



(51) International Patent Classification:

A61K 9/19 (2006.01) A61K 31/137 (2006.01)
A61K 47/48 (2006.01) A61P 5/14 (2006.01)

(21) International Application Number:

PCT/EP2010/000418

(22) International Filing Date:

25 January 2010 (25.01.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

09001103.2 27 January 2009 (27.01.2009) EP

(71) Applicant (for all designated States except US):
RATHIOPHARM GMBH [—/DE]; Graf-Arco-Strasse
3, 89079 UIm (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PUSKÁS, István**
[HU/HU]; Dózsa György út 71, H-2111 Szada (HU).
SZENTE, Lajos [HU/HU]; Gombocz Zoltan utca17,
H-1118 Budapest (HU). **PAETZ, Jana** [DE/DE];
Schleifwiesen 3, 82272 Moorenweis (DE).

(74) Agent: **AECHTER, Bernd**; Ter Meer Steinmeister &
Partner GbR, Mauerkircherstrasse 45, 81679 München
(DE).

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

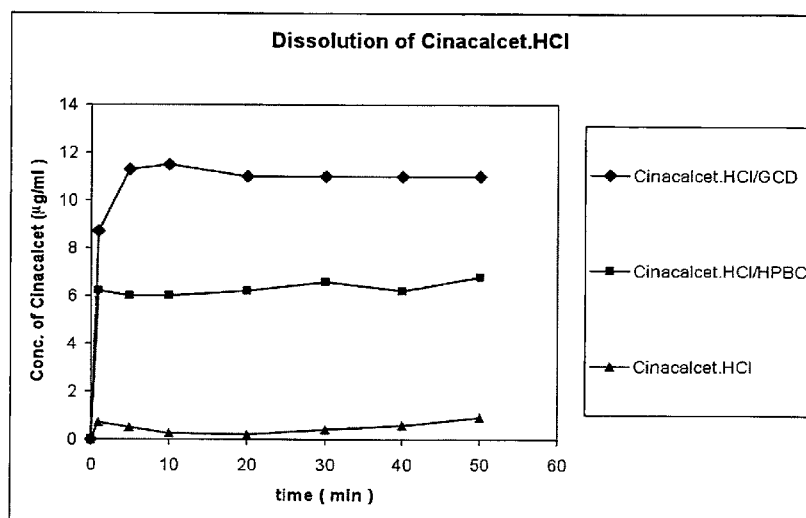
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: INCLUSION COMPLEX COMPRISING CINACALCET AND CYCLODEXTRIN

Figure 8:

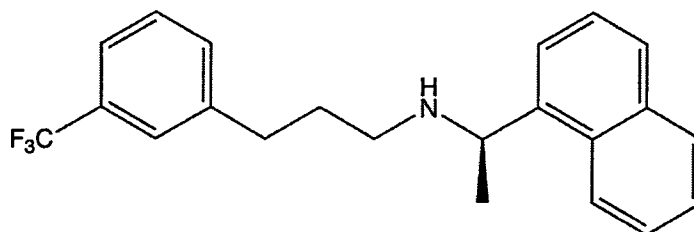


(57) Abstract: The present invention relates to Inclusion complexes comprising cyclodextrin, preferably gamma-cyclodextrin and cinacalcet, wherein the molar ratio of cyclodextrin to cinacalcet is 1 : 1 to 5 : 1, preferably about 1 : 2. The invention further relates to a process for producing said cinacalcet inclusion complexes and to pharmaceutical composition comprising said complexes. Finally, the invention relates to the use of gamma-cyclodextrin for producing cinacalcet containing pharmaceutical formulations.

Inclusion Complex Comprising Cinacalcet and Cyclodextrin

The present invention relates to cinacalcet inclusion complexes, preferably to molecularly dispersed cinacalcet in a molecularly dispersed form of inclusion complexes, comprising cyclodextrin, preferably gamma-cyclodextrin, and cinacalcet, wherein the molar ratio of cyclodextrin to cinacalcet is 1 : 1 to 3 : 1, preferably about 2 : 1. The invention further relates to a process for producing said cinacalcet inclusion complexes and to pharmaceutical compositions comprising said complexes. Finally, the invention relates to the use of gamma-cyclodextrin for producing cinacalcet containing pharmaceutical formulations.

"Cinacalcet" is the INN name of N-[(1R)-1-(1-naphthyl)ethyl]-3- [3-(trifluormethyl)phenyl]propane-1-amine and is characterized by the following chemical formula:



Cinacalcet acts as a calcimimetic (i.e. it mimics the action of calcium on tissues) by allosteric activation of the calcium-sensing receptor and is used to treat hyperparathyroidism (elevated parathyroid hormone levels), a consequence of parathyroid tumors and chronic renal failure. In particular, cinacalcet is indicated for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease on dialysis and hypercalcaemia in patients with parathyroid carcinoma.

The synthesis of cinacalcet is described in EP 1 203 761 B1. Cinacalcet is currently marketed under the trade name "Sensipar[®]" or "Mimpara[®]" in the form of film-coated tablets.

According to the FDA Biopharmaceutics Classification System (BCS), crystalline cinacalcet is a class IV substance, i.e. having a low solubility and low permeability.

In the art, several cinacalcet formulations are known. WO 2008/064202 describes compositions containing cinacalcet with prolonged release. Dosage forms with prolonged release are usually applied for specific administrations. However, for a plurality of administrations, dosage forms with immediate release are desirable.

The currently marketed film-coated tablets are tablets with immediate release and are described in WO 2005/034928. The tablets contain cinacalcet in micronized form, comprising cinacalcet as the active ingredient in an amount of approximately 18%. The film-coated tablets are to be taken with or shortly after a meal, as the
5 bioavailability increases by 50% to 80% when taken together with the food.

The micronization of cinacalcet, however, involves some disadvantages. Firstly, the micronization in the active ingredient results in an undesired low flowability. Furthermore, the micronized active ingredient is more difficult to be compressed and
10 occasionally irregular distribution of the active ingredient occurs within the pharmaceutical formulation to be compressed. Caused by the large extension of the surface during micronization, the tendency of the active ingredient to oxidate increases.

15 Cinacalcet is available not only in crystalline form but also by spray-drying in amorphous form, cf. WO 2008/00422 A1. Active ingredients in amorphous form, however, show disadvantageous properties with regard to storage stability.

Hence, it was an object of the present invention to overcome the drawbacks of the
20 above-mentioned formulations.

In particular, cinacalcet should be provided in a form having superior solubility and superior permeability. Preferably, cinacalcet should be provided in a form, which is regarded as a BCS class I substance (high permeability, high solubility). In addition,
25 cinacalcet should be provided in a form, which allows oral application independently from meals. The increase in solubility and permeability should particularly be achieved without a micronization step. Moreover, cinacalcet should be provided in a non-hygroscopic form.

30 Furthermore, it was an object of the invention to provide cinacalcet in a form having superior storage properties. Preferably, storage stability for 12 months at 40 °C and 75 % humidity should be achieved. After storage under said conditions, impurities should be less than 2 wt.-%, more preferably less than 1 wt.-%.

35 Particularly, the above-mentioned objects should be solved simultaneously, that means, cinacalcet should be provided in a non-hygroscopic form having high solubility, high permeability and showing high storage stability.

The objects of the present invention can be solved by a "genuine" cinacalcet-
40 cyclodextrin inclusion complex and a method for forming such a "genuine" cinacalcet-cyclodextrin inclusion complex. Preferably, said inclusion complex can be regarded as

a supramolecular, non-covalent inclusion complex. The genuine inclusion complex leads to a novel solid form of cinacalcet, preferably to a form of molecular dispersity, and when re-wetted in a form having liquid crystalline or liquid crystalline-like properties. The novel solid form is described as glassy-amorphous solid form.

5

A subject of the present invention thus is an inclusion complex comprising cyclodextrin and cinacalcet, wherein the molar ratio of cyclodextrin to cinacalcet is 1 : 1 to 3 : 1.

10 A further subject of the present invention is an inclusion complex comprising gamma-cyclodextrin and cinacalcet.

Still a further subject of the present invention is an inclusion complex comprising cyclodextrin and cinacalcet, wherein in a Raman spectrum the characteristic bond of
15 crystalline cinacalcet at a wavelength of about 1586 cm^{-1} is shifted to lower wave numbers in the inclusion complex. Generally, the shift indicates the formation of the above mentioned "genuine" inclusion complex, i.e. the formation of a novel, molecularly dispersed state of the drug, active in the inclusion complex.

