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(54) Title: PHARMACEUTICAL COMPOSITION OF CINACALCET

(57) Abstract: The present invention relates to a bioavailable and stable pharmaceutical composition comprising cinacalcet or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients, characterized in that the composition is prepared by wet granulation without binding agent.



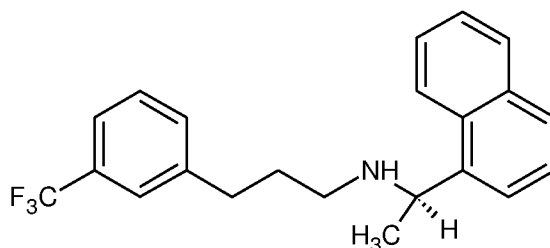
PHARMACEUTICAL COMPOSITION OF CINACALCET

Technical Field of the Invention

The present invention is directed to a bioavailable and stable pharmaceutical composition comprising cinacalcet or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients, characterized in that the composition is prepared by wet granulation without binding agent.

Background of the Invention

Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. Cinacalcet is described chemically as N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane and has the following structural formula:



Formula I

Its empirical formula is $C_{22}H_{22}F_3N$ with a molecular weight of 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity. Cinacalcet is commercially available in particular in hydrochloride salt form. Cinacalcet HCl is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water.

The commercial cinacalcet hydrochloride tablet formulation is marketed under the trade name Sensipar[®] in the United States and Australia, and as Mimpara[®] in Europe. These tablets are formulated as light-green, film-coated, oval-shaped tablets 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 hydrochloride salt, respectively). Each tablet contains pregelatinized starch, microcrystalline cellulose,

povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. Tablets are coated with color (Opadry® II green) and clear film-coat (Opadry® clear), carnauba wax, and Opacode® black ink.

Cinacalcet was first disclosed in the patent numbered EP0724561 by NPS Pharmaceuticals. The patent also discloses usage of cinacalcet and its pharmaceutically acceptable salts, for treatment of primary or secondary hyperparathyroidism.

EP1663182 discloses improving bioavailability of cinacalcet hydrochloride by using from 45% to 85% by weight of at least one diluent and from 1% to 5% by weight of at least one binder in a composition. Further disclosed are compositions containing povidone as a binder and crospovidone as an excipient.

WO2011146583 describes a composition comprising nanoparticulate cinacalcet or a pharmaceutically acceptable salt thereof, and at least one surface stabilizer which is adsorbed onto or associated with the surface of the drug. Exemplified are compositions containing Plasdone (PVP) as a surface stabilizer.

EP2490674 relates to a tablet formulation comprising an intermediate which is obtained by the melt-extrusion of cinacalcet or a pharmaceutically acceptable salt thereof and matrix former. Exemplified is a composition containing crospovidone as a disintegrant.

EP1945184 relates to a composition comprising solid composite of cinacalcet in intimate association with at least one carrier which is selected from the group consisting of povidone, poloxamer, hydroxypropyl methylcellulose, polyethylene glycol, copovidone, copolymers of methacrylate, copolymers of methacrylic acid, lower aliphatic alcohols and C3-C8 ketones. EP 2334284 relates to an intermediate for preparation of a tablet, obtainable by jointly compacting crystalline cinacalcet with a hydrophilic polymer, such as PVP, a copolymer of vinyl pyrrolidone and vinyl acetate and/or PEG.

EP 2642980 discloses formulations comprising cinacalcet hydrochloride admixed with at least 2-5% w/w of silicon dioxide, in particular a powder formulation or pellets filled in a hard shell capsule. The compositions disclosed also contain povidone.

Considering the aforesaid documents, they have serious disadvantages such as time, cost, the need of special equipment. However; the present invention provides improved simple, cost effective and stable pharmaceutical compositions with a reduced risk of degradation of cinacalcet.

Summary of the Invention

The present invention is directed to a bioavailable and stable pharmaceutical composition comprising cinacalcet or pharmaceutically acceptable salt thereof and at least one or more pharmaceutically acceptable excipients, characterized in that the composition is prepared by wet granulation without binding agent (s). It was surprisingly found that such a pharmaceutical composition is stable and can be prepared by a simple and cost effective process.

