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(54) Title: MODIFIED-RELEASE FORMULATIONS OF CALCIUM RECEPTOR-ACTIVE COMPOUNDS

(57) Abstract: Modified-release pharmaceutical formulations comprising calcium receptor-active compounds, processes for preparing such formulations, and their methods of use. In an embodiment, the present invention relates to modified-release pharmaceutical formulations comprising cinacalcet or a pharmaceutically acceptable salt thereof.

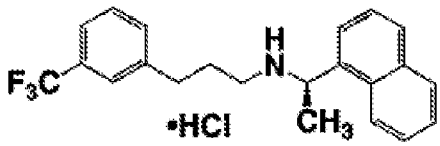
MODIFIED-RELEASE FORMULATIONS OF CALCIUM RECEPTOR-ACTIVE COMPOUNDS

INTRODUCTION TO THE INVENTION

The present invention relates to modified-release pharmaceutical formulations comprising calcium receptor-active compounds, processes for preparing such formulations, and their methods of use. More particularly, the present invention relates to modified-release pharmaceutical formulations comprising cinacalcet or its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, polymorphs or mixtures thereof for oral administration.

Calcium receptor-active compounds, especially calcimimetic agents, are small organic molecules that act as allosteric activators of calcium sensing receptors. At the parathyroid cell, they lower the threshold of receptor activation by extra-cellular calcium ions and diminish parathyroid hormone secretion. Cinacalcet is one of the first calcimimetic agents in its class to have reached the marketplace successfully.

Cinacalcet, a highly lipophilic moiety, is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extra-cellular calcium. Cinacalcet HCl has a chemical name N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-trifluoromethyl)phenyl]-1-aminopropane hydrochloride and has structural Formula I. It has a molecular weight of 357.4 g/mol (free base) and 393.9 g/mol (hydrochloride salt).



Formula I

Cinacalcet HCl is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water. Cinacalcet is commercially available as SENSIPAR™ tablets (Amgen Inc. USA) and as MIMPARA™ in Europe for oral administration in strengths of 30 mg, 60 mg, and 90 mg of cinacalcet HCl as the free base equivalent (33 mg, 66 mg, and 99 mg as the HCL salt, respectively). SENSIPAR™ tablets are indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on

dialysis, and for the treatment of hypercalcemia in patients with parathyroid carcinoma.

U.S. Patent Nos. 6,011,068; 6,031,003; 6,211,244 and 6,313,146 disclose calcium receptor-active compounds including cinacalcet and its salts.

U.S. Patent Application Publication No. 2005/0147669 describes a rapid dissolution formulation of a calcium receptor-active compound.

U.S. Patent Application Publication Nos. 2007/0054963 and 2007/0185211 relate to compositions comprising different forms of cinacalcet.

According to the labeling of SENSIPAR™ tablets, the approved dosing regimen for cinacalcet is 30 mg once daily for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, and 30/60/90 mg twice-daily or thrice-daily for the treatment of hypercalcemia in patients with parathyroid carcinoma. SENSIPAR™ has also been reported to show high incidences of adverse events, viz. nausea (31 %) and vomiting (27 %), against placebo (19 % and 15 %, respectively). Further, SENSIPAR™ should to be taken with food or shortly after a meal. Often the adverse events like nausea and vomiting are related to high local concentrations (and rapid absorption) resulting from rapid release of cinacalcet from SENSIPAR™ tablets. The prevalence of these adverse events is further complicated when SENSIPAR™ is administered under fed conditions, thus aggravating the intolerance and likely to reduce the patient compliance further.

The modified-release pharmaceutical formulations of the present invention release the contained cinacalcet or salts thereof at a slower rate and over a prolonged period of time as compared to SENSIPAR™. The modified-release pharmaceutical formulations of the present invention reduce the fluctuation of plasma cinacalcet levels arising from twice- or thrice-daily oral administration. It is also believed that a modified release of cinacalcet from the formulation will reduce the high local concentration generated in the gastro-intestinal tract ("GIT"), unlike a rapidly dissolving formulation. Thus, by manipulating the release of cinacalcet or a salt thereof from the modified-release formulation, and without being bound by any particular theory, it is believed that the adverse events like nausea and vomiting can be avoided, or at least minimized significantly, after oral administration, and this would lead to enhanced patient compliance.

This and other such needs are addressed by the present invention.

SUMMARY OF THE INVENTION

The present invention relates to modified-release pharmaceutical formulations comprising calcium receptor-active compound, processes for preparing such formulations, and their methods of use. More particularly, the present invention relates to modified-release pharmaceutical formulations comprising cinacalcet or its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, polymorphs or mixtures thereof for oral administration.

An aspect of the present invention provides a modified-release pharmaceutical formulation comprising therapeutically effective amount of cinacalcet or a salt thereof, and a pharmaceutically acceptable release-controlling polymer, wherein the modified-release pharmaceutical formulation releases the contained cinacalcet or a salt thereof over a prolonged period of time.

In an embodiment, the modified-release formulation of the present invention releases about 90 % of the contained cinacalcet or a salt thereof into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a United States Pharmacopeia ("USP") apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 revolutions per minute ("r.p.m."), within about 1 hour to about 20 hours from the start of the test.

Another aspect of the present invention provides a modified-release pharmaceutical formulation comprising therapeutically effective amount of cinacalcet or a salt thereof, and a pharmaceutically acceptable release-controlling polymer, wherein the formulation releases about 5 % to about 70 % of the contained cinacalcet or salt into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., within about 30 minutes from the start of the test.

In an embodiment, the modified-release pharmaceutical formulation of the present invention releases about 10 % to about 45 % of the contained cinacalcet or salt thereof into 0.05 N hydrochloric acid within about 30 minutes from the start of the test, measured using the above-described set of experimental conditions.

The modified-release pharmaceutical formulations of the present inventions, in some embodiments, exhibit C_{max} and AUC values comparable with those exhibited by the currently marketed cinacalcet formulation when orally administered to humans at the same doses under the same conditions.

In certain embodiments, the modified-release pharmaceutical formulations of the present invention contain about 30 mg to about 300 mg, or about 60 mg to about 270 mg, of cinacalcet or a salt thereof.

In some embodiments of the present invention, a release-controlling polymer comprises about 1 % to about 90 % by weight of the total weight of a modified-release formulation.

The present invention also relates to methods of reducing adverse events associated with calcimimetic therapy in subjects in need thereof, wherein a method comprises orally administering such subjects a modified-release pharmaceutical formulation comprising a therapeutically effective amount of cinacalcet or a salt thereof and a pharmaceutically acceptable release-controlling polymer.

A further aspect of the present invention provides enhanced-solubility forms of cinacalcet or a salt thereof, and pharmaceutical formulations thereof.

In another aspect, the invention provides enhanced-solubility forms of cinacalcet or a salt thereof that can be obtained by techniques including complexation, solid dispersion, co-precipitate formation, premix formation and the like. In another embodiment, the pharmaceutical formulations comprising cinacalcet or a salt thereof further contain pharmaceutically acceptable excipients including at least one of an emulsifier, surfactant, wetting agent, solubilizer, complexing agent, and crystallization inhibitor, to provide improved wetting and solubility parameters.

A still further aspect of the present invention provides pharmaceutical formulations comprising therapeutically effective amounts of a cinacalcet or a salt thereof, wherein the mean particle size of cinacalcet or salt is in the range of about 50 µm to about 500 µm.