20 The above illustrated subjects of the present invention are alternative solutions to the above outlined objects.

Moreover, the present invention is directed to a process for producing an inclusion complex comprising cinacalcet and cyclodextrin comprising the steps of

25

- a) wetting and/or dispersing cyclodextrin in a solvent, preferably water,
- b) adding cinacalcet, preferably in particulate form, wherein the molar ratio of cyclodextrin to cinacalcet is preferably from 1 : 1 to 5 : 1;
- c) subjecting the mixture resulting from step (b) to a mechanical treatment; and
- 30 d) removing the solvent from the reaction mixture, preferably by freeze-drying or spray-drying.

Finally, the present invention relates to the use of gamma-cyclodextrin for producing a cinacalcet-containing pharmaceutical formulation.

35

The term "cinacalcet" as used in the present application refers to cinacalcet in the form of the free base as well as to its pharmaceutically acceptable salts (preferably derived from inorganic or organic acids), solvates, hydrates, enantiomers, polymorphs or mixtures thereof. Examples for pharmaceutically acceptable salts are acetate,
40 adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate,

ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmate, pectinate, persulfate, 2-phenylpropionate, picrate, 5 pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. Preferably, cinacalcet is used in the form of the free base, as hydrochloride or as methanesulfonate.

10 As mentioned above, the present invention refers to a genuine cinacalcet-cyclodextrin inclusion complex. The term "genuine" indicates that the entire and complete amount of cinacalcet is entrapped intercalated into the molecular cavities of the cyclodextrin, i.e. cinacalcet is only present in intercalated form, no adsorbed, un-entrapped crystalline or amorphous (i.e. amorphous as described in WO 2008/00422) cinacalcet occurs. The formation of the genuine inclusion complex generally leads to a glassy- 15 amorphous solid form of cinacalcet.

Preferably, all inclusion complexes of the present invention are non-covalent inclusion complexes. Furthermore, preferably all inclusion complexes of the present invention are supramolecular inclusion complexes. In particular, all inclusion complexes of the 20 present invention are non-covalent and supramolecular inclusion complexes. The term "supramolecular" is understood as describing self-organizing molecular interactions that result in the formation of new structures that stay together without establishing a covalent linkage.

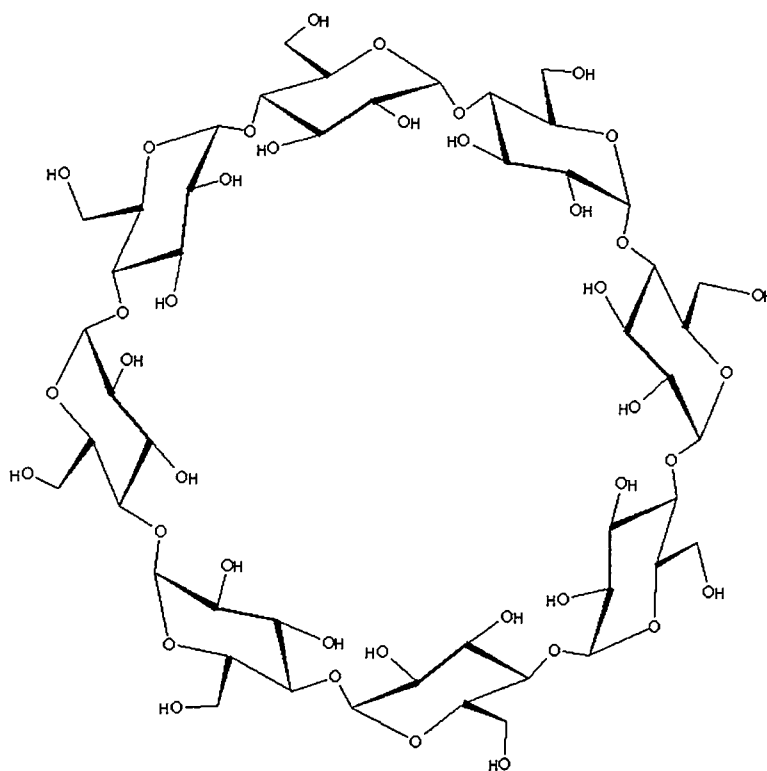
25 Generally, the genuine cinacalcet-cyclodextrin inclusion complexes of the present invention will be achieved if the molar ratio of cyclodextrin to cinacalcet is from 1 : 1 to 3 : 1, preferably from 1.0 : 1.0 to 3.0 : 1.0, more preferably from 1.5 : 1.0 to 2.5 : 1.0, still more preferably about 2 : 1, particularly about 2.0 : 1.0. Thus, it is particularly preferred that the cinacalcet functions as "bifunctional guest" within the 30 cyclodextrin cavity.

Furthermore, in the case of gamma-cyclodextrin, the genuine cinacalcet-cyclodextrin inclusion complexes of the present invention will also be achieved if the molar ratio of cyclodextrin to cinacalcet is from 1 : 1 to 5 : 1, preferably 1 : 1 to 3 : 1, more 35 preferably from 1.5 : 1.0 to 2.5 : 1.0, still more preferably about 2 : 1, particularly about 2.0 : 1.0.

The term "cyclodextrin" generally refers to non-reducing cyclic saccharides. Preferably, said cyclic saccharides comprise six, seven or eight glucose units linked by alpha-1,4 40 interglycosidic bonds. In the present invention cyclodextrins comprising eight glucopyranose units (cyclooctaamylose) are preferred.

Furthermore, it is particularly preferred that in all embodiments of the present invention cyclodextrins are used in the form of cyclodextrin hydrate, particularly gamma cyclodextrin is used in the form of gamma cyclodextrin hydrate. In a preferred embodiment the water content of the cyclodextrin used for making the inclusion complex is from 6 to 12 wt.-%, particularly from 8 to 12 wt.-% based on the total weight of the cyclodextrin.

Generally, the genuine cinacalcet-cyclodextrin inclusion complex of the present invention will be achieved if gamma-cyclodextrin is used. Gamma-cyclodextrin is a ring-shaped molecule made up of eight glucose units linked by alpha-1,4 bonds. Gamma-cyclodextrin comprises the following structure:



15

The term "gamma cyclodextrin" preferably refers (as shown in the above formula) to a "non-substituted form". This means, the gamma cyclodextrin preferably is not chemically modified e.g. neither alkylated nor hydroxyl-alkylated. Moreover, preferably gamma-cyclodextrin having a bulk density of from 400 to 700 milligram/cm³ is used.

Furthermore, as mentioned above, the gamma cyclodextrin is preferably used in form of a crystalline hydrate. Generally, gamma cyclodextrins can exist in two main classes of crystal structures, namely the cage and tubular (or columnar) structure. In the cage

structure (often called also a HERRING BONE arrangement), the cyclodextrin cavities are not aligned. Contrary, in the tubular structure, gamma cyclodextrin monomers stick to each other on their top, forming a cylindrical multi-molecular channel, where e.g. slim but long molecules (e.g. linear polymers) could fit in and form a stable complex. In the present invention it is preferred that gamma cyclodextrin having a cage structure is used.

Furthermore, it is preferred that gamma cyclodextrin is used in the form of a hydrate, wherein each molecule of gamma cyclodextrin comprises between 12 and 14 molecules of water. In addition, crystalline gamma cyclodextrin having a monoclinic space group is used.

Generally, cyclodextrins form an inner cavity. Within this application said cavity is referred to as "nanocavity".

A genuine cinacalcet-cyclodextrin inclusion complex of the present invention is usually characterized by the complete inclusion of the cinacalcet molecule into the nanocavity of the cyclodextrin(s). The completeness of the inclusion process can be monitored via solid state Raman microscopy/spectroscopy and/or by the SEM-ESD electron-microscopic surface mapping.

Under ambient conditions crystalline cinacalcet shows a characteristic bond at a wave number of about 1586 cm^{-1} . Said bond is shifted to lower wave numbers due to the inclusion process as cinacalcet gets included into the gamma-cyclodextrin nanocavity. Hence, a further subject of the present invention is an inclusion complex comprising cyclodextrin (preferably gamma-cyclodextrin) and cinacalcet, wherein in a Raman spectrum the characteristic bond of crystalline cinacalcet at a wave number of about 1586 cm^{-1} is shifted to lower wave numbers in the inclusion complex. In a preferred embodiment the shift to lower wave numbers is at least 3 cm^{-1} , more preferably from 4 cm^{-1} to 8 cm^{-1} .

The shift to lower wave numbers is illustrated in **Figures 1 and 1a**. In Figure 1 Raman spectra of crystalline cinacalcet (first upper curve), a physical mixture of cinacalcet and gamma-cyclodextrin hydrate (second curve), a gamma-cyclodextrin/cinacalcet inclusion complex (third curve) as well as gamma-cyclodextrin hydrate alone (fourth bottom curve) are shown. It can be derived from Figure 1 that in the genuine inclusion complex the characteristic bond of cinacalcet at a wave number of about 1586 cm^{-1} is shifted to a wave number of about 1581 cm^{-1} in the inclusion complex. A respective Raman measuring method is given in the experimental part of this application.