In a standard wet granulation process a solution of a binder in water or another suitable solvent is sprayed onto the dry mixture of excipients. However, the formation of agglomerates of the binder at the spray nozzles has been observed. This leads to inhomogenous blends. The subsequent drying step may require longer drying times and/or higher temperature if a binder is present, which should be avoided for sensitive substances.

In the present invention only pure water is sprayed onto the dry powder, thus avoiding any agglomeration at the spray nozzles.

In addition, due to the binder in standard compositions known in the art there is a risk of overgranulation and of tablet hardening during storage over a longer time. One object of the present invention is to provide a binder-free pharmaceutical composition of cinacalcet comprising pregelatinized starch in an amount from 0 % to 25 % by weight; preferably it is 5-15% by weight, and more preferably about 7 % by weight of the total pharmaceutical composition to achieve the desired dissolution profile. Pregelatinized starch has the function of a disintegrant, as can be seen in Test Example 2.

Another object of the invention is to provide a pharmaceutical composition of cinacalcet which is free of povidone or crospovidone. Cinacalcet compositions known in the art like the tablets of the commercial product Mimpara® contain polymer excipients based on pyrrole monomers, such as polyvinylpyrrolidone (PVP, povidone) or crospovidone. These excipients frequently contain peroxides and other secondary oxidation impurities, and it is known that reactive peroxides in povidone often lead to degradation of oxidation-labile drugs [Journal of Pharmaceutical Sciences 2012;101(1):127-39] in the tablet. Stability studies of cinacalcet under various stress conditions revealed that this substance is especially sensitive towards peroxide oxidation, and degradation upon treatment with peroxides was observed (see Test Example 3).

As the cinacalcet compositions of the present invention are free of binding agents, in particular do not contain any povidone, the risk of degradation caused by peroxide impurities is reduced.

The presence of a binder in a formulation also requires the addition of (strong) disintegrants for a rapid dissolution. The typical disintegrant used is crospovidone, which contributes to even higher levels of peroxide impurities.

A further object of the present invention is pharmaceutical compositions of cinacalcet which do not contain crospovidone as a disintegrant, thus reducing the risk of peroxide degradation (see Example 2).

Another object of the present invention is to provide a simple, cost-effective and time saving process for the preparation of solid composition of cinacalcet. It is known that binding agent is critical for attaining consistent granulation during the process of wet granulation. However, drying of wet granular mass containing binder agent(s) necessitates the utilization of higher temperatures for longer duration of time. Thus, exposure of the active ingredient to higher temperatures for longer duration may influence the impurity profile with respect to thermal and oxidative degradation of the active agent.

Further problems observed with the application of binding agents in wet granulations are processing difficulties such as rapid over-granulation. In addition, hardening of tablets can be found sometimes due to changes of the binding agent over time. This leads to an undesired change in the disintegration time and dissolution profile. During the granulation process, a solution of the binder is usually added to the granulation blend through a spray gun. Often the binder solution is sticky and tends to adhere on the spray nozzles and to form larger agglomerates which can fall down into the granules and which have to be removed by additional milling or sieving steps.

In the present invention, we have surprisingly found that the compositions manufactured without any binding agent(s) resulted in obtaining satisfactory results with respect to the manufacturing process (such as granulation, potency, flow attributes of granules and final blend including compression properties).

For the process of the present invention, wet granulation is performed by adding pure water onto the dry blend of cinacalcet and excipients, thus avoiding the aforementioned agglomeration and sticking to the spray nozzles. In general compositions manufactured without binding agent exhibit processing problems such as poor flowability, poor content uniformity, sticking and picking during the course of tablet compression. In prior art, it was mentioned that utilization of higher concentrations of lubricating agents such as magnesium stearate and stearic acid will prevent the occurrence of said sticking and picking problems. However, utilization of higher levels of hydrophobic lubricating agents such as magnesium stearate in compositions containing hydrophobic actives such as cinacalcet HCl may prolong the disintegration time which in turn effects the dissolution behavior. In order to prevent the occurrence of such processing problems, inventors of the present invention surprisingly

found that the utilization of pregelatinized starch in an amount of 1% to 25 % by weight and combination of talc and magnesium stearate in weight ratio between 1:3 and 1:0.1, preferably between 1:2 and 1:0.5, and more preferably of about 1:0.5 (w/w) prevents these said problems and supports in achieving the desired pharmaceutical attributes such as disintegration time and dissolution behavior.