In certain embodiments, the pharmaceutical formulations of the present invention comprising a therapeutically effective amount of cinacalcet or a salt thereof exhibit desired *in vivo* pharmacokinetic parameters, when administered orally to humans at safe doses. Such *in vivo* pharmacokinetic parameters are comparable to those exhibited by the commercially available rapid-dissolving formulation when orally administered to humans at similar doses. In certain embodiments, the pharmaceutical formulations of the present invention

comprising therapeutically effective amount of a cinacalcet or a salt thereof also exhibit improved bioavailability when orally administered to human.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to modified-release pharmaceutical formulations comprising calcium receptor-active compound, processes for preparing such formulations, and their methods of use. More particularly, the present invention relates to modified-release pharmaceutical formulations comprising cinacalcet or its pharmaceutically acceptable salts, solvates, hydrates, enantiomers, polymorphs or mixtures thereof for oral administration.

The terms “active” or “active agent” or “active substance” or “active ingredient” have been used synonymously with calcium receptor-active compound such as cinacalcet or a salt thereof, solvates, hydrates, enantiomers, polymorphs or mixtures thereof, in the foregoing description.

An aspect of the present invention provides modified-release pharmaceutical formulations comprising a therapeutically effective amount of cinacalcet or a salt thereof, and a pharmaceutically acceptable release-controlling polymer, wherein the modified-release pharmaceutical formulations release the contained cinacalcet or a salt thereof over a prolonged period of time.

The term “modified-release” in the context of present invention refers to a drug release rate, which is different than the drug release rate exhibited by formulations such as the commercially marketed rapid-dissolving formulation SENSIPAR™, when measured under identical conditions at the same doses of contained cinacalcet or a salt thereof. Such formulations do not contain a polymer that affects the rate and/or timing of drug solubility when a dosage unit is exposed to aqueous fluids. The term “modified-release” may be construed synonymously as “sustained release” or “slow release” or “extended release’ or “delayed release” or “controlled release” or “programmed release” or “pulsed release,” as is known to a skilled person.

In an embodiment, the modified-release formulation of the present invention releases about 90 % of the contained cinacalcet or a salt thereof into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., within about 1 hour to about 20 hours from the start of the test.

In another embodiments, the modified-release pharmaceutical formulation of the present invention releases contained cinacalcet or a salt thereof over prolong period of time, typically about 90 % of the contained active being released in a period of more than about 30 minutes, e.g., about 1 hour, or about 2 hours, or about 4 hours, or about 8 hours, or about 12 hours, or about 16 hours, or about 20 hours, or about 24 hours.

SENSIPAR™ tablets release more than about 90 % of the contained cinacalcet or a salt thereof into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., within about 30 minutes from the start of the test. Unlike SENSIPAR™, the modified-release pharmaceutical formulations of the present invention release about 5 % to about 70 %, or about 10 % to about 45 %, of the contained cinacalcet or a salt thereof within about 30 minutes from the start of the test under the experimental conditions described above.

In certain embodiments, the modified-release pharmaceutical formulations of the present invention comprising a cinacalcet or a salt thereof release about 10 %, or about 20 %, or about 30 %, or about 40 %, or about 45 %, of the contained cinacalcet or a salt thereof into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m., within about 30 minutes from the start of the test.

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, a therapeutically effective amount of cinacalcet or its pharmaceutically acceptable salts in the pharmaceutical formulations is about 15 mg, about 30 mg, about 45 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 240 mg, about 270 mg, or about 360 mg, equivalent to cinacalcet base. In certain embodiments, modified-release pharmaceutical formulations of the present invention contain about 30 mg to about 300 mg, or about 60 mg to about 270 mg, of cinacalcet equivalent.

In embodiments, the modified-release pharmaceutical formulations of the present invention release the contained cinacalcet or a salt thereof in an extended

release manner or a delayed release manner, or combination of delayed and extended release manners.

In the context of the present invention, the desired *in vitro* drug release of cinacalcet or a salt thereof contained in the pharmaceutical formulation can be achieved by various means, such as but not limited to, use of surfactants/solubilizers, complexing agents, altering the hardness of the granules/tablet, use of suitable binders in required concentrations, use of hydrophobic and/or hydrophilic pharmaceutical excipients, altering the particle size and/or polymorphic form of the cinacalcet or a salt thereof, use of pharmaceutically acceptable coating excipients, and the like, or combinations thereof.

Surprisingly, it has been observed that the solubility of cinacalcet base and salts such as its hydrochloride (HCl) salt can be significantly improved by use of certain surfactants/solubilizers including a polysorbate and a poloxamer, and complexing agents including beta-cyclodextrin. These surfactants/solubilizers and complexing agents can be used in admixture with the cinacalcet or a salt thereof or as separate entities (such as layer or coating) in the pharmaceutical formulations to achieve the desired *in vitro* dissolution and *in vivo* absorption profiles in the context of present invention.

A still further aspect of the present invention provides for an enhanced-solubility form of cinacalcet or a salt thereof, and pharmaceutical formulations thereof.

The “enhanced-solubility form” as used herein refers to a form of cinacalcet or a salt thereof that exhibits enhanced or improved solubility as compared to the known form(s) of the same at given conditions.

In another embodiment, the invention provides an enhanced-solubility form of cinacalcet or a salt thereof that can be obtained by techniques comprising complexation, solid dispersion, co-precipitate formation, premix formation, and the like. In an embodiment, the pharmaceutical formulations comprising cinacalcet or a salt thereof further contain pharmaceutically acceptable excipients including emulsifiers, surfactants, wetting agents, solubilizers, complexing agents, crystallization inhibitors to provide improved wetting and solubility parameters. The coprecipitates, solid dispersions and inclusion complexes can further be adsorbed on suitable substrates to improve solubility. Typically, weight ratios of

cinacalcet base or its salt to surfactant/solubilizer or complexing agent ranges between about 1:0.1 to about 1:3, or about 1:0.5 to about 1:2.

Coprecipitates and solid dispersions are prepared by various techniques like melt-fusion, spray freezing, spray congealing, melt extrusion, supercritical fluid precipitation, or dissolving the active and one or more excipients in a solvent and removing the solvent by known techniques like spray drying, lyophilization, agitated thin film drying, or vacuum drying. Solvents that are useful in the process include water, methanol, ethanol, propanol, isopropanol, butanol, isobutanol, higher alcohols, benzene, toluene, acetone, chloroform, carbon tetrachloride, dichloromethane or combinations thereof.

Co-precipitates or solid dispersions of cinacalcet or its pharmaceutically acceptable salts can be made using hydrophilic or hydrophobic carriers or both. The most commonly used carriers include but are not limited to polyvinylpyrrolidone, polyethylene glycols, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, polyvinyl alcohol, mannitol, dextran, lectins, carbopols, maltodextrins, lactose, fructose, polysaccharides, inositol, trehalose, maltose, raffinose, and lipids such as polyglycolized glycerides (Gelucire®) and their combinations in different ratios. Other hydrophilic or hydrophobic materials acceptable for the preparation of solid dispersions are well within the scope of this invention without limitation as long as these materials improve the solubility properties of the active.

Cyclodextrins that may be used in the present invention for forming inclusion complexes include but are not limited to natural cyclodextrins and their derivatives, including the alkylated and hydroxyalkylated derivatives and the branched cyclodextrins. Examples of useful cyclodextrins are hydroxypropyl beta-cyclodextrin, hydroxyethyl beta-cyclodextrin, hydroxypropyl gamma-cyclodextrin, hydroxyethyl gamma-cyclodextrin, dihydroxypropyl beta-cyclodextrin, glucosyl beta-cyclodextrin, diglucosyl beta-cyclodextrin, maltosyl beta-cyclodextrin, maltosyl gamma-cyclodextrin, maltotriosyl beta-cyclodextrin, maltotriosyl gamma-cyclodextrin and dimaltosyl beta-cyclodextrin, and mixtures thereof such as maltosyl beta-cyclodextrin/dimaltosyl beta-cyclodextrin. Inclusion complexes can be prepared using various techniques including solvent evaporation, dry mixing, co-milling, granulation, homogenization, and the like.

