissolution
pH
Time (min)
0
25
50
75
100
125
150

FIG.14