Detailed Description of the Invention

The main object of the present invention is to provide a binder-free pharmaceutical composition comprising cinacalcet and at least one or more pharmaceutically acceptable excipients.

The term "Cinacalcet" used throughout the text refers to cinacalcet or its pharmaceutically acceptable salt, solvate, polymorph, hydrate or enantiomer or a combination thereof. Preferably, cinacalcet is used in hydrochloride salt form in the formulations of the present invention.

The term "composition" as used herein may include other pharmaceutically acceptable excipients routinely used in the art of manufacturing pharmaceutical dosage forms. For example, the pharmaceutically acceptable excipients include one or more fillers, disintegrants, lubricants, glidants, coloring agents, flavoring agents and coatings.

The composition of the present invention is used by oral route. Pharmaceutical composition to be used orally can be in the form of tablet (including film coated tablets, chewable tablets, effervescent tablets, layered tablet, soluble tablets, sublingual tablets, oral disintegrating tablets), capsule (including soft capsule and microcapsule), granules, grains, powders, pills, or combinations thereof. The compositions of the present invention are preferably in tablet form and can optionally be film coated.

The term "binder" means a substance which is capable of facilitating granulation of the active agent into larger, denser, and more free-flowing particles, so it helps bind the active ingredient and other excipients together after compression. Examples of binders include but are not limited to, polyvinylpyrrolidone (povidone, PVP), polyethylene glycol (PEG), cross-linked polyvinylpyrrolidone, cellulose derivatives (such as hydroxymethyl cellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, ethyl cellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose), sucrose, alginic acid or sodium alginate, carbomer, cottonseed oil, dextrin, dextrose, guar gum, hydrogenated vegetable oil type I, magnesium aluminium silicate, maltodextrin, maltose, polydextrose, polyethylene oxide, stearic acid and zein. The composition does not contain any binder agent; more specifically does not contain polyvinylpyrrolidone or copovidone for granulation.

The granulation solvent is selected from water and mixtures of aqueous and non-aqueous solvents such as ethanol, isopropanol alcohol and dichloromethane.

The term "disintegrant" as used in herein refers to any material that facilitates the break up of a tablet prepared from the composition when placed in contact with an aqueous medium. Suitable disintegrants include, but are not limited to, crospovidone, sodium starch glycolate, hydroxypropyl starch, microcrystalline cellulose, carboxymethylcellulose sodium or calcium, croscarmellose, pregelatinized starch, polacrillin potassium, low-substituted hydroxypropylcellulose, sodium or calcium alginate, agar, guar gum, chitosan, alginic acid and mixtures thereof. The composition preferably comprises from 2% to 10 % of disintegrant, in particular about 7 %, based on the weight of the total composition.

The term 'filler' and the term 'diluent' are herein used interchangeably. It is known that, in general, the term 'filler' is used in the context of capsular formulations and the term 'diluent' in tablet formulations. Fillers fill out the size of a composition, making it practical to produce and convenient for the consumer to use. Suitable filler/diluent include, but are not limited to, calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose (e.g. spray-dried lactose, α -lactose, β -lactose, Tabletose, various grades of Pharmatose®, Microtose® or Fast-Floc®), methylcellulose polymers such as, e.g., Methocel A, Methocel A4C, Methocel A 15C, Metocel A4M), hydroxyethylcellulose, hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, starches or modified starches (including potato starch, wheat starch, corn starch, rice starch, pregelatinised maize starch), magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol, erytritol. Preferably, the diluent/filler is lactose, microcrystalline cellulose or pregelatinized starch. The amount of diluents used according to the present invention may be 20 to 95 w/w % , preferably about 50 to about 90 w/w % of a diluent, in particular about 60 to about 90 w/w % of a diluent, based on the total weight of the composition.

The term "glidant" as used in herein refers to any substance that is added to a powder to improve its flowability. Suitable glidants include, but are not limited, to at least one or a mixture of colloidal silicone dioxide, talc, aluminum silicate, magnesium silicate. Preferably the glidant is talc.

The presence of a lubricant is particularly preferred when the composition is a tablet as lubricants improve the tableting process. Lubricants prevent composition ingredients from clumping together and from sticking to the tablet punches or capsule filling machine and improve flowability of the composition mixture. Suitable lubricants are preferably selected from stearic acid, stearic acid salts such as magnesium stearate, palmitic acid salts such as magnesium palmitate, oleic acid salts such as magnesium oleate, sodium lauryl sulfate, magnesium lauryl sulfate, hydrogenated vegetable oil,

hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols or mixtures thereof. Preferably, the lubricant is magnesium stearate. The composition preferably comprises 0.5 to 5 wt % of lubricant.