As used herein, the term "mean particle size" refers to the distribution of particles wherein about 50 volume percent of all particles measured have particle sizes less than the defined mean particle size value, and about 50 volume percent of all measurable particles measured have particle sizes greater than the defined mean particle size value; this can be identified by the term "D_{50}." Similarly, a particle size distribution where 90 volume percent of the particles have sizes less than a specified size is referred to as "D_{90}" and a distribution where 10 volume percent of particles have sizes less than a specified size is referred to as "D_{10}." The desired particle size range material is obtained directly from a synthesis process or any known particle size reduction processes can be used, such as but not limited to sifting, milling, micronization, fluid energy milling, ball milling, and the like. Methods for determining D_{10}, D_{50} and D_{90} include laser diffraction, such as using Malvern Instruments Ltd. (Malvern, Worcestershire, United Kingdom) equipment. Other techniques like sieve analysis can also be used to demonstrate the particle size distribution of the active or granules thereof, as known to a skilled person.

A still further aspect of the present invention provides for a pharmaceutical formulation comprising therapeutically effective amount of a cinacalcet or a salt thereof, wherein the mean particle size (D_{50}) of cinacalcet or a salt thereof is in the range of about 50 µm to about 500 µm, or about 50 µm to about 350 µm, or about 50 µm to about 200 µm. Cinacalcet or a salt thereof having D_{50} in the range of about 50 µm to about 150 µm has been found to be particularly useful in the present invention. Such particles of cinacalcet or its salt exhibit required micromeritic properties such as but not limited to bulk density, tapped density, angle of repose, Carr index, compressibility ratio, and the like.

Bulk density as used herein is defined as the ratio of apparent volume to mass of the material taken, called untapped bulk density, and also the ratio of tapped volume to mass of material taken, called tapped bulk density. A useful procedure for measuring these bulk densities is described in *United States Pharmacopeia 24*, Test 616 "Bulk Density and Tapped Density," United States Pharmacopeial Convention, Inc., Rockville, Maryland, 1999.

Carr index as used herein is defined as the percent compressibility, which is a percentage ratio of the difference between tapped bulk density and initial bulk density, divided by tapped bulk density and expressed as a percentage. Carr

index values between 5-15% represent materials with excellent flowability, values between 18-21% represent fair flowability and values above 40% represent very poor flowability.

Hausner ratio used herein is defined as the ratio of tapped to untapped bulk densities. A Hausner ratio less than about 1.2 indicates good flow properties, while a ratio greater than about 1.5 indicates poor flow properties.

Therapeutically effective amounts of cinacalcet or a salt thereof can be provided in the form of pharmaceutical formulations as a single dose, in multiple doses, or as a partial dose in the form of tablets, capsules, granules (synonymously, “beads” or “particles” or “pellets”), suspensions, emulsions, powders, dry syrups, and the like.

The granules of the present invention comprising cinacalcet or a salt thereof have mean particle sizes (D_{50}) in the range of about 50 µm to about 900 µm, or in the range of about 150 µm to about 500 µm, and exhibit required micromeritic properties such as but not limited to bulk density, tapped density, angle of repose Carr index, compressibility ratio, and the like as described above.

The granules can be formed by any known processes, using operations such as one or more of dry granulation, wet granulation, extrusion-spheronization, and the like. In an embodiment, the granulation of cinacalcet or a salt thereof, optionally with pharmaceutically acceptable excipients like diluents or fillers, is carried out in equipment such as a planetary mixer, rapid mixer granulator (RMG), fluid bed processor and the like. A fluid bed processor with top spray attachment has been found to be particularly useful. In general granulation can be carried out by dissolving or dispersing the active ingredient in an organic solvent, optionally with a binder and/or solubilizer, and spraying the solution onto a substrate comprising pharmaceutically acceptable excipients. The granules obtained may further be compressed into tablets or filled in the capsules using techniques known in the art. Alternatively, tablets can be prepared by a direct compression technique, using powder blends.

The modified-release pharmaceutical formulations of the present invention may be matrix-type or reservoir-type delivery systems (e.g. osmotic pumps, and the like), which can be further coated to achieve a desired *in vitro* drug dissolution. Such matrix-type or reservoir-type pharmaceutical formulations comprise cinacalcet or a salt thereof, release controlling polymer, and pharmaceutically

acceptable excipients. The release controlling polymers can be, for example, in the form of a matrix or a coating. Formulations comprising cinacalcet or a salt thereof in modified-release form may be, for example, a particle of the active agent that is combined with a release-controlling polymer. The release controlling polymers is a material that permits release of the active agent at a sustained rate in an aqueous medium. The release controlling polymers can be selectively chosen so as to achieve, in combination with the other stated properties, a desired *in vitro* release rate.

A release-controlling polymer, in the context of the present invention, includes hydrophilic polymers, hydrophobic polymers, delayed release (enteric) polymers, bioadhesive (or mucoadhesive) polymers, hydrophobic substances like waxes and fats, and combinations thereof. The content of release-controlling polymer in the formulations of the present invention may vary from about 1 % to about 90 %, or from about 5 % to about 80 %, by weight, of the total weight of the formulation.

Useful hydrophilic polymers of various grades include, but are not limited to: cellulose derivatives such as carboxymethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), cross-linked sodium carboxymethyl cellulose, and cross-linked hydroxypropyl cellulose; carboxymethylamide; potassium methacrylate/divinylbenzene copolymers; polyhydroxyalkyl methacrylates; polyvinylpyrrolidones and cross-linked polyvinylpyrrolidones; high molecular weight polyvinylalcohols; gums such as natural gum, guar, agar, agrose, sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheums, gum arabic, gum ghatti, gum karaya, gum tragacanth and locust bean gum; hydrophilic colloids such as alginates, carbopol and polyacrylamides; other substances such as arbinoglactan, pectin, amylopectin, gelatin, N-vinyl lactams, polysaccharides; and the like. Combinations of any two or more of these polymers, and other polymers having the required properties are within the scope of the invention.

Useful hydrophobic polymers or combinations thereof used in various ratios include, but are not limited to, celluloses such as methyl cellulose, ethyl cellulose, cellulose acetates and their derivatives, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di-

and tri-cellulose alkanylates, mono-, di-, and tri-cellulose arylates, and mono-, di- and tri-cellulose alkenylates, crosslinked vinylpyrrolidone polymers (crospovidone), polymethacrylic acid based polymers and copolymers sold as EUDRAGIT™ (including Eudragit RL and RS, and NE-30D), zein, and aliphatic polyesters. Other classes of polymers, copolymers of these polymers or their mixtures in various ratios and proportions as required are within the scope of this invention without limitation.

