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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 April 2016 (21.04.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/059192 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/277* (2006.01)
A61K 31/165 (2006.01)

(21) International Application Number:
PCT/EP2015/073957

(22) International Filing Date:
16 October 2015 (16.10.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
14189341.2 17 October 2014 (17.10.2014) EP

(71) Applicant: **RATIOPHARM GMBH** [DE/DE]; Graf-Arco-Straße 3, 89079 Ulm (DE).

(72) Inventors: **RIMKUS, Katrin**; Tannenstrasse 9, 82049 Pullach (DE). **HOLFINGER, Konstantin**; Seumestrasse 11, 81379 Munich (DE). **MIKA, Hans-Jürgen**; Am Rehsprung 20, 53229 Bonn (DE).

(74) Agent: **AECHTER, Bernd**; Ter Meer Steinmeister & Partner Patentanwälte mbB, Nymphenburger Straße 4, 80335 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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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.

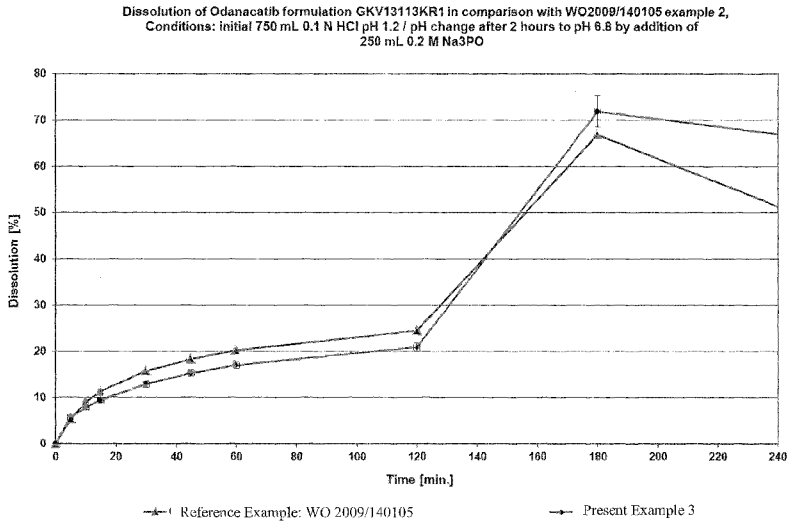
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,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

Published:

— *with international search report (Art. 21(3))*

(54) Title: COMPOSITION COMPRISING ODANACATIB

Figure 1



(57) Abstract: The invention essentially relates to a pharmaceutical composition comprising an agglomerate of odanacatib and a releaser modifying polymer and further excipient, and a process of preparing such a pharmaceutical composition.

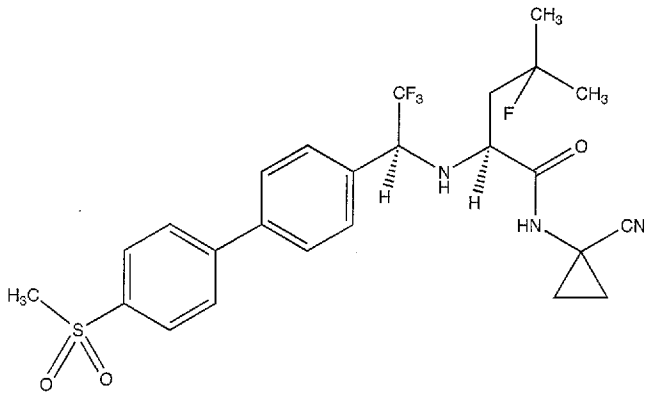
WO 2016/059192 A1

Composition Comprising Odanacatib

Background of the invention

The invention essentially relates to a pharmaceutical composition comprising an agglomerate of odanacatib and a release modifying polymer and further excipient and a process of preparing such a pharmaceutical composition.

"Odanacatib" is reported to be the INN name of (2*S*)-*N*-(1-cyanocyclopropyl)-4-fluoro-4-methyl-2-[[(1*S*)-2,2,2-trifluoro-1-[4-(4-methylsulfonylphenyl)phenyl]ethyl]-amino]-pentanamid and is characterized by the following chemical formula (I):



formula (I)

Odanacatib is considered to selectively inhibit the enzyme cathepsin, in particular cathepsin K. Cathepsin K, a lysosomal cysteine protease, is expressed by osteoclasts during the process of bone resorption and acts as the major collagenase, responsible for the degradation of the organic bone matrix during the bone remodelling process. Odanacatib is reported to increase the bone mineral density and to reduce bone turnover markers, in particular in post-menopausal women with low bone mineral density. For this purpose, odanacatib is suggested to be used in the treatment of osteoporosis and bone metastasis, in particular in the treatment of post-menopausal osteoporosis.