Suitable coloring agents include one or more FDA approved colors for oral use.

It has been surprisingly found that the pharmaceutical formulations according to the present invention have the same dissolution profiles when compared to the reference product Mimpara[®], and especially have lower variability among different samples of a pharmaceutical formulation. According to the present invention, the variability of dissolution is measured using USP apparatus 2, placing each of the 6 formulation examples in 900 ml 0.05 N HCl at 37 ± 0.5 °C with paddle speed of 75 rpm after 10, 15, 20, 30 and 45 minutes (see Fig. 1).

The term ‘dissolution stability’ as used herein refers to the similarity of dissolution profiles (similarity factor greater than 50, in comparison to initial) obtained at different periods of storage at varying temperature and humidity conditions.

The term ‘similarity factor’ or ‘f2 factor’ as used herein refers to one way of comparing dissolution profiles of two different products. This model-independent mathematical approach compares the dissolution profile of the two products: test and reference or two strengths, or pre-and post-approved products from the same manufacturers. Tests are recommended to be performed under the same test conditions. The dissolution time points for both the profiles should be the same, for example for immediate release products e.g. 10, 15, 20, 30, 45 minutes. Only one time point should be considered after 85% dissolution of any product. An f2 value of 50 or greater (50-100) ensures sameness or equivalence of two curves, and thus performance of the two products. The similarity factor f2 should be computed using the equation:

$$f_2 = 50 * \log \frac{100}{\sqrt{1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2}}$$

Where R_t and T_t are the cumulative percentage of the drug dissolved at each of the selected n time points of the comparison (reference) and (test) product respectively. For products which are very rapidly dissolving, i.e. more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

Another object of the present invention is to provide a binder-free pharmaceutical composition of cinacalcet or pharmaceutically acceptable salt thereof, characterized in that the composition is comprising:

- about 10% to 40% of cinacalcet hydrochloride,
- about 1% to about 25% of pregelatinized starch as a diluent,
- about 3% to about 30% crospovidone as a disintegrant,
- about 10% to about 60% microcrystalline cellulose as a diluent,
- about 20% to about 60% lactose as a diluent,
- about 0.5% to about 2% talc as a glidant,
- about 0.5% to about 2% magnesium stearate as a lubricant,

wherein the percentage by weight is relative to the total weight of the composition and wherein the composition does not contain povidone.

In a further object, the disintegrant, e.g. crospovidone or sodium starch glycolate, can be present both in intragranular part and extragranular part, wherein the weight ratio of disintegrant in intragranular part to extragranular part is 1:0.5 to 1:3, preferably 1:0.5 to achieve desired dissolution profile.

Another object of the invention is a method for preparing a pharmaceutical composition as disclosed above, comprising the steps of:

- a. Mixing cinacalcet hydrochloride, lactose monohydrate, microcrystalline cellulose, pregelatinized starch and crospovidone,
- b. Performing wet granulation process thereon without using binding agent,
- c. Drying and then sieving the wet granules obtained in step b;
- d. Second part of microcrystalline cellulose and lactose monohydrate are weighed and mixed with granules obtained in step c;
- e. Admixing finally talc and magnesium stearate into the mixture obtained in step d;
- f. Compressing the resulting mixture of step e into tablets.

The particle D_{50} of the granules comprising cinacalcet hydrochloride is ranging from 100- 500 μm , preferably from 200-350 μm . The particle size is determined by using Malvern Mastersizer analyzer or sieve analysis and it is important to achieve content uniformity and desired dissolution profile.

Examples

The present invention will be described in more detail by way of the following examples, but scope of the present invention is not limited thereto.