An enteric coating is a coating that prevents release of the active agent until the dosage form reaches a pH environment higher than that of the stomach. A delayed release dosage form comprises active agent and is coated with an enteric polymer. The enteric polymer should be non-toxic and is predominantly soluble in the intestinal fluid, but substantially insoluble in the gastric juices. Examples of such delayed release (enteric) polymers include polyvinylacetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), methacrylic acid copolymers, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, hydroxypropyl methylcellulose hexahydrophthalate, hydroxypropyl methylcellulose phthalate (HPMCP), cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate trimellitate, cellulose acetate butyrate, cellulose acetate propionate, methacrylic acid/methacrylate polymer (acid number 300 to 330 and also known as EUDRAGIT® L), which is an anionic copolymer based on methacrylate and available as a powder (also known as methacrylic acid copolymer, type A NF, methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl methacrylate copolymer, and the like), and combinations comprising one or more of the foregoing enteric polymers. Other examples include natural resins, such as shellac, copal collophorium, and combinations comprising one or more of the foregoing polymers. Yet other examples of enteric polymers include synthetic resin bearing carboxyl groups. The methacrylic acid:acrylic acid ethyl ester 1:1 copolymer solid substance of the acrylic dispersion sold under the trade designation "EUDRAGIT L-100-55™" is suitable.

A bioadhesive polymer may be included in oral dosage forms to increase the contact time between the dosage form and the mucosa of the most efficiently absorbing section of the gastrointestinal tract. Non-limiting examples of known

bioadhesives include carbopol (various grades), sodium carboxymethyl cellulose, methyl cellulose, polycarbophil (NOVEON™), hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium alginate, sodium hyaluronate, and combinations comprising two or more of the foregoing.

The hydrophobic substances like waxes and fats may have a melting point of about 30 °C to about 200 °C, or about 45 °C to about 90 °C. The hydrophobic substances can include neutral or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol, hydrophobic and hydrophilic materials having hydrocarbon backbones, and combinations comprising one or more of the foregoing materials. Suitable waxes include beeswax, Glycowax™ synthetic waxes, commercially available in different grades including S-932 and 765, castor wax, carnauba wax and wax-like substances, e.g., materials normally solid at room temperature and having a melting point of about 30 °C to about 100 °C, and combinations comprising one or more of the foregoing waxes.

Of course, any other release-controlling polymers, which demonstrate similar characteristics, are also acceptable in the working of this invention.

In some embodiments of the present invention, pharmaceutically acceptable excipients serving as inert cores comprise: insoluble inert materials, such as glass particles/beads or silicon dioxide, calcium phosphate dihydrate, dicalcium phosphate, calcium sulfate dihydrate, microcrystalline cellulose (MCC) or cellulose derivatives; or soluble cores such as acid cores like tartaric acid and sugar spheres of sugars like dextrose, lactose, anhydrous lactose, spray-dried lactose, lactose monohydrate, mannitol, starches, sorbitol, sucrose; insoluble inert plastic materials such as spherical or nearly spherical core beads of polyvinyl chloride, polystyrene, or any other pharmaceutically acceptable insoluble synthetic polymeric material; and the like and mixtures thereof.

The modified-release formulations comprising cinacalcet or a salt thereof and a release-controlling polymer may be prepared by any suitable technique including those described in detail below. The active agent and a release-controlling polymer may, for example, be prepared by wet granulation techniques, melt extrusion techniques, etc. The active agent in modified-release formulations

can include a plurality of substrates comprising the active ingredient, which substrates are coated with a sustained-release coating comprising a release-controlling polymer. The modified-release formulations may thus be made in conjunction with a multiparticulate system, such as beads, ion-exchange resin beads, spheroids, micro-spheres, seeds, pellets, granules, and other multiparticulate systems in order to obtain a desired modified release of the active agent. The multiparticulate system can be presented in a tablet or capsule or other suitable unit dosage form. In certain cases, more than one multiparticulate system can be used, each exhibiting different characteristics, such as pH dependence of release, time for release in various media (e.g., acid, base, simulated intestinal fluid), release *in vivo*, size, and formulation.

In some cases, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose and hydrous lactose impalpable are examples of such agents. Additionally (or alternatively), the spheroids can contain a water insoluble polymer, preferably an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In this formulation, the release-modifying coating will generally include a water insoluble material such as a wax, either alone or in admixture with a fatty alcohol, or shellac or zein. Spheroids or beads, coated with an active ingredient can be prepared, for example, by dissolving or dispersing the active ingredient in a solvent and then spraying the solution onto a substrate, for example, sugar spheres NF-21, 18/20 mesh, using a Wurster insert. Optionally, additional ingredients are also added prior to coating the beads in order to enhance the active ingredient binding to the substrates, and/or to color the resulting beads, etc. The resulting substrate-active material may optionally be over-coated with a barrier material, to separate the therapeutically active agent from the next coating of material, e.g., a release-controlling polymer.

The pharmaceutical formulations of the present invention can be prepared by various other methods and techniques as known to the skilled person so as to achieve desired *in vitro* drug release profile. Specific embodiments of processes comprise any of:

1. Direct compression, using appropriate punches and dies; the punches and dies being fitted to a suitable rotary tableting press.

2. Injection or compression molding using suitable molds fitted to a compression unit.

3. Granulation followed by compression.

4. Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes this is important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when compression pressure is relieved. Typically lubricants are added in a concentration of from 0.25% to 3% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

Oral dosage forms may be prepared to include an effective amount of melt-extruded subunits in the form of multiparticles within a capsule. For example, a plurality of the melt-extruded muliparticulates can be placed in a gelatin capsule in an amount sufficient to provide an effective release dose when ingested and contacted by gastric fluid. The subunits, e.g., in the form of multiparticulates, can be compressed into oral tablets using conventional tableting equipment using standard techniques.

The compositions may be in the form of micro-tablets enclosed inside a capsule, e.g. a gelatin capsule. For this, any gelatin capsule employed in the pharmaceutical formulation field can be used, such as the hard gelatin capsules known as CAPSUGEL™, available from Pfizer.

In an embodiment, pharmaceutical formulations of the present invention can be prepared using a granulation process comprising:

a) dissolving or dispersing the active ingredient optionally with binder and/or solubilizer in a solvent,

b) granulating the pharmaceutically acceptable excipient blend with the solution comprising active,

c) drying and lubricating the granules, and

d) compressing the granules into tablets, or alternatively filling into capsules.

In another embodiment, pharmaceutical formulations of the present invention can be prepared using a direct compression process comprising:

a) mixing the active ingredient and a release-controlling polymer, optionally with other pharmaceutically acceptable excipients, and

b) compressing the blend of a) into tablets, or alternatively filling into capsules.

Alternatively, the formulations of the present invention can be prepared by dissolving the active ingredient in a suitable solvent, and layering the dissolved active, optionally with other excipients, onto the surface of inert cores such as tartaric acid and the like as described above. Such drug-layered cores or pellets may further be granulated or coated with a release-controlling polymer to produce pharmaceutical formulations of the present invention.

The granules/beads or tablets or capsules may further be coated with a release-controlling polymer, optionally with other excipients. Such coating can be done using various known techniques such as dip coating, pan coating, fluidized bed coating, and the like.

The residual solvent content of cinacalcet or a salt thereof and its pharmaceutical formulations, as mentioned herein, may be less than about 5000 ppm. The concentration of residual solvent(s) can further be reduced to such limits as acceptable by the regulatory agencies, such as using drying steps.