Figure 1a is the enlargement of the Raman spectrum, discussed above, for the most characteristic wavenumber ranges (1350-1600 nm). The upper curve represents crystalline cinacalcet, the middle curve represents a physical mixture of cinacalcet and gamma-cyclodextrin, and the lower curve represents the inclusion complex according to Example 1.

The genuine cinacalcet-cyclodextrin inclusion complex of the present invention is different from the complexes as described in WO 2008/064202. In Example 1 of WO 2008/064202 mixtures of beta-cyclodextrin and cinacalcet are described, wherein the molar ratio is more than 3:1. In the disclosed example beta-cyclodextrin and cinacalcet predominantly are present in form of a mere physical mixture. The predominant amount of cinacalcet is adhered to the cyclodextrin surface by physical forces (adsorption) but not included into the cyclodextrin cavity, stabilized by secondary apolar-apolar interactions (e.g. via van der Waals forces and London-type dispersion forces). This partial, incomplete inclusion and highly dispersed surface-located adsorbed cinacalcet fraction may have a negative effect on the chemical stability and shelf life of the cinacalcet-beta-cyclodextrin formulation according to the cited invention WO 2008/064202.

On the contrary, the cinacalcet-cyclodextrin inclusion complexes of the present invention are usually characterized by the complete inclusion of the cinacalcet into the cavity of the cyclodextrin. The term "*complete inclusion*" means that the molecular entrapment of cinacalcet is essentially quantitative. In other words, preferably no surface-bound, adsorbed fraction of the cinacalcet will occur in the cinacalcet/cyclodextrin, particularly in the cinacalcet/gama-cyclodextrin complexes according to the present invention.

Hence, the cinacalcet-cyclodextrin inclusion complexes of the present invention preferably are essentially free of "solid" cinacalcet, i.e. essentially free of crystalline and/or amorphous cinacalcet (in this regard the term "amorphous" refers to conventional amorphous cinacalcet, e.g. as described in WO 2008/004222). The term "essentially" free means that the inclusion complexes of the present invention do not contain significant amounts of crystalline or amorphous cinacalcet bound to the surface of complex particles. Preferably, the cinacalcet inclusion complexes of the present invention comprise less than 5 wt.-%, more preferably less than 2 wt.-%, more preferably less than 0.5 wt-% cinacalcet in crystalline or amorphous form, based on the total weight of the inclusion complex.

In **Figure 2** a Scanning Electron Microscopy (SEM) photograph of a genuine cinacalcet/gamma-cyclodextrin-inclusion complex of the present invention is shown. For comparative reasons, in **Figure 3** a SEM photograph of crystalline cinacalcet and in

Figure 4 a SEM photograph of a physical cinacalcet/gamma-cyclodextrin mixture is shown.

5 These high-resolution electron-microscopic scans indicate the appearance of a novel solid phase of cinacalcet, namely cinacalcet being molecularly entrapped into the cyclodextrin nanocavity.

10 In a preferred embodiment the residual water content of the inclusion complexes of the present invention is less than 6 wt.-%, more preferably less than 4 wt.-%, in particular, less than 3 wt.-%, based on the total weight of the inclusion complex. Preferably, the water content of the inclusion complexes of the present invention does not increase more than 10 % (in particular, not more than 6 %) during a storage period of 3 months at a temperature of 25 °C and a humidity of 60 %.

15 The average particle size of cyclodextrin cinacalcet inclusion complexes, preferably of the gamma-cyclodextrin cinacalcet inclusion complexes, is usually between 2 and 20 micrometers, preferably between 5-15 micrometers and particularly between 6 and 12 micrometers.

20 The term "average particle size" refers to the volume average particle size (D_{50}), which is determined by the light scattering method, using a Mastersizer 2000 apparatus made by Malvern Instruments (wet measurement, 2000 rpm, ultrasonic waves for 60 sec., data interpretation via Fraunhofer method).

25 Furthermore, the cyclodextrin cinacalcet inclusion complexes of the present invention preferably are provided in a solid, particulate form having a bulk density of 450 to 900 mg/cm³.

30 The cinacalcet inclusion complexes of the present invention can be regarded as a novel glassy-amorphous solid phase of cinacalcet. The glassy-amorphous solid phase of cinacalcet re-wetted in an aqueous system preferably shows some liquid crystalline properties that remind of the lyotropic liquid crystalline material.

35 When viewed under a polarized light, different liquid crystal phases will appear having a distinct Schlieren-texture. The contrasting areas in the texture each correspond to a domain where the liquid crystalline molecules are oriented in a different direction. Within a domain, however, the molecules are well ordered. The polarized light microscopic photos taken from the cinacalcet/gamma cyclodextrin complex according to Example 1 of this invention clearly indicate the specific, liquid crystalline-like
40 mesophase texture.

The present invention further relates to a process for producing genuine non-covalent cinacalcet-cyclodextrin inclusion complexes. Hence, a further subject of the present invention is a process for producing an inclusion complex comprising cinacalcet and cyclodextrin comprising the steps of

5

- a) wetting and/or dispersing cyclodextrin in a solvent, preferably water;
- b) adding cinacalcet, preferably in particulate form, wherein the molar ratio of cyclodextrin to cinacalcet is preferably from 1 : 1 to 5 : 1;
- c) subjecting the mixture resulting from step (b) to a mechanical treatment; and
- 10 d) removing the solvent, preferably the water from the reaction mixture, preferably by freeze-drying or spray-drying.

15

Generally, the comments made above for cinacalcet and cyclodextrin also apply for the process of the present invention. Thus, for example, preferably gamma-cyclodextrin is used, particularly gamma-cyclodextrin hydrate (particularly having the above illustrated water content) is used in the above mentioned process.

20

In step (a) of the process of the present invention cyclodextrin is wetted and/or dispersed in a suitable solvent. The solvent may be water or an organic solvent, preferably an alcohol, e.g. ethanol. Furthermore, the solvent may also be a mixture of alcohol and water, wherein the mixing ratio alcohol : water is e.g. 1 to 10 to 2 : 1. In a particularly preferred embodiment the solvent is deionized water.

25

The term "wetting and/or dispersing" means that cyclodextrin is brought into contact with the solvent, preferably with the water, wherein the solvent wets the surface of the cyclodextrin or the cyclodextrin is dispersed (i.e. suspended and optionally partially dissolved) in the solvent. In the second case, the surface is – of course – also wetted.

30

The weight ratio of cyclodextrin : solvent usually ranges from 1 : 10 to 10 : 1, preferably from 1 : 1 to 1 : 5.

Optionally, the cyclodextrins are stirred during the wetting and/or dispersing step, preferably at a stirring speed from 300 to 450 rpm (rotation per minute).

35

In an optional but preferred embodiment the wetted and/or dispersed cyclodextrin is subjected to a grinding step (referred to as step (aa)). The grinding step (aa) leads to a kind of "activation" of the cyclodextrin. Usually, grinding is carried out for 1 to 30 minutes, preferably for 2 to 10 minutes. Grinding in step (aa) may be carried out in known milling devices, e.g. a ball mill.

40

In step b) of the process cinacalcet is added, preferably in particulate form. More preferably, cinacalcet is added in crystalline form to the solution of step a). The molar ratio of cyclodextrin to cinacalcet is preferably from 1 : 1 to 5 : 1, more preferably from 1 : 1 to 4 : 1, particularly from 1 : 1 to 3 : 1.

5

Optionally, the mixture of step (b) is stirred, preferably at a stirring speed from 300 to 450 rpm. Stirring may be carried out for 1 to 10 minutes.

Optionally, cinacalcet can be (partially or completely) dissolved in a co-solvent (= step 10 bb)) before being added in step (b).

In step (c) the mixture resulting from step (b) is subjected to a mechanical treatment.

Generally, any mechanical treatment is suitable to enable the inclusion of the 15 cinacalcet into the nanocavity. Preferably, the mechanical treatment step comprises ultrasonic treatment, optionally combined with stirring. Alternatively, but also preferred, mechanical treatment can be carried out by grinding, preferably by co-grinding wetted and/or dispersed cyclodextrin with cinacalcet.

Generally, ultrasonic treatment is carried out by immersing the mixture resulting from 20 step (b) into an ultrasonic device, e.g. an ultrasonic bath. Examples of ultrasonic-treatment are hydrodynamic cavitation, sono-fragmentation and/or sono-cavitation or co-grinding. For example, ultrasonic treatment can be carried out with Tesla ultrasonic equipment.