Example 1

Three pharmaceutical compositions with targeted amounts of 30 mg, 60 mg and 90 mg active ingredient with the following components were prepared:

Ingredients	Unit Formula [mg]		
	30 mg Tablet	60 mg Tablet	90 mg Tablet
Cinacalcet Hydrochloride (equivalent to 30 mg, 60 mg & 90 mg Cinacalcet)	33.06	66.12	99.18
Lactose monohydrate	66.66	133.33	150.00
Pregelatinized starch	12.60	25.20	37.80
Microcrystalline cellulose	7.33	14.67	15.00
Crospovidone	25.68	51.35	134.02
*Purified water	q.s.	q.s.	q.s.
Extragranular			
Microcrystalline cellulose	26.67	53.34	80.00
Crospovidone	3.33	6.67	10.00
Talc	1.67	3.33	5.00
Magnesium stearate	3.00	6.00	9.00
Weight of core tablet	180.00	360.00	540.00
Sheffcoat green	5.00	10.00	20.00
Deionized water	q.s.	q.s.	q.s.
Weight of coated tablet	185.00	370.00	560.00

*q.s.means a sufficient amount

Manufacturing Method:

- Mixing cinacalcet hydrochloride , lactose monohydrate, microcrystalline cellulose , pregelatinized starch and crospovidone until a homogenous mixture is obtained, in high-shear mixture granulator;
- Performing wet granulation process thereon without using binding agent;
- Wet granules obtained in step (ii) are loaded into fluid-bed dryer and dried at 50-60 °C;
- Sieving of dried granules;

- v. Second part of microcrystalline cellulose and lactose monohydrate are weighed and mixed with granules obtained in step iv;
- vi. Talc and magnesium stearate are weighed and added into powders of step v, and mixed;
- vii. Powders of step vi are compressed using suitable punches;
- viii. Compressed tablets are coated with determined coating material.

Example 2

Ingredients	Unit Formula [mg]		
	30 mg Tablet	60 mg Tablet	90 mg Tablet
Cinacalcet Hydrochloride (equivalent to 30 mg, 60 mg & 90 mg Cinacalcet)	33.06	66.12	99.18
Lactose monohydrate	85.84	171.68	257.52
Pregelatinized starch	14.40	28.80	43.20
Microcrystalline cellulose	7.00	14.00	21.00
Sodium starch glycolate	4.00	8.00	12.00
*Purified water	q.s.	q.s.	q.s.
Extragranular			
Microcrystalline cellulose	27.00	54.00	81.00
Sodium starch glycolate	5.00	10.00	15.00
Talc	1.70	3.40	5.10
Sodium stearyl fumarate	2.00	4.00	6.00
Weight of core tablet	180.00	360.00	540.00
Opadry II	5.00	10.00	20.00
Deionized water	q.s.	q.s.	q.s.
Weight of coated tablet	185.00	370.00	560.00

Tablets were prepared by wet granulation process without binding agent(s) as same method described in the Example 1.

Test Example 1: Dissolution Test

The dissolution profile of tablet is obtained according to Example 1 is tested by dissolution protocol described in USP 26/NF 21, chapter 711.

They key parameters are as follows:

Medium: 0.05 N HCl

Volume: 900 ±9 ml

Temperature: 37.0 ±0.5 °C

Batch Type: USP apparatus 2

Stirrer: 75 rpm ±2rpm

The dissolution of tablet was compared with commercial reference product. The results are shown in Table 1.

Table 1: Dissolution profiles of commercial reference product and Example 1

Time (Minutes)	%Dissolved	
	Reference Product (Mimpara [®])	Cinacalcet 90 mg Film Tablet (Example 1)
10	67,7	66,7
15	81,3	81,0
20	88,1	88,2
30	93,4	94,9
45	96,4	98,5

f2 value was found to be 96,4.

Test Example 2: Function study of pregelatinized starch

According to Handbook of Pharmaceutical Excipients (R. Rowe et al., Pharmaceutical Press, 6th Ed., 2009), pregelatinized starch can be used as binder, disintegrant or diluent. The dissolution test was performed to understand function of pregelatinized starch in present invention. For this purpose, dissolution profiles of Test example 2A (without pregelatinized starch), test example 2B (with 7% pregelatinized starch) and test example 2C (with 10% pregelatinized starch) and commercial reference product (Mimpara[®]) were compared. The dissolution tests were performed according to Test Example 1.