Surfactants/solubilizers that may be useful in the formulations of the present invention include but are not limited to: anionic surfactants like potassium laurate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl choline, phosphatidyl glycerol, phosphatidyl inosine, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, cholic acid and other bile acids (for example, cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid and glycodeoxycholic acid) and salts thereof (for example, sodium deoxycholate); cationic surfactants like quaternary ammonium compounds (for example, benzalkonium chloride, cetyltrimethylammonium bromide, lauryldimethylbenzylammonium chloride, acyl carnitine hydrochlorides and alkyl pyridinium halides); nonionic surfactants like polyoxyethylene fatty alcohol ethers (MACROGOL™ and BRIJ™), polyoxyethylene sorbitan fatty acid esters (polysorbate or TWEEN™), polyoxyethylene fatty acid esters (MYRJ™), sorbitan esters (SPAN™), glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether

alcohols, polyoxyethylene-polyoxypropylene copolymers (poloxamer), polaxamines, and the like; and mixtures thereof.

In context of the present invention, during the processing of the pharmaceutical formulations into finished dosage forms, one or more pharmaceutically acceptable excipients may optionally be used, including but not limited to: diluents such as microcrystalline cellulose ("MCC"), silicified MCC (e.g., PROSOLV™), microfine cellulose, lactose, starch, pregelatinized starch, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, calcium carbonate, calcium sulfate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide and the like; cores/beads such as insoluble inert materials like glass particles/beads or silicon dioxide, calcium phosphate dihydrate, dicalcium phosphate, calcium sulfate dihydrate, microcrystalline cellulose, cellulose derivatives; soluble cores such as sugar spheres of sugars like dextrose, lactose, mannitol, starches, sorbitol, or sucrose; insoluble inert plastic materials such as spherical or nearly spherical core beads of polyvinyl chloride, polystyrene or any other pharmaceutically acceptable insoluble synthetic polymeric material, and the like or mixtures thereof; binders or adherents such as acacia, guar gum, alginic acid, dextrin, maltodextrin, methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g., KLUCEL®), hydroxypropyl methylcellulose (e.g., METHOCEL®), carboxymethyl cellulose sodium, povidone (various grades of KOLLIDON®, PLASDONE®), starch and the like; disintegrants such as carboxymethyl cellulose sodium (e.g., Ac-Di-Sol®, PRIMELLOSE®), crospovidone (e.g., KOLLIDON®, POLYPLASDONE®), povidone K-30, polacrilin potassium, starch, pregelatinized starch, sodium starch glycolate (e.g. EXPLOTAB®), and the like; plasticizers such as acetyltributyl citrate, phosphate esters, phthalate esters, amides, mineral oils, fatty acids and esters, glycerin, triacetin or sugars, fatty alcohols, polyethylene glycol, ethers of polyethylene glycol, fatty alcohols such as cetostearyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol, myristyl alcohol and the like. Solvents that may be used in granulation or layering or coating include water, methanol, ethanol, isopropyl alcohol, acetone, methylene chloride, dichloromethane, and the like and mixtures thereof.

Pharmaceutical formulations of the present invention may further include any one or more of pharmaceutically acceptable glidants, lubricants like sodium stearyl fumarate, opacifiers, colorants, and other commonly used excipients.

The *in vitro* pharmacokinetic parameters often used to make comparisons between two or more pharmaceutical formulations upon oral administration include maximum plasma concentration ("C_{max}"), area under the plasma concentration-time plot curve ("AUC"), plasma concentration at steady state (C_{ss}), fluctuation index ("FI"), mean residence time ("MRT"), and the like.

The modified-release pharmaceutical formulations of the present invention comprising therapeutically effective amount of a cinacalcet or a salt thereof can exhibit a reduceds fluctuation in the plasma concentrations of the active. To measure the fluctuation between C_{min} and C_{max}, the plasma levels are measured at the steady state, and the fluctuation index ("FI") is calculated according to following formula:

$$FI = (C_{max}-C_{min}) \div C_{avg}$$

where C_{max} is the maximum plasma concentration, C_{min} is the minimum plasma concentration, and C_{avg} is the average plasma concentration of cinacalcet or a salt thereof, observed within a certain time interval, e.g., 24 hours, at the steady state.

In a further embodiment, the pharmaceutical formulations of the present invention comprising therapeutically effective amounts of cinacalcet or a salt thereof exhibit desired *in vivo* pharmacokinetic parameters, when administered orally to humans at safe doses. Such *in vivo* pharmacokinetic parameters, particularly C_{max} and AUC, are comparable with those exhibited by the marketed cinacalcet formulations (commercially available as SENSIPAR™ or MIMPARA™ tablets) when orally administered to human at the same doses. The term "comparable" refers to the C_{max} and AUC values being within about 80 % to about 125 % of those exhibited by the marketed cinacalcet formulations when orally administered to humans at the same doses under identical conditions.

The present invention also relates to methods of reducing adverse events associated with calcimimetic therapy in subjects in need thereof, wherein a method comprises orally administering to such subjects a modified-release pharmaceutical formulation comprising therapeutically effective amounts of

cinacalcet or a salt thereof, and a pharmaceutically acceptable release-controlling polymer.

Cinacalcet is a low solubility, low permeability drug (Class IV in the Biopharmaceutic Classification System). Rapidly dissolving cinacalcet tablets (SENSIPAR™) exhibit rapid oral absorption with C_{max} reached in about 2 to 6 hours following oral administration. Although the extent of absorption is about 80 %, bioavailability is about 20 % at a fasted condition, and about 30 % at a fed condition in humans. This is likely due to extensive first pass drug metabolism. The modified-release pharmaceutical formulations or the formulations with an enhanced-solubility form of cinacalcet or a salt thereof of the present invention, in certain cases, increase the C_{max} and AUC when administered orally to human subjects.

In certain embodiments, the pharmaceutical formulations of the present invention comprising therapeutically effective amounts of cinacalcet or a salt thereof exhibit improved bioavailability (in terms of C_{max} and AUC) as compared to marketed cinacalcet formulations when orally administered to human at the same doses under identical conditions.

In an embodiment, the C_{ss} values obtained after oral administration of the pharmaceutical formulations of the present invention are comparable to those obtained after oral administration of SENSIPAR™ tablets under similar conditions in human subjects. In certain embodiments, the FI of the modified-release pharmaceutical formulations of the present invention will be less than the FI obtained after oral administration of SENSIPAR™ tablets under similar conditions in human subjects. This helps to reduce the adverse events related to high fluctuation of cinacalcet or its salt in the body, observed with conventional rapidly releasing formulations.

The pharmaceutical formulations of the invention may contain one or more active ingredients in addition to the cinacalcet or a salt thereof. An 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.

The pharmaceutical formulations disclosed herein comprise a therapeutically effective amount of cinacalcet or a pharmaceutically acceptable

salt thereof, and can be used for the treatment of hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, parathyroid carcinoma, hyperphosphonia, hypercalcemia, elevated calcium-phosphorus product and other disease conditions.

The following examples illustrate certain specific aspects and embodiments of the invention and demonstrate the practice and advantages thereof. It is to be understood that the examples are given only for purposes of illustration and are not intended to limit the scope of the invention in any manner.

EXAMPLE 1: Solubility of cinacalcet base and cinacalcet hydrochloride solid dispersions in phosphate buffer having pH 6.8, at 37 °C.

Composition	Solubility (mg/ml)
Cinacalcet base	0.042
Solid dispersion of cinacalcet base with poloxamer 407* (1:1 w/w)	0.187
Solid dispersion of cinacalcet base with polysorbate 80** (1:1 w/w)	0.702
Solid dispersion of cinacalcet base with β-cyclodextrin (1:1 w/w)	0.089
Cinacalcet hydrochloride#	0.088
Solid dispersion of cinacalcet HCl with poloxamer 407 (1:1 w/w)	0.268
Solid dispersion of cinacalcet HCl with polysorbate 80 (1:1 w/w)	1.245
Solid dispersion of cinacalcet HCl with β-cyclodextrin (1:1 w/w)	0.103

*Poloxamer 407 chemically is polyethylene-polypropylene glycol.