25

Ultrasonic treatment is preferably performed by using ultrasonic waves having a frequency of 5 to 100 kHz, more preferably of 10 to 80 kHz. Furthermore, ultrasonic treatment is preferably performed by using ultrasonic waves having an intensity of 50 30 to 5000 W, more preferably 500 to 1000 W. As an example, 1000 W and 20 kHz or 500 W and 58 kHz can be used.

This means that instead of the relatively long 6-8 hours stirring time for reaching complete inclusion that is used traditionally in the art for complexation, the stirring 35 time can significantly be reduced by the above-mentioned sono-fragmentation or sono-cavitation process. By this high-energy ultrasonic treatment, the inclusion complexation technology becomes more efficient and economic.

In addition to the ultrasonic treatment (e.g. hydrodynamic cavitation, sono-fragmentation or sonocavitation), the reaction mixture may be agitated (e.g. using 40 traditional propeller stirrer), preferably with a rotation speed of 300-450 rpm (rotation per minute).

As mentioned above, the mechanical treatment step can also be carried out by grinding, preferably by co-grinding wetted and/or dispersed cyclodextrin with cinacalcet. Generally, grinding is carried out in known milling devices, e.g. a ball mill or a pin mill. It is preferred that if the mechanical treatment step (c) is carried out by grinding, then, the optional step (aa) (= activation of cyclodextrin) is carried out.

Usually, the mechanical treatment is carried out for 1 to 30 minutes, preferably for 5 to 20 minutes. Furthermore, mechanical treatment is carried out at a temperature from 5 to 50 °C, preferably at room temperature (about 20 °C).

Once solid phase transformation (occurring in step c) is completed, the solvent of the reaction mixture is removed in step (d).

Generally, the methods known in the art for removing solvents are suitable. Preferably, the solvent is removed by freeze-drying or spray-drying. The removal of the solvent by a spray-drying step is particularly preferred.

Generally, spray-drying can be carried out using an inlet temperature of 150 to 200 °C, preferably about 180 °C, and an outlet temperature of about 80 to 100 °C, preferably of about 95 °C. For example, spray-drying can be carried out by using a Büchi® Lab Niro spray-drier.

After removing the water the cinacalcet-cyclodextrin complexes of the present invention can be rewetted. The fastest dissolving form of the cinacalcet inclusion complexes of the present invention usually is achieved, if in step (d) the solvent is removed by freeze-drying (lyophilisation) the inclusion complex.

Steps (a) to (c) can be carried out subsequently or simultaneously. In a preferred embodiment steps (a), (b) and (c) are carried out subsequently.

Generally, the process of the present invention is suitable for preparing the inclusion complexes of the present invention, preferably achieving a yield of from 80 to 99 %, more preferably from 90 to 98 %.

A further subject of the present invention are inclusion complexes, obtainable by the above mentioned process. The inclusion complexes of the present invention can be applied in the form of a pharmaceutical formulation.

Hence, a further subject of the present invention is a pharmaceutical formulation comprising a cinacalcet inclusion complex according to the present invention and one or more pharmaceutical excipients.

In the pharmaceutical formulation of the present invention one or more pharmaceutically acceptable excipient(s), such as fillers, binding agents, lubricants, glidants, anti-sticking agents, and disintegrating agents, can be employed. Regarding the above-mentioned pharmaceutically acceptable excipients, the application refers to

5 "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", edited by H. P. Fiedler, 4th Edition, Editio Cantor, Aulendorf and earlier editions, and "Handbook of Pharmaceutical Excipients", Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

10 Generally, the comments given above about preferred embodiments of the cinacalcet/cyclodextrin inclusion complexes also apply for the pharmaceutical formulation of the present invention. In particular, the pharmaceutical formulation of the present invention is essentially free of "solid" cinacalcet, i.e. essentially free of

15 crystalline and/or amorphous cinacalcet. The term "essentially" free means that the pharmaceutical formulations of the present invention do not contain significant amounts of crystalline or amorphous cinacalcet. Preferably, the pharmaceutical formulations of the present invention comprise less than 5 wt.-%, more preferably less than 1 wt.-%, more preferably less than 0.1 wt.-% cinacalcet in crystalline or amor-

20 phous form, based on the total weight of the formulation.

Preferably, the pharmaceutical composition of the present invention comprises the cinacalcet-cyclodextrin-complex of the present invention, a binding agent, a disintegrant and a lubricant. Preferably, the pharmaceutical composition is present in

25 form of a tablet.

A binding agent may be added to the pharmaceutical formulation in order to ensure that oral dosage forms, preferably tablets, can be formed with the required mechanical strength. The binding agent can, for example, be starch or preferably microcrystalline

30 cellulose. Usually, the binding agent is present in an amount of 0 to 35 wt.-%, preferably of 1 to 30 wt.-%, more preferably of 5 to 25 wt.-%, still more preferably of 10 to 20 wt.-%, based on the total weight of the final pharmaceutical composition. In case of tablets, these values refer to the uncoated tablet.

35 A disintegrant is a compound, which enhances the ability of the dosage form, preferably the ability of the tablet, when in contact with a liquid, preferably water, to break up into smaller fragments. Preferred disintegrating agents are croscarmellose sodium, sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone (crospovidone, e.g. Kollidon® CL) or sodium carboxymethyl glycolate (e.g. Explotab®), or

40 sodium bicarbonate. In particular, crospovidone is used. The disintegrating agent is suitably present in an amount of 0 to 25 wt.-%, more preferably of about 1 to 20 wt.-%

of the total weight of the final pharmaceutical composition. In case of tablets, these values refer to the uncoated tablet.

The function of the lubricant is to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. The lubricant is preferably a stearate or fatty acid, more preferably an earth alkali metal stearate, such as magnesium stearate. The lubricant is suitably present in an amount of 0 to 2 wt.-%, preferably of about 0.1 to 1.0 wt.-% of the total weight of the final pharmaceutical composition. In case of tablets, these values refer to the uncoated tablet.

The pharmaceutical composition can be compressed to tablets. The compression step (ii) can be carried out with a rotary press, e.g. on a Fette® 102i (Fette GmbH, Germany) or a Riva® piccola (Riva, Argentina). Furthermore, an eccentric press like a Korsch® EK0 could be used. Usually, the main compaction force ranges from 1 to 50 kN, preferably from 2 to 30 kN, more preferably from 3 to 15 kN.

The dosage forms, preferably the tablets of the present invention, usually have a content uniformity of 85 to 115 %, preferably of 95 to 105 %, more preferably of 96 to 104 %, still more preferably of 97 to 103 %, particularly preferred of 98 to 102 %, and most preferred from 99 % to 101 %. The content uniformity is determined according to the European Pharmacopoeia (Ph.Eur), 6th edition, 2008, section 2.9.6.

The tablets of the present invention can be film-coated tablets for peroral use or dispersing tablets. The film-coating agent is for example hydroxypropylmethyl cellulose or methacrylate and may be present in an amount of 1 to 10 wt.-%, more preferably in an amount of 2 to 8 wt.-%, based on the total weight of the composition. Preferably, a film, not imparting modified-release properties, is used.

The present invention is illustrated by the following examples.

EXAMPLES

Example 1:

Preparation of a Cinacalcet/Gamma-Cyclodextrin Inclusion Complex by Sonocavitation

26.0 grams (about 0.02 mole) of crystalline gamma-cyclodextrin hydrate was wetted and dispersed in 80 milliliters of deionised water at room temperature for 5 minutes, using a normal laboratory stirrer with 300-450 rpm.

To the thoroughly dispersed and continuously stirred gamma-cyclodextrin hydrate slurry, 3.6 grams of crystalline Cinacalcet.HCl (about 0.01 mole) was added without any further co-solvent or additive. The above cinacalcet and gamma-cyclodextrin-containing aqueous dispersion was intensively homogenized for 5 minutes, using normal stirring.

The reaction mixture was then treated with high energy (20 kHz 1000 Watt) sono-fragmentation and sono cavitation by a Tesla ultrasonic equipment at room temperature for 15 up to 20 minutes. During this mechano-chemical sono-cavitation process, the above-mentioned normal stirring 300-450 rpm was maintained to provide homogeneity of the dispersion. The sono-fragmentation assisted complex formation was followed by taking samples and investigating the normal optical and cross-polarised light microscopic appearance of both the cinacalcet and gamma-cyclodextrin solid-phase transitions during the inclusion process.

Once solid phase transformation was completed, the reaction mixture was spray-dried on a Büchi® Lab Niro spray-drier using the following drying conditions:

- Inlet temperature: 180 °C
- Outlet temperature: 94 – 95 °C

Yield: Altogether 28.6 grams of white solid powder (96,62 %) were obtained containing 12.6 % Cinacalcet.HCl (by weight).