Table 2: Test examples 1A, 1B and 1C

Ingredients	Quantity (mg)/tablet		
	Test Example 2A (without pregelatinized starch)	Test Example 2B (with 7% pregelatinized starch)	Test Example 2C (with 10% pregelatinized starch)
Cinacalcet HCl equivalent to Cinacalcet	99,18	99,18	99,18
Lactose monohydrate	200	200	200
Pregelatinized starch	--	37,8	54
Microcrystalline cellulose	114,82	77,02	60,82
Crospovidone	22	22	22
Purified water	-	-	-
Microcrystalline cellulose	80	80	80
Crospovidone	10	10	10
Talc	5	5	5
Magnesium stearate	9	9	9
Core tablet weight	540	540	540
Purified water	-	-	-
Sheffcoat green	20	20	20
Coated tablet weight	560	560	560

Table 3: Dissolution profiles of commercial reference product and Test Example 2A, 2B and 2C

	Reference product Mimpara [®]	Test Example 2A	Test Example 2B	Test Example 2C
Time point (min.)	% Cinacalcet released			
5	40,8	36,1	42,2	41
10	67,7	53,3	66,7	71,4
15	81,3	69,1	81	87
20	88,1	76,7	88,2	95,4
30	93,4	84,7	94,9	101,9
45	96,4	88,1	98,5	104,6
f2	-	49	93.5	69.6

As can be seen in Table 3, the dissolution was slower in the absence of starch, so it is demonstrated that the pregelatinized starch functions as a disintegrant in the present invention.

Test Example 3: Stress stability

Stress stability studies of cinacalcet hydrochloride were performed under various conditions. The results are shown in Table 4.

Table 4: Stress stability studies

Degradation Type	Conditions	Cinacalcet (%)	Degradation impurities (%)
Untreated	-	100.00%	Not observed
Acid treated	72 hrs, Conc HCl hydroxide Refluxed	100.00%	Not observed
Alkali treated	72 hrs, 5 N sodium hydroxide Refluxed	100.00%	Not observed
Peroxide treated	7.0 hrs, 30% hydrogen peroxide solution	71.55%	28,0%
Thermal degradation	7 days, 105°C	100.00%	Not observed
Photolytic degradation	1,2 million lux hrs under UV light., 200 watt under florescent light	100.00%	Not observed

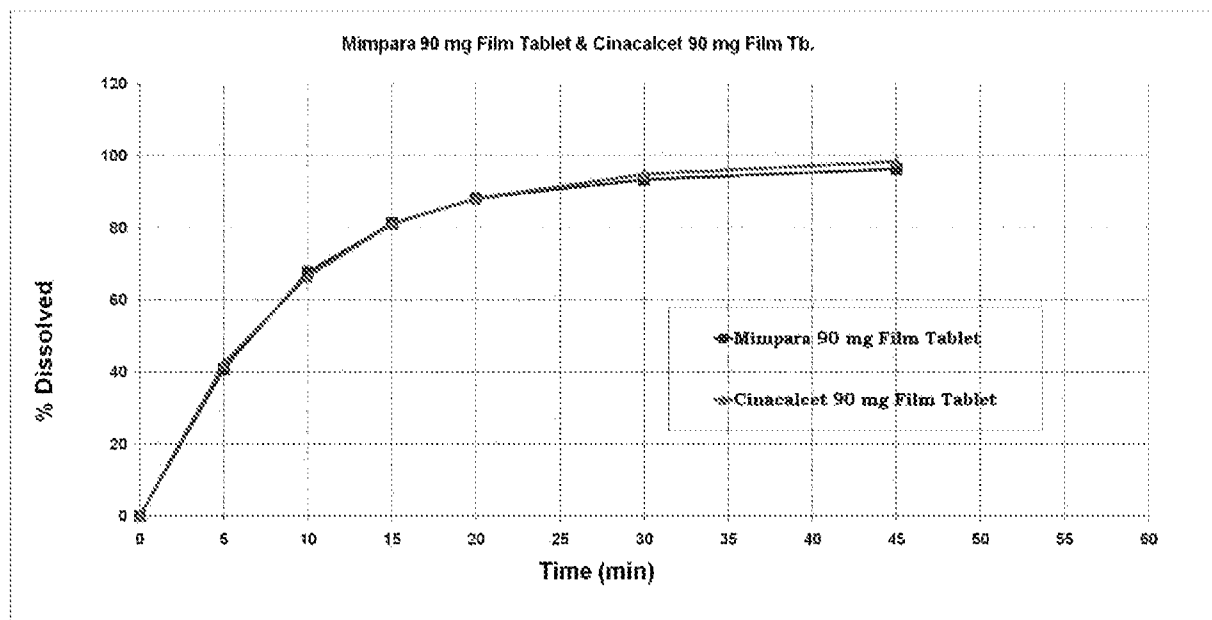
As can be seen in Table 4, Cinacalcet hydrochloride is especially sensitive to peroxide oxidation. For this reason, pharmaceutical excipients which contribute to peroxide content in the composition, such as povidone, were not used in the present invention to reduce peroxide degradation impurities.