**Polysorbate 80 chemically is polyoxyethylene (20) sorbitan monooleate.

Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

Manufacturing process for solid dispersions:

1. Active ingredient (100 mg) and solubilizer or surfactant (100 mg) were dissolved in ethanol (0.8 ml).

2. Mannitol (500 mg) was mixed with the solution prepared in step 1.

3. The mixture was dried in a vacuum tray drier at 60 °C.

The saturation solubility of the compositions as prepared above was determined by mechanically shaking a mixture of 400 mg of a composition and 25 ml of water in a flask at 37 °C for 24 hours. The suspensions were filtered and the filtrate was analyzed by high performance liquid chromatography ("HPLC") to determine the active ingredient content.

EXAMPLES 2-4: Formulations of cinacalcet 30 mg modified-release tablets.

Ingredient	**mg/Batch**		
	Example 2	**Example 3**	**Example 4**
Cinacalcet hydrochloride*	660	660	660
Mannitol	2960	2860	2660
Microcrystalline cellulose (Avicel® PH 101)**	1800	1800	1800
HPMC E 5 cP (Methocel® E 5 LV)#	100	200	400
HPMC E 15 cP (Methocel® E 15 LV)#	300	300	300
Talc	60	60	60
Colloidal silicon dioxide (Aerosil® 200)$	60	60	60
Magnesium stearate	60	60	60
Unit tablet weight	**300**	**300**	**300**

* Quantity equivalent to 600 mg cinacalcet base (30 mg/tablet).

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

** Avicel® is manufactured by FMC Bioploymer Inc.

Methocel® is supplied by Colorcon Inc.

$ Aerosil® is manufactured by Degussa Corp.

Manufacturing process:

1. Cinacalcet HCl was dissolved in 6 ml of ethanol.

2. Mannitol, microcrystalline cellulose and HPMC E (5cP) were mixed together by blending.

3. Blend of step 2 was granulated with solution of step 1.

4. The granules were dried and blended with HPMC E 15 cP.

5. Blend of step 4 was lubricated by mixing with talc, colloidal silicon dioxide, and magnesium stearate for 5 minutes.

6. Lubricated blend of step 5 was compressed into tablets using a 12.8×6.4 mm punch set on a compression machine.

Tablet properties:

Parameter	Example 2	Example 3	Example 4
Hardness, Kiloponds (Kp)	14-16	14-16	14-16
Disintegration time in 0.05 N HCl (minutes)	20	15	15

In vitro release profile of formulations of Examples 2-4 was determined using the conditions:

Media: 0.05 N Hydrochloric acid (900 ml).

Apparatus: USP apparatus II (Paddle) from Test 711 “Dissolution” in *United States Pharmacopeia 29*, United States Pharmacopeial Convention, Inc., Rockville, Maryland, 2005 (“USP”).

Speed: 75 rpm.

Time (minutes)	Cumulative % Drug Dissolved			
	Example 2	Example 3	Example 4	SENSIPAR 30 mg
0	0	0	0	0
10	12	11	7	76.33
30	48	47	28	94.33
60	93	77	74	96.33

EXAMPLES 5-6: Formulations of cinacalcet 30 mg tablets with enhanced solubility.

Ingredient	mg/Batch	
	Example 5	Example 6
Cinacalcet hydrochloride*	660	660
Polysorbate 80	320	-
Poloxamer 407	-	660
Mannitol	2100	2580
Microcrystalline cellulose	2500	1800
Povidone	120	-
Crospovidone	120	120
Talc	60	60
Colloidal silicon dioxide (Aerosil® 200)	60	60
Magnesium stearate	60	60
Tablet weight	**300**	**300**

* Quantity equivalent to 600 mg cinacalcet base (30 mg/tablet).

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

Manufacturing process:

Example 5:

1. Cinacalcet HCl, polysorbate 80 and povidone were dissolved in 6 ml of ethanol.
2. Mannitol and microcrystalline cellulose were mixed together by blending.
3. Blend of step 2 was granulated with solution of step 1.
4. The granules were dried and blended with crospovidone.
5. Blend of step 4 was lubricated using talc, colloidal silicon dioxide and magnesium stearate by mixing for 5 minutes.
6. Lubricated blend of step 5 was compressed into tablets using a 12.8×6.4 mm punch set on a compression machine.

Example 6:

1. Cinacalcet HCl was weighed and dissolved in 6 ml ethanol.

2. Poloxamer 407 was added to the solution from step 1.

3. Dichloromethane (1.5 ml) was added to the ethanol solution to completely dissolve poloxamer 407.

4. Mannitol and microcrystalline cellulose were mixed together by blending.

5. Blend of step 4 was granulated with the solution from step 2.

6. The granules were dried and blended with crospovidone.

7. Blend of step 6 was mixed with talc, colloidal silicon dioxide and magnesium stearate for 5 minutes.

8. Lubricated blend of step 7 was compressed into tablets using a 12.8×6.4 mm punch set on a compression machine.

Tablet properties:

Parameter	Example 5	Example 6
Hardness (Kp)	8-10	8-10
Disintegration time in pH 6.8 phosphate buffer (minutes)	7-10	10-12

In vitro release profile was determined using the same set of conditions as described in Examples 2-4, except the dissolution media was pH 6.8 phosphate buffer instead of 0.05 N Hydrochloric acid.

Time (minutes)	Cumulative % Drug Dissolved		
	Example 5	Example 6	SENSIPAR 90 mg
0	0	0	0
10	28	6.7	5.67
30	47	20	10.00
60	55	35.3	12.33

EXAMPLES 7-8: Formulations of cinacalcet 30 mg extended release tablets.

Ingredient	mg/Batch	
	Example 7	Example 8
Cinacalcet hydrochloride*	660	660
Mannitol	1620	2760

Microcrystalline cellulose (Avicel® PH 101)	800	1800
Hydroxypropyl methylcellulose E 5 cP (Methocel® E 5 LV)	800	400
Hydroxypropyl methylcellulose E 15 cP (Methocel® E 15 LV)	-	200
Talc	40	60
Colloidal silicon dioxide (Aerosil® 200)	40	60
Magnesium stearate	40	60
Tablet Weight (mg)	**200**	**300**

* Quantity equivalent to 600 mg cinacalcet base (30 mg/tablet).

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

Manufacturing process:

1. Cinacalcet HCl was dissolved in 5 ml of ethanol.
2. Mannitol, microcrystalline cellulose and HPMC E (5cP) were mixed together by blending.
3. Blend of step 2 was granulated with solution of step 1.
4. The granules were dried and blended with HPMC E 15 cps, if used.
5. Blend of step 4 was mixed with talc, colloidal silicon dioxide, and magnesium stearate for 5 minutes.
6. Lubricated blend of step 5 was compressed into tablets using a 12.4×6.8 mm punch set on a compression machine.

Tablet properties:

Parameter	**Example 7**	**Example 8**
Hardness (Kp)	15 -18	14 -16

In vitro release profile was determined using the same set of conditions as described in Examples 2-4.

Time (minutes)	**Cumulative % Drug Dissolved**		
	Example 7	**Example 8**	**SENSIPAR 30 mg**
0	0	0	0

20	12.3	10.7	76.33
40	21.3	21.3	94.33
60	39.7	37	96.33

EXAMPLES 9-10: Formulations of cinacalcet 30 mg delayed release tablets.