Residual water content: 4.2%.

Bulk density of resulting product was between: 46-52 g/100 ml.

The cinacalcet/gamma-cyclodextrin complex according to Example 1 after re-dissolving in pH 7 buffer provided a dissolved cinacalcet concentration between 11-12 mg/mL within 8-12 minutes.

Example 1a:

A process as described in Example 1 was carried out, provided that in the last step freeze-drying (instead of spray-drying) was carried out.

This process according to Example 1a yielded a more fluffy (flying, very spongiform) amorphous solid than spray-drying according to Example 1 did.

For freeze-drying, the reaction mixture was chilled to minus 60 °C and the ice was sublimed at 50 millitorr vacuum, followed by a secondary drying cycle for 4 hours at the temperature range of 25-40°C.

Residual water content: 2 - 4 % by weight.

Bulk density of resulting product was between: 75-85 g/100 ml.

5 The freeze-dried cinacalcet/gamma-cyclodextrin complex, according to Example 1a, after re-dissolving it in natural pH buffer provided a dissolved cinacalcet concentration between 12-15 mg/mL in 1- 2 minutes.

Example 2:

10 Preparation of a Cinacalcet/Gamma-Cyclodextrin by Mechanochemical Co-grinding

7.2 grams of crystalline gamma-cyclodextrin hydrate were wetted with 10 milliliters of 33 vol.% aqueous ethanol for 5 minutes in achate mortar.

15

To the thoroughly pre-wetted gamma-cyclodextrin hydrate, 1.0 gram of crystalline Cinacalcet HCl was added and the mixture was further ground for 1 minute. The mixture suddenly became a very dense, sticky material. Further 3 milliliters of aqueous ethanol were added and grinding continued for 3 minutes, when again the mixture was a sticky semisolid. The addition of a third portion of 5 milliliters of aqueous ethanol enabled easy grinding a creamy reaction mixture for five minutes. The wet, co-ground cinacalcet/gamma-cyclodextrin complex was dried in an oven at 40 °C over phosphorous pentoxide.

25 Yield: 7.2 grams (87.8 %) of white free-flowing powder of a cinacalcet/gamma-cyclodextrin complex containing 12.9 % cinacalcet (by weight).

The residual water content of the co-ground complex was 2.7 % by weight (Karl Fisher titrimetry).

30

Example 3:

Raman Spectroscopy

35 The inclusion complex as obtained in Example 1 was characterized by Raman spectroscopy.

The result is shown in Figure 1, third curve. As mentioned above, for comparative reasons also spectra of pure crystalline cinacalcet, of pure gamma-cyclodextrin and of a physical mixture are shown in Figure 1.

40

All Raman surface microanalyses have been performed by using LabRam HR Type Raman microscope, termed also "LabRAM HR UV-VIS-NIR High Resolution Single Spectrometer" (Jobin Yvon, France).

- 5 The comparative physical mixture samples were prepared by thorough grinding of the respective cyclodextrins and the drug active in an achate mortar for three minutes.

Laser source: frequency-doubled Nd-YAG (532 nm) laser beam.

- 10 Objective lens: short focusing 100 × (excitation laser beam diameter at focus point was 0.7 μm).

- The studies were performed by a resolution used for the mapping of powder solid samples between 0.8 μm - 10 μm. The recordings were made by scanning 30 by 30 μm surface scales with 1 μm shooting intervals.
- 15

Example 4:

SEM Photographs

20

The inclusion complex, as obtained in Example 1, was characterized by SEM with X-ray microanalysis. The resulting photograph is shown in Figure 2. As mentioned above, for comparative reasons also photographs of pure crystalline cinacalcet and of a physical mixture are shown in Figures 3 and 4, respectively.

25

The electron-dispersive Scanning Electronmicroscopy studies were performed on a JEOL 5500 LV type scanning electronmicroscope under the following applied parameters: 15 kV accelerator voltage, Spotsize 68, 10 mm, count number 5000-12000 cps T2.

30

Example 5:

XRPD Spectroscopy

- 35 The inclusion complex as obtained in Example 1 was characterized by X-ray powder diffraction. The resulting XRPD's are shown in Figures 5, 6 and 7.

The X-powder diffraction investigations were performed by using a standard normal CuK_{alpha} radiation. The reflection peaks were registered in the 2-theta angle range of

5-40 degrees. The solid cinacalcet/cyclodextrin complexes were prepared by using not yet optimized co-precipitation and aqueous suspension technologies.

Figure 5 represents an XRPD of crystalline cinacalcet hydrochloride. The X-ray powder diffractograms registered from the cinacalcet substance indicate that the drug substance before inclusion complex formation shows a well-defined crystallinity and typical pattern. A crystallographic pattern almost identical with that disclosed in U.S. Patent 2007/0238790 A1. X-ray powder diffractogram on Figure 5 indicates the high crystallinity of cinacalcet HCl plain drug substance.

Figure 6 depicts the XRPD registered on starting gamma-cyclodextrin hydrate before binding cinacalcet by inclusion.

Figure 7 shows an XRPD of the cinacalcet-cyclodextrin inclusion complex as received in Example 1. After formation of a "genuine" inclusion complex between cinacalcet and gamma-cyclodextrin hydrate, the new solid products have a completely different X-ray pattern. This X-ray pattern does not resemble either on the Cinacalcet.HCl or the gamma-cyclodextrin hydrate crystalline properties indicating the formation of a novel glassy-amorphous solid phase.

Example 6:

***In vitro* Dissolution Profile of the Inventive Complex**

The *in vitro* dissolution profile of the inclusion complex as received in Example 1 is determined and shown in Figure 8. For comparative reasons the *in vitro* dissolution profile of pure crystalline cinacalcet and of a physical mixture of cinacalcet and hydroxypropyl-beta-cyclodextrin (obtained as described in WO 2008/064202, wherein the weight ratio of cinacalcet and hydroxypropyl-beta-cyclodextrin is 1 : 1) is also shown in Figure 8.

In Figure 8, the inclusion complex of the present invention is marked as "cinacalcet/GCD".

The *in vitro* dissolution testing was performed under the non-pharmacopoeial conditions, as the cinacalcet/cyclodextrins inclusion complexes cannot be regarded as finished pharmaceutical products. We used the so-called dispersed amount method as follows:

The input amount of tested cinacalcet cyclodextrins complex according to Example 1 was 80.5 mg.

Dissolution medium: pH 7.2 phosphate buffer, according to McIlvaine (containing citric acid and Na_2HPO_4) the dissolution volume was 50 mL.

Temperature: 37 °C

Stirring rate: 80 rotations per minute, paddle

5 Sampling time intervals were 1, 5, 10, 20, 30, 40, 50, 60 minutes, respectively.

The withdrawn samples were filtered across a 0.45 μm membrane and assayed for dissolved cinacalcet by UV spectrophotometry.

10 **Example 7:**

Tablets Comprising a Cinacalcet/Gamma-Cyclodextrin Inclusion Complex

The following composition was used for the production of tablets:

15

Cinacalcet-HCl/Gamma-Cyclodextrin inclusion complex ^{*1)}	273 mg
Microcrystalline cellulose	60 mg
Crospovidone	50 mg
Sodium stearyl fumarate	2.0 mg

20

^{*1)} comprising 30 mg cinacalcet and preferably prepared according to Example 2

The cinacalcet inclusion complex of the present invention, microcrystalline cellulose and crospovidone were blended in a free fall mixer Turbula® TB10 for 10 minutes.

25

Sodium stearyl fumarate was sieved over a 0.3 mm sieve and added to the blended mixture. Subsequently, blending was continued for further 5 minutes. The resulting mixture was compressed to tablets on a Korsch® EKO, wherein a compaction force of 4.5 kN was applied. The resulting tablets showed a hardness of 100 N.

30

Example 8:

***In vitro* Dissolution Profile of the Inventive Tablets**

The dissolution properties of tablets obtained from Example 7 were determined. The results have been benchmarked with currently marketed Mimpara® tablets (30 mg) as reference. The dissolution test was carried out according to USP, paddle (0.1 N HCl, pH 1.2, 75 rpm, 37 °C).