CLAIMS

1. A pharmaceutical composition comprising cinacalcet or pharmaceutically acceptable salt thereof and at least one or more excipients characterized in that the composition is free of binding agent and prepared by wet granulation.
2. A pharmaceutical composition according to claim 1, characterized in that said binding agent is selected from polyvinylpyrrolidone, polyethylene glycol, cellulose derivatives, sucrose, alginic acid or sodium alginate, carbomer, cottonseed oil, dextrin, dextrose, guar gum, hydrogenated vegetable oil type I, magnesium aluminium silicate, maltodextrin, maltose, polydextrose, polyethylene oxide, stearic acid and zein.
3. A pharmaceutical composition according to claim 1a, characterized in that said composition does not comprise polyvinylpyrrolidone.
4. The composition according to claim 1, wherein said excipient comprises at least one or a mixture of diluents, disintegrants, glidants and lubricants.
5. The composition according to any of the preceding claims, characterized in that said diluent contains at least one or a mixture of lactose, microcrystalline cellulose, pregelatinized starch, methylcellulose polymers and sucrose; said diluent being preferably selected from lactose, microcrystalline cellulose, pregelatinized starch or mixtures thereof.
6. The composition according to any of the preceding claims, characterized in that said disintegrant contains at least one or a mixture of crospovidone, croscarmellose, hydroxypropylcellulose, sodium starch glycolate, sodium alginate or calcium alginate; said disintegrant being preferably crospovidone.
7. The composition according to any of the preceding claims, characterized in that said lubricant contains at least one or a mixture of magnesium stearate, sodium stearyl fumarate, stearic acid; said lubricant being preferably magnesium stearate.
8. The composition according to any of the preceding claims, characterized in that said glidant contains at least one or a mixture of talc, aluminium silicate and colloidal silicon dioxide; said glidant being preferably talc.
9. A binder-free pharmaceutical composition of cinacalcet or a pharmaceutically acceptable salt thereof, characterized in that the composition is comprising about 1% to about 25% pregelatinized starch and about 0.25% to about 3% combination of magnesium stearate and talc, wherein the weight ratio of talc and magnesium stearate is in the range of between 1:3 and 1:0.1 (w/w), preferably it is 1:2, more preferably 1:0.5.
10. A method for preparing a pharmaceutical composition according to any of the preceding claims, comprising the steps of:
 - a. Mixing cinacalcet hydrochloride, lactose monohydrate, microcrystalline cellulose, pregelatinized starch and crospovidone,

- b. Performing wet granulation process thereon,
 - c. Drying and then sieving the wet granules obtained in step b,
 - d. Admixing the remaining excipients with the granules obtained in step c,
 - e. Admixing finally talc and magnesium stearate into the mixture,
 - f. Compressing the resulting mixture into tablets.
11. A binder-free pharmaceutical composition of cinacalcet or a pharmaceutically acceptable salt thereof, characterized in that the composition is comprising:
- about 10 % to 40 %by weight of cinacalcet hydrochloride,
 - about 1% to about 25% by weight of pregelatinized starch as a diluent,
 - about 3% to about 30% by weight of crospovidone as a disintegrant,
 - about 10% to about 60% by weight of microcrystalline cellulose as a diluent,
 - about 25% to about 60% by weight of lactose as a diluent,
 - about 0.5% to about 2% by weight of talc as a glidant,
 - about 0.5% to about 2% by weight of magnesium stearate as a lubricant,
- wherein the percentage by weight is relative to the total weight of the composition.
12. Use of a composition according to any of the preceding claims for the preparation of a medicament for the treatment of hyperparathyroidism, hypercalcemia, and hyperphosphonia or elevated calcium phosphorous product in a patient.

Figure 1. Dissolution profile of Cinacalcet Hydrochloride 90 mg film tablet according to Example 1 and Mimpara[®] 90 mg film tablet



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/059787

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/137 A61K9/16 A61P5/18 A61P3/14 A61P43/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 1 December 2014	Date of mailing of the international search report 17/12/2014	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Blott, Catherine	

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