Ingredient	**mg/Batch**	
	Example 9	**Example 10**
CORE TABLET		
Cinacalcet hydrochloride*	660	660
Mannitol	3000	2500
Microcrystalline cellulose (Avicel® PH 101)	1800	2000
Povidone	-	200
Crospovidone	360	360
Sodium starch glycolate	-	100
Talc	60	60
Colloidal silicon dioxide (Aerosil® 200)	60	60
Magnesium stearate	60	60
SEAL COATING		
Meglumine	330	-
Glyceryl monostearate	-	240
Hydroxypropyl methylcellulose 5 cps	170	200
Talc	70	40
ENTERIC COATING		
Eudragit® L 30 D**	132	-
Hydroxypropyl methylcellulose phthalate succinate	-	132
Triacetin	12	12
Talc	6	6

* Quantity equivalent to 600 mg cinacalcet base (30 mg/tablet).

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

** Manufactured by Rohm and Haas Inc.

Manufacturing process:

1. Cinacalcet HCl and povidone, if used, are dissolved in ethanol.

2. Mannitol and microcrystalline cellulose are mixed together by blending.

3. Blend of step 2 is granulated with solution of step 1.

4. To the granules of step 3, crospovidone and sodium starch glycolate, if any, are added, and further the granules are lubricated using talc, colloidal silicon dioxide, and magnesium stearate.

5. Lubricated blend of step 4 is compressed into tablets using suitable punch set on a compression machine.

6. The tablets of step 5 are seal coated, and further enteric coated.

EXAMPLES 11-12: Formulations of cinacalcet 90 mg modified release tablets.

Ingredient	**Grams/Batch**	
	Example 11 (500 tablets)	**Example 12** (1000 tablets)
Cinacalcet hydrochloride*	49.5	99
Mannitol	94	120
HPMC 5 cps	37.5	60
Microcrystalline cellulose	78.25	100
Methanol ‡	105	210
EXTRAGRANULAR		
HPMC 15 cps	7.5	15
Microcrystalline cellulose	25	139.5
Talc	2.75	5.5
Colloidal silicon dioxide (Aerosil® 200)	2.75	5.5
Magnesium stearate	2.75	5.5
Tablet Weight (mg)	**600**	**550**

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

‡ Evaporates during processing.

Manufacturing process:

1. Cinacalcet HCl was dissolved in methanol under stirring.

2. Mannitol, microcrystalline cellulose and HPMC 5 cps were passed through a ASTM # 40 sieve and blended thoroughly.

3. The blend of step 2 was placed in a fluid bed granulator and then granulated by top spray granulation using cinacalcet HCl solution prepared in step 1.

4. After the granulation was complete, the granules were dried and passed through a ASTM # 30 sieve.

5. The granules of step 4 were blended with HPMC, microcrystalline cellulose and Aerosil.

6. The granules of step 5 were blended with talc and magnesium stearate, and then compressed into tablets using 17.5×7.2 mm oval punches on a CADMACH compression machine.

The hardness of the tablets obtained in Examples 11 and 12 was in the range of 10-12 Kp.

EXAMPLE 13: Modified-release formulation of cinacalcet 90 mg tablets, tablets of Example 12 being coated with a coating composition.

Coating Ingredient	Grams for 1000 Tablets
HPMC E 15 LV	42.4
PEG 400	11
Ferric oxide	0.6
Titanium dioxide	1.1
Water ‡	945
Coated tablet weight (mg)	**605**

‡ Evaporates during processing.

Manufacturing process:

1. HPMC, PEG 400, ferric oxide and titanium dioxide were dispersed in water with stirring, and further homogenized.

2. Tablets of Example 12 (750 g) were coated with the coating composition of step 1 using a Ganscoater to produce a weight gain of about 10 % w/w.

In vitro release profile of coated tablets was determined using the same set of conditions described in Examples 2-4.

Time (minutes)	Cumulative % Drug Dissolved			
	Example 11	Example 12	Example 13	SENSIPAR 90 mg
0	0	0	0	0
10	49.3	58.3	0.7	72.3
20	53.3	57.3	1.3	92.0
30	56.3	59.7	1.2	98.7
40	60.7	64.7	3.5	101.7
60	67.3	65.3	8.3	-

EXAMPLES 14-15: Formulations of cinacalcet 90 mg modified release tablets prepared by direct compression.

Ingredient	Grams/Batch	
	Example 14	Example 15
Cinacalcet hydrochloride*	99	99
MCC	324.5	324.5
HPMC K100M	110	-
HPMC K15M	-	110
Talc	5.5	5.5
Aerosil 200	5.5	5.5
Magnesium stearate	5.5	5.5
Tablet weight (mg)	**550**	**550**

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

Manufacturing process:

1. Cinacalcet HCl, MCC, HPMC (K 100 M in Example 14 and K 15 M in Example 15), Aerosil 200 were passed through a ASTM # 40 mesh sieve.
2. Talc and magnesium stearate were passed through a ASTM # 60 mesh sieve, and mixed with the mixture of step 1.
3. The blend of step 2 was compressed into tablets using a Cadmach multi-station compression machine fitted with 17.5×8.5 mm oval shaped punch sets. The tablet hardness was about 12 to about 20 kP.

In vitro release profile of formulations of Example 14 was determined under the same set of conditions as described in Examples 2-4.

Time (hours)	Cumulative % Drug Dissolved
0	0
1	9.0
2	12.33
4	18.0
6	24.33
8	30.0
12	41.33

EXAMPLES 16-17: Formulations of cinacalcet 180 mg delayed release tablets with enteric coating.

Ingredient	Grams/Batch of 20 Tablets	
	Example 16	Example 17
Cinacalcet hydrochloride*	3.96	3.96
Mannitol	4.8	4.8
HPMC 5 cps	2.4	2.4
MCC	4	4
Methanol ‡	8	8
EXTRAGRANULAR		
HPMC 15 cps	0.6	0.6
HPMC K 15 M	2.2	2.2
MCC	5.58	5.58
Talc	0.22	0.22
Aerosil 200	0.22	0.22
Magnesium stearate	0.22	0.22
Core tablet weight (mg)	**1210**	**1210**
ENTERIC COATING		
Eudragit L 30 D 55	0.5	1.0
HPMC 5 cps	0.5	1.0
Talc	0.06	0.11

Triethyl citrate	0.1	0.2
Water ‡	10.36	20.73
Total tablet weight (mg)	**1268.17**	**1326.34**

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

‡ Evaporates during processing.

The manufacturing process for preparation of core tablets was similar to that described in Examples 11-12, except the granulation process was carried out in a planetary mixer instead of a fluid bed granulator.

Enteric coating process:

1. Eudragit, HPMC, talc and triethyl citrate were dispersed in water with stirring, and further homogenized.

2. The core tablets were coated with the coating dispersion of step 1 using a Ganscoater to produce a weight gain of about 5 % w/w (Example 15) and about 10 % w/w (Example 16).

EXAMPLES 18-19: Formulation of cinacalcet 90 mg modified-release tablets.

Ingredient	**Grams/Batch**	
	Example 18	**Example 19**
Cinacalcet hydrochloride*	99	1.98
Mannitol	120	2.4
HPMC 5 cps	60	1.2
MCC	100	2.0
Methanol ‡	200	4
EXTRAGRANULAR		
HPMC 15 cps	15	0.3
HPMC K 15 M	28	0.44
MCC	139.5	2.79
Talc	5.5	0.11
Aerosil 200	5.5	0.11
Magnesium stearate	5.5	0.11
Tablet weight (mg)	**578**	**572**

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

‡ Evaporates during processing.