40

Table 1

time [min]	Example 7 mean dissolved [%]	SD	Reference mean dissolved [%]	SD
0	0.0	0.0	0.0	0.0
5	85.3	2.6	55.6	2.2
10	92.8	0.7	77.8	1.5
15	93.1	0.7	88.1	1.7

SD = standard deviation

Claims

1. Inclusion complex comprising cyclodextrin and cinacalcet, wherein the molar
5 ratio of cyclodextrin to cinacalcet is from 1 : 1 to 3 : 1.
2. Inclusion complex according to claim 1, wherein cyclodextrin is an eight
glucose-membered cyclo-octaamylose.
- 10 3. Inclusion complex comprising gamma-cyclodextrin and cinacalcet.
4. Inclusion complex comprising cyclodextrin and cinacalcet, wherein in a Raman
spectrum the characteristic bond of crystalline cinacalcet at a wave number of about
1586 cm^{-1} is shifted to lower wave numbers in the inclusion complex.
15
5. Inclusion complex according to claim 4, wherein the shift to lower wave
numbers is at least 3 cm^{-1} .
6. Inclusion complex according to any one of claims 1 to 5, wherein the molar
20 ratio of cyclodextrin to cinacalcet is about 2 : 1.
7. Inclusion complex according to any one of claims 1 to 6, wherein the residual
water content is less than 5 wt.-%.
- 25 8. Inclusion complex according to claim 7, wherein the water content does not
increase more than 10 % during a storage period of 3 months at a temperature of
25 °C and a humidity of 60 %.
9. Inclusion complex comprising cyclodextrin and cinacalcet according to anyone
30 of claims 1 to 8, forming a solid phase having liquid crystalline properties.
10. Inclusion complex according to any one of claims 1 to 10 being essentially free
of crystalline and amorphous cinacalcet.
- 35 11. Process for producing an inclusion complex comprising cinacalcet and
cyclodextrin comprising the steps of
 - a) wetting and/or dispersing cyclodextrin in a solvent;
 - b) adding cinacalcet, wherein the molar ratio of cyclodextrin to
40 cinacalcet is preferably from 1 : 1 to 5 : 1;
 - c) subjecting the mixture resulting from step (b) to a mechanical treatment; and

d) removing the solvent from the reaction mixture, preferably by freeze-drying or spray-drying.

12. An inclusion complex obtainable by a process according to claim 11.

5

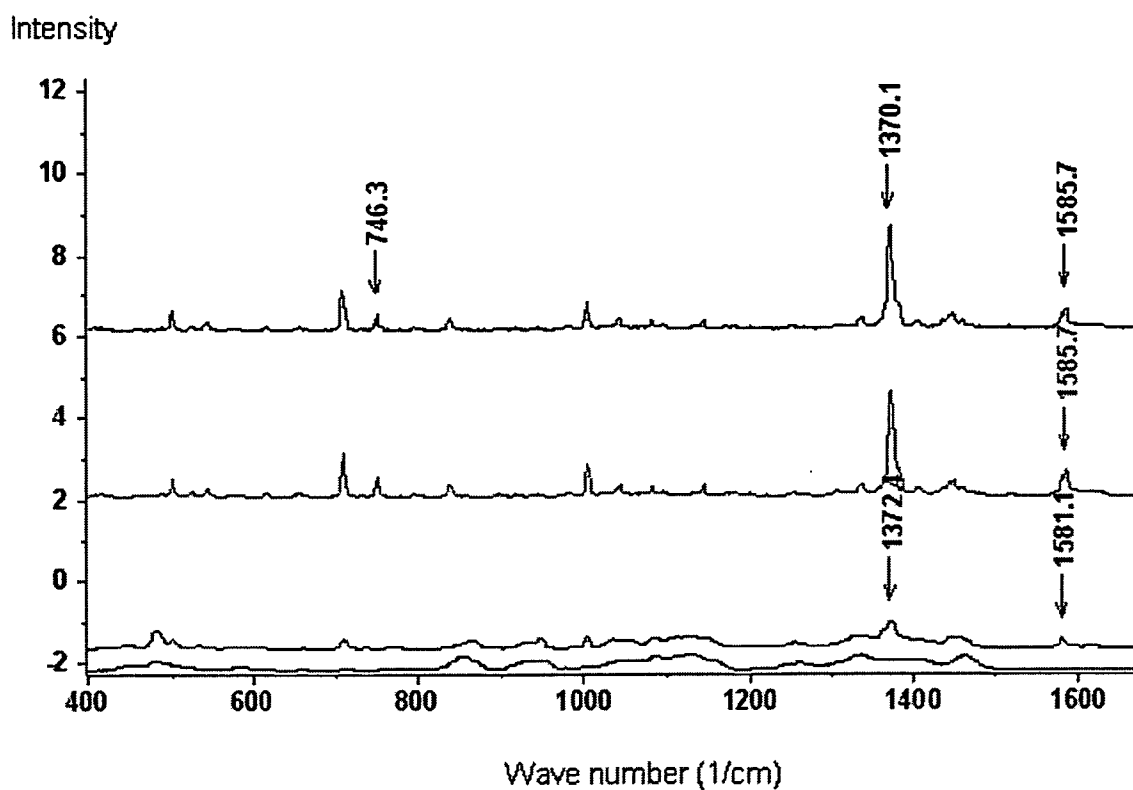
13. Pharmaceutical formulation comprising a cinacalcet inclusion complex according to any of claims 1 to 10 or 12 and one or more pharmaceutical excipients.

14. Pharmaceutical formulation according to claim 13 being essentially free of crystalline and amorphous cinacalcet.

10

15. Use of gamma-cyclodextrin for producing a cinacalcet-containing pharmaceutical formulation.

15

Figure 1:

5

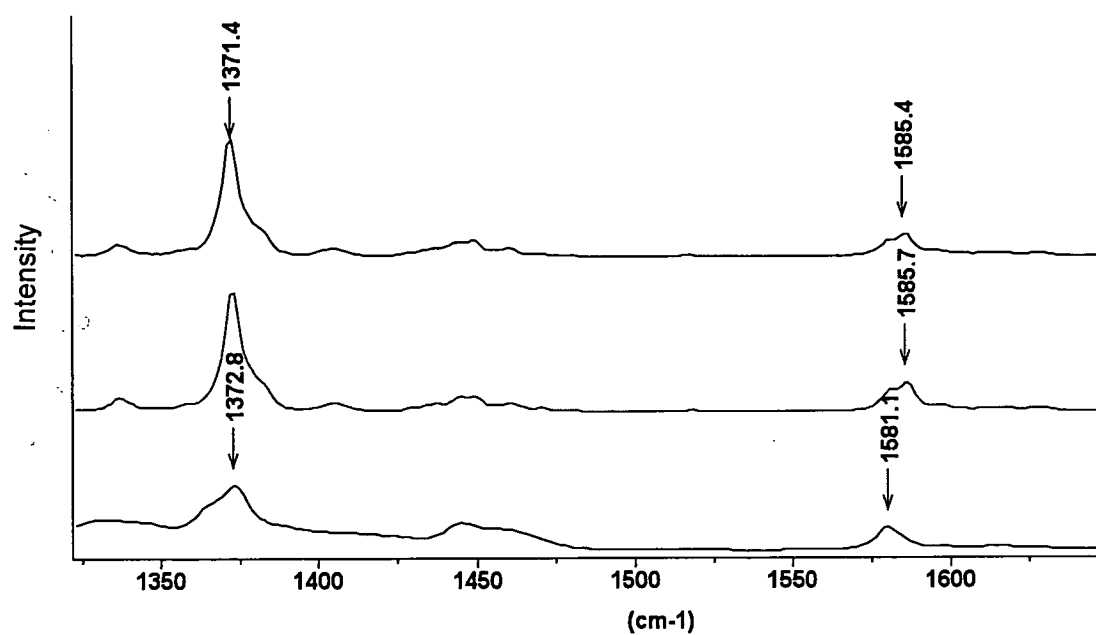
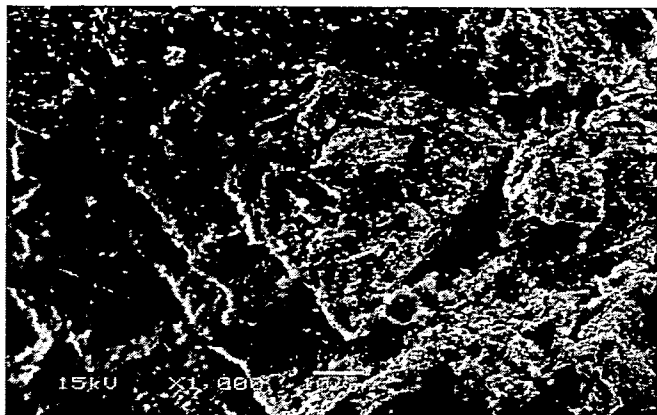
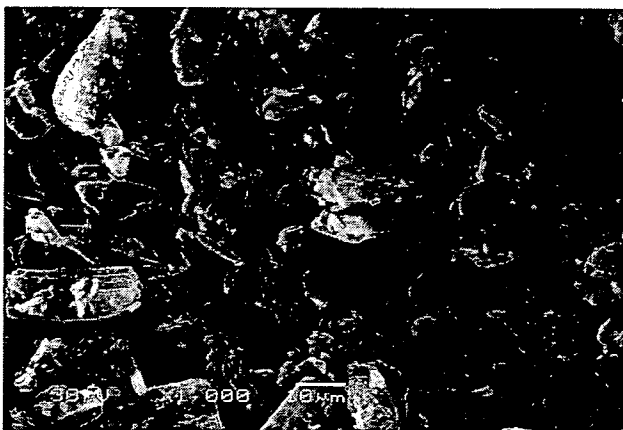
Figure 1a

Figure 2



5

Figure 3



10 **Figure 4**

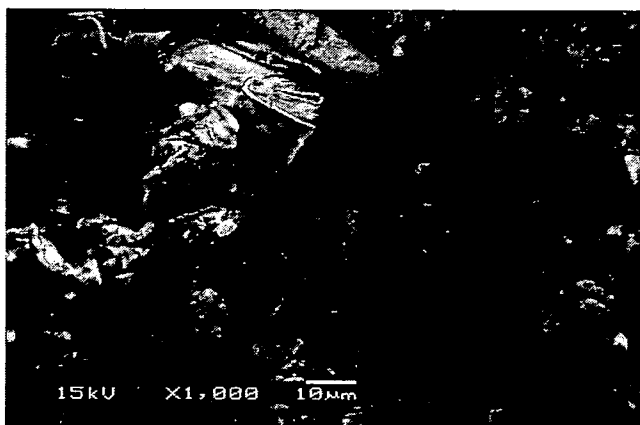


Figure 5

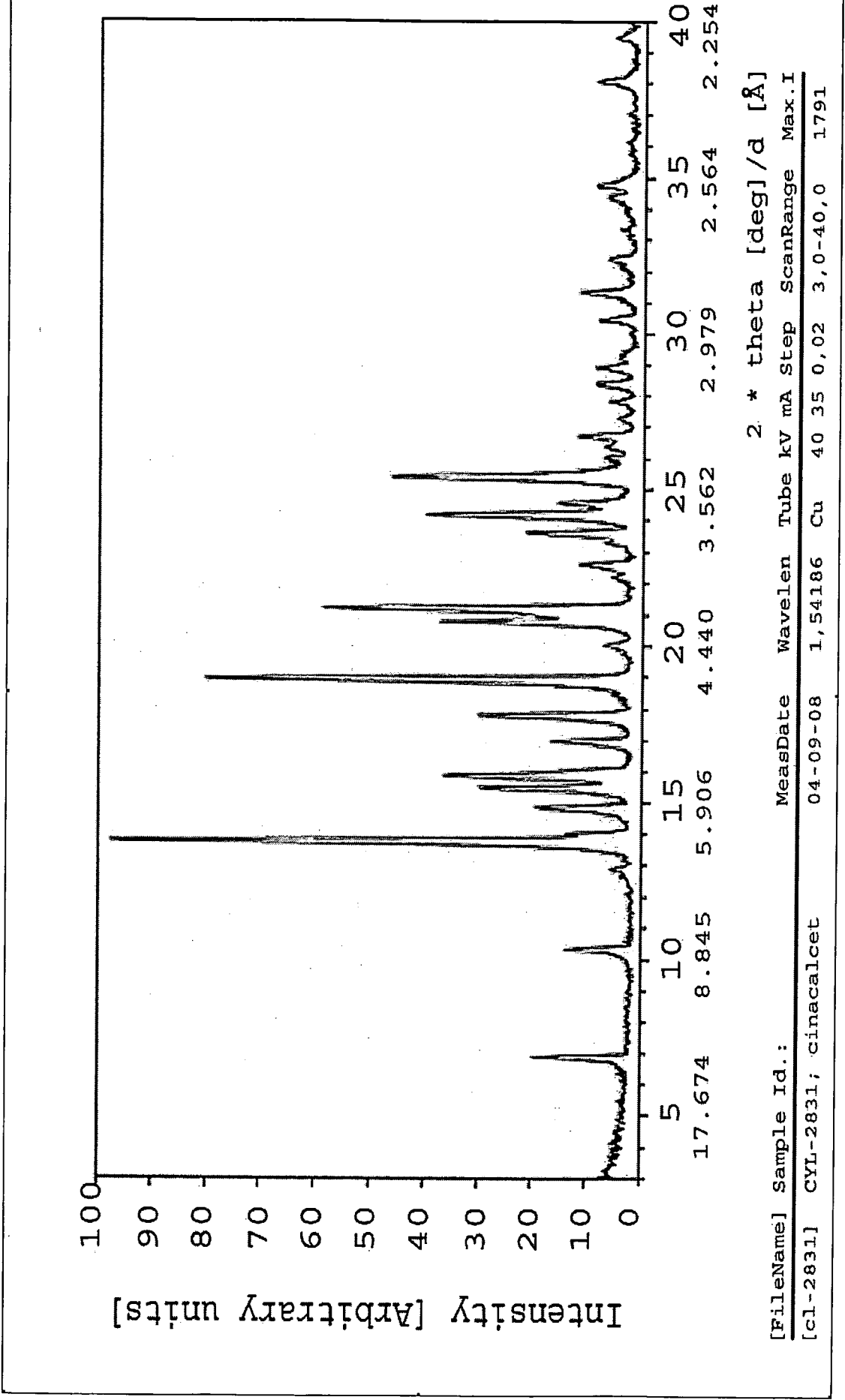


Figure 6

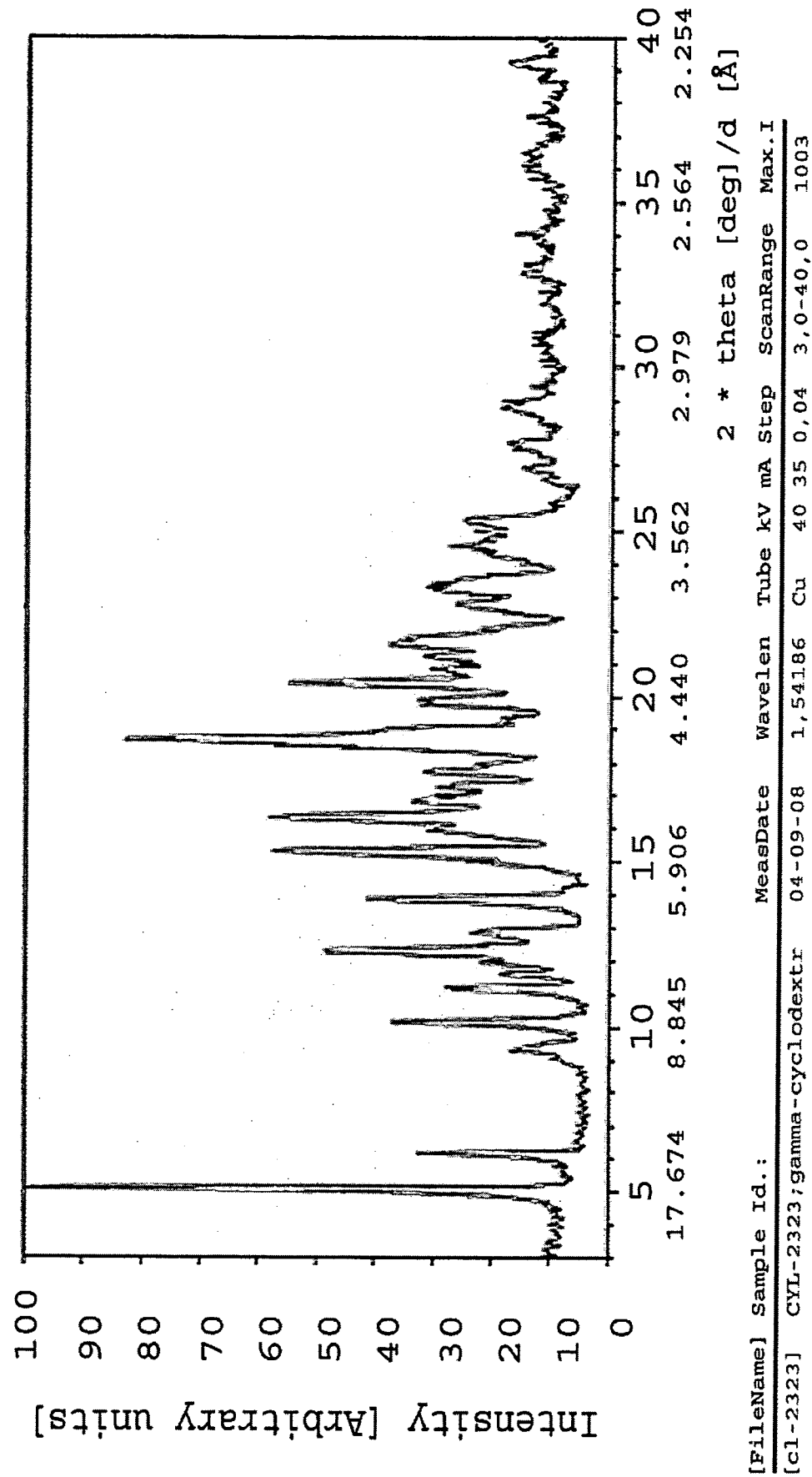


Figure 7

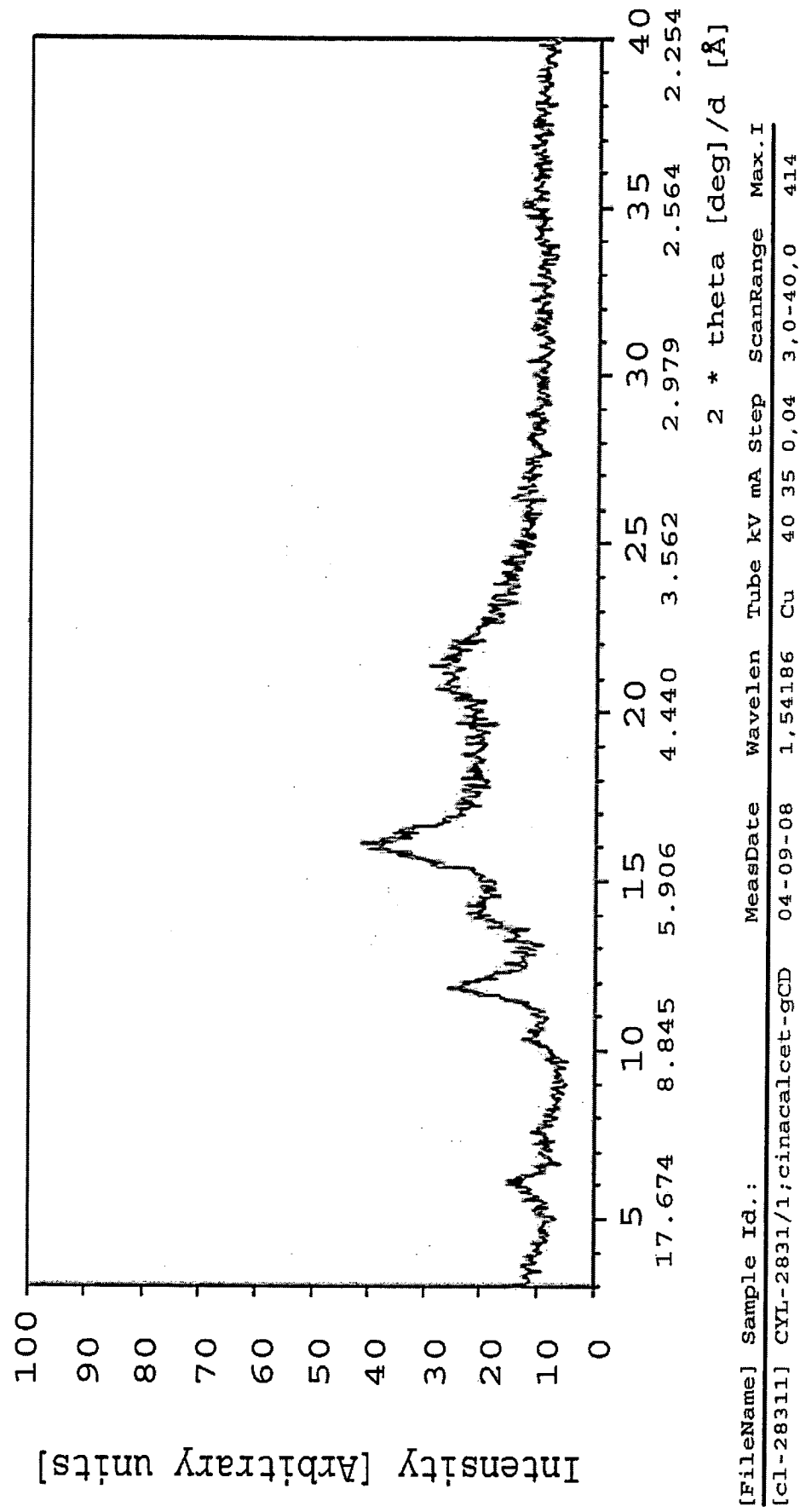
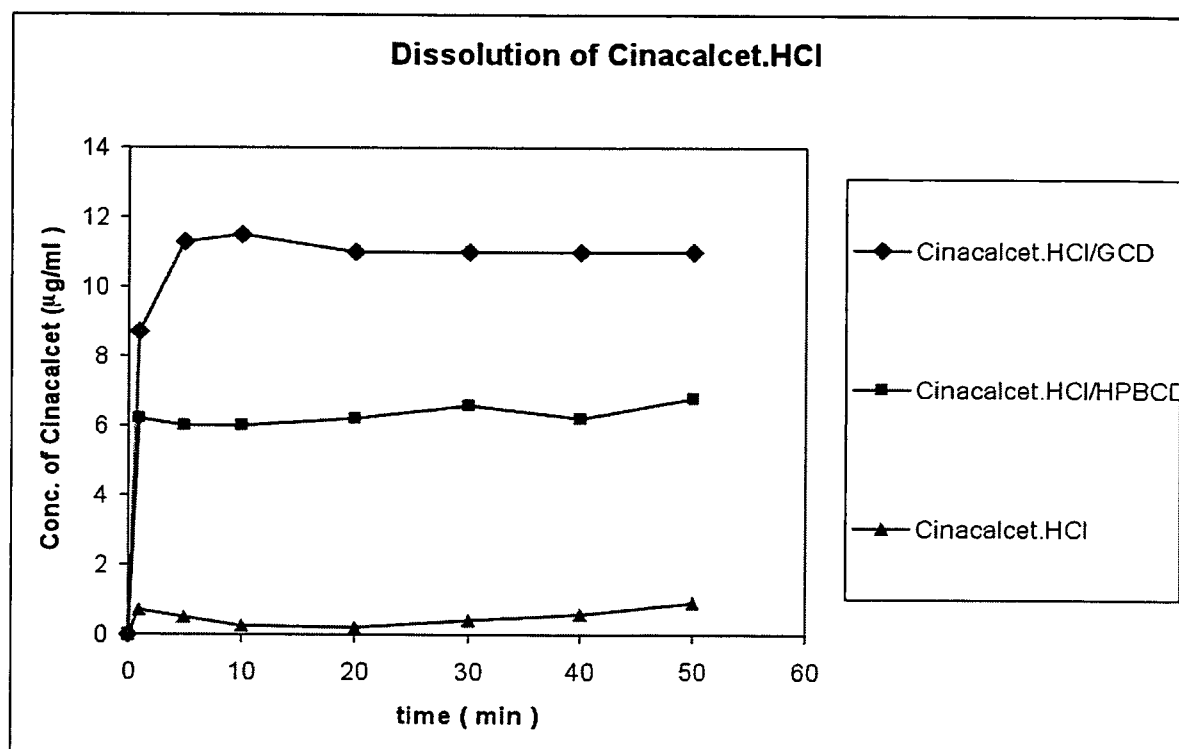


Figure 8:



5

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/000418

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/19 A61K47/48 A61K31/137 A61P5/14
 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 practical, search terms used)

EPO-Internal, WPI Data, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/064202 A (REDDY S LABORTORIES LTD DR [IN]; REDDYS LAB INC DR [US]; SNEHALATHA MO) 29 May 2008 (2008-05-29) cited in the application page 7, line 12 - page 8, line 34 example 1	1-15
A	WO 2008/000422 A (SANDOZ AG [CH]; LUDESCHER JOHANNES [AT]; GRIESSER ULRICH [AT]; BRAUN D) 3 January 2008 (2008-01-03) page 2, line 26 page 3, line 36 ----- -/--	1-15



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 document 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

12 May 2010

Date of mailing of the international search report

31/05/2010

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

S. von Eggelkraut-G.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/000418

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHMID G, DUCHENE D (ED): "Preparation and Application of Gamma-Cyclodextrin" in "New Trends in Cyclodextrins and Derivatives" 1 January 1991 (1991-01-01), EDITION DE SANTE , PARIS , XP008107760 page 27 - page 54 page 37, paragraph 4 - last paragraph -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/000418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008064202 A	29-05-2008	NONE	
WO 2008000422 A	03-01-2008	EP 2069285 A1 US 2009258949 A1	17-06-2009 15-10-2009