Manufacturing process for preparation of the tablets was similar to that described in Examples 11-12 except the granulation was carried out in a planetary mixer instead of a fluid bed granulator.

The lubricated granules (blended with extra-granular ingredients) for tablet compression prepared as per Example 18 have following micromeritic properties: Bulk density= 0.53 g/mL; Tapped density= 0.66 g/mL, Carr index = 20 %.

In vitro release profile was determined under the same set of conditions as described in Examples 2-4.

Time (minutes)	Cumulative % Drug Dissolved	
	Example 18	Example 19
0	0	0
10	4.7	8.7
30	20.7	39.7
60	49.0	74.0
90	69.7	-
120	81.3	-

EXAMPLE 20: Formulation of cinacalcet 180 mg modified-release tablets.

Ingredient	Grams/Batch of 20 Tablets
Cinacalcet hydrochloride*	3.96
Mannitol	4.8
HPMC E 5 LV	2.4
MCC	4.0
Methanol ‡	8
EXTRAGRANULAR	
HPMC E 15 LV	0.6
HPMC K 15 MCR	2.2
MCC	5.58

Talc	0.22
Aerosil 200	0.22
Magnesium stearate	0.22
Tablet weight (mg)	**1210**

* Particle size distribution D_{10} = 12.81 µm, D_{50} = 52.78 µm, D_{90} = 129.74 µm.

‡ Evaporates during processing.

The manufacturing process for preparation of the tablets was similar to that described in Examples 11-12, except the granulation was carried out in a planetary mixer instead of a fluid bed granulator.

In vitro release profile was determined under the same set of conditions as described in Examples 2-4.

Time (hours)	**Cumulative % Drug Dissolved**
0	0
1	42
2	52.3
4	59.3
6	65.0
8	69.6
12	79.0

EXAMPLE 21: Particle size distribution of cinacalcet hydrochloride by sieve analysis.

ASTM Sieve No.	**Pore size (µm)**	**% Retained**	**Cumulative % Retained**
12	1200	1.5	-
30	600	25.8	27.3
60	250	64.9	92.2
80	180	7.8	100

EXAMPLE 22: Formulation of cinacalcet 90 mg modified-release capsules.

Ingredient	Grams/Batch of 100 capsules
Cinacalcet hydrochloride (Example 21)	9.9
HPMC 5 cps	6
MCC	10
Methanol ‡	20
EXTRAGRANULAR	
HPMC 15 cps	0.8
HPMC K 15 M	3
MCC	8
Talc	0.45
Aerosil 200	0.4
Magnesium stearate	0.45
Capsule weight (mg)	**390**

‡ Evaporates during processing.

The granulation and blending processes for preparation of the capsules were similar to that described in Examples 11-12, except the granulation was carried out in a planetary mixer instead of a fluid bed granulator. After blending, the granules (equivalent to 90 mg cinacalcet/capsule) were filled into size "0el" hard gelatin capsules.

EXAMPLE 23: Formulation of cinacalcet 90 mg modified-release capsules prepared by a drug layering technique.

Ingredient	Grams/Batch
DRUG LAYERING	
Sugar spheres (20/25 mesh)	300
Cinacalcet hydrochloride (Example 21)	150
HPMC 5 cps	40
Methanol ‡	400

MODIFIED RELEASE COATING	
Ethyl cellulose 7 cps	36
HPMC 5 cps	5
Dibutyl sebacate	4
Methylene chloride ‡	450
Methanol ‡	450

‡ Evaporates during processing.

Manufacturing process:

1. HPMC and cinacalcet HCl were dispersed in methanol with stirring.
2. The dispersion of step 1 was layered onto sugar spheres using a fluid bed processor, and dried.
3. Ethyl cellulose, HPMC and dibutyl sebacate were dispersed in a mixture of methylene chloride and methanol under stirring.
4. The dispersion of step 3 was coated onto 200 grams of the drug layered pellets from step 2 in a fluid bed processor, and dried.
5. The dried pellets (equivalent to 90 mg cinacalcet/capsule) were filled into size “0el” hard gelatin capsules.

CLAIMS:

1. A pharmaceutical formulation comprising cinacalcet or a salt thereof and a release-controlling polymer that delays, prolongs, or both delays and prolongs, release of contained cinacalcet or a salt thereof from the formulation into a fluid.

2. The pharmaceutical formulation of claim 1, releasing about 10 percent to about 45 percent of contained cinacalcet or a salt thereof into 0.05 N hydrochloric acid, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C and at a rotation speed of about 75 r.p.m., within about 30 minutes from starting the test.

3. The pharmaceutical formulation of claim 1, being a matrix composition wherein substantially complete release of contained cinacalcet or a salt thereof occurs after about 1 hour and up to about 20 hours, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m. in 0.05 N hydrochloric acid.

4. The pharmaceutical formulation of claim 1, being a reservoir composition wherein substantially complete release of contained cinacalcet or a salt thereof occurs after about 1 hour and up to about 20 hours, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m. in 0.05 N hydrochloric acid.

5. The pharmaceutical formulation of claim 1, wherein substantially complete release of the contained cinacalcet or a salt thereof occurs after about 1 hour and up to about 2 hours, measured according to a dissolution test conducted in a USP apparatus II at a temperature of about 37 °C, and at a rotation speed of about 75 r.p.m. in 0.05 N hydrochloric acid.

6. The pharmaceutical formulation of claim 1, containing about 30 mg to about 300 mg of cinacalcet or a salt thereof.

7. The pharmaceutical formulation of claim 1, containing about 60 mg to about 270 mg of cinacalcet or a salt thereof.

8. The pharmaceutical formulation of claim 1, wherein a release-controlling polymer comprises about 1 percent to about 90 percent by weight of the total weight of the formulation.

9. The pharmaceutical formulation of claim 1, wherein a release-controlling polymer comprises about 5 percent to about 80 percent by weight of the total weight of the formulation.

10. A method of reducing adverse events associated with calcimimetic therapy, comprising orally administering a pharmaceutical formulation of any of claims 1-9.

11. A pharmaceutical formulation comprising a therapeutically effective amount of cinacalcet or a salt thereof, wherein mean particle sizes of cinacalcet or a salt thereof are about 50 μm to about 500 μm.

12. The pharmaceutical formulation of claim 11, wherein mean particle sizes of cinacalcet or a salt thereof are about 50 μm to about 350 μm.

13. A pharmaceutical formulation comprising a therapeutically effective amount of a solubility-enhanced form of cinacalcet or a salt thereof, wherein a solubility-enhanced form comprises a complex with cyclodextrin, a solid dispersion, a co-precipitate or a premix.

14. The pharmaceutical formulation of claim 13, wherein a solubility-enhanced form comprises cinacalcet or a salt thereof and a surfactant.

15. The pharmaceutical formulation of claim 14, wherein a surfactant comprises an anionic surfactant, cationic surfactant, non-ionic surfactant, or a mixture of two or more thereof.

16. The pharmaceutical formulation of any of claims 1-15, wherein the formulation comprises multiparticulate compositions comprising cinacalcet or a salt thereof.

17. The pharmaceutical formulation of any of claims 1-15, wherein the formulation comprises a granular composition comprising cinacalcet or a salt thereof.

18. The pharmaceutical formulation of any of claims 1-15, wherein the formulation comprises powder compositions comprising cinacalcet or a salt thereof.

19. The pharmaceutical formulation of any of claims 1-18, wherein cinacalcet or a salt thereof comprises cinacalcet hydrochloride.