The synthesis of odanacatib has previously been described, for example in WO 03/075836 and WO 2006/017455. However, these documents seem to describe processes for the generation of the crystalline form of odanacatib, which is described as being poorly soluble. For example, WO 2008/106059 allegedly describes formulations of odanacatib having an undesirable slow release profile. In order to overcome the poor aqueous solubility, WO 2013/025449 suggests amorphous dispersions of odanacatib (referred to therein as N1-(l-cyanocyclopropyl)-4-fluoro-N2-{(1S)-2,2,2-trifluoro-1-[4'-methylsulfonyl]-1,1'-biphenyl-4-yl}ethyl}-L-leucinamide).

Further, WO 2009/140105 is related to a tablet containing odanacatib, showing suitable dissolution properties, wherein the tablets are produced by spray-drying for converting the active agent into an amorphous form and subsequent compaction. However, the teaching of WO 2009/140105 only results in tablets having a low drug load of about 6.5 wt.%. In order to generate for example a tablet with a content of 50 mg of odanacatib, such tablet as described in WO 2009/140105 would have a weight of about 750 mg. Thus, the tablet would be undesirable large in size and, therefore, would be difficult to swallow. In particular, elderly persons, like post-menopausal women, might show poor patient compliance due to the size of the tablet.

Additionally, the above mentioned tablets seem to be still improvable with regard to the stability of the active pharmaceutical ingredient.

Hence, it was an object of the present invention to overcome the above problems.

An object of the present invention is to provide a pharmaceutical composition, preferably in form of a tablet, containing odanacatib with dissolution properties similar or equal to the ones of the tablets as described in WO 2009/140105. Preferably the dissolution profile should be so similar as possible to the above tablets of WO 2009/140105 that the bioequivalent criteria set forth by the authorities like FDA or EMEA are met.

Further, a pharmaceutical composition having a high drug load and a reduced total weight compared to the tablets according to WO 2009/140105 should be provided.

Additionally, the pharmaceutical composition should have a suitable size, which enables administering an effective amount (e.g. 25, 50, or 100 mg per dosage form) to patients, preferably mammals, e.g. post-menopausal women.

For many countries the WHO estimates the patient compliance to be about 50%. Good patient compliance is related to improved efficiency of the medial treatment, while inadequate patient compliance is related to an enhanced mortality rate.

"Maßnahmen zur Verbesserung der Compliance bzw. Adherence in der Arzneimitteltherapie mit Hinblick auf den Therapieerfolg" Vitali Gorenoi, Matthias P. Schönermark, Anja Hagen, Bundesministerium für Gesundheit" refers to different procedures in order to improve the patient compliance. These procedures can, for example, be directed to

- indication directed treatment; for example, indication and treatment comorbidities which negatively influence the patient compliance, such as depression and gastritis,
- therapy directed treatment, for example selection of an adequate dosage form, selection of an adequate packaging, reduction of the daily administration (in amount ad number) and the development of medicaments with a reduced side effect profile.

Further, it can be referred to : "Difficult to swallow: patient preferences for alternative valproate pharmaceutical formulations" by Monali Bhosle, Joshua S Benner, Mitch DeKoven, and Jeff Shelton.

"In this study, users of VP indicated that they would prefer a formulation that is easier to swallow, even if it needed to be taken twice per day. This study provides preliminary data upon which further investigation should be based...

When presented conceptually with a choice between taking their current VP tablet once daily and taking a smaller, soft gel capsule ('Product X') with equivalent safety and effectiveness twice daily, the majority (82.8%, n = 331) preferred the soft gel capsule medication. An even larger majority of respondents (85.3%, n = 341) indicated preferring the soft gel medication when asked, 'If both medications were available when you first began taking VP, which would you have preferred".

Further, a pharmaceutical composition should be provided which has good tableting properties and, moreover, has superior high content uniformity, superior friability, superior hardness and/or superior stability with regard to the state of the art.

Summary of the invention

According to the present invention, the above objectives preferably are achieved by specific compositions, comprising an agglomerate containing odanacatib and release modifying polymer, which preferably is pH-dependent, as well as specific amounts of filler and disintegrant. Furthermore, the above drawbacks can be overcome by a process for producing said compositions.

Thus, the subject of the present invention is a pharmaceutical composition comprising

(a) agglomerate containing (a1) odanacatib and (a2) a compound selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropylmethylcelluose acetate phthalate, hydroxypropyl-methylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures thereof,

(b) 0 – 30 wt. % filler,

(c) 15 - 70 wt. % disintegrant.

It was found that the present pharmaceutical composition provides a dissolution profile similar to the formulations described in WO 2009/14010.

Further a pharmaceutical composition, preferably in form of a tablet, can be provided, which has an adequate size and allows effective treatment, including excellent patient compliance. In addition, it was found that the present composition can be surprisingly stable over a long period of time, even under common stress conditions. Finally, the present composition has excellent properties, such as advantageous friability and/or hardness.

A further subject of the present invention is a process for manufacturing the pharmaceutical composition of the present invention, preferably in form of a modified release tablet. The process for manufacturing a pharmaceutical composition comprising the steps of

(i) dissolving components (a1) and (a2) in a solvent or a mixture of solvents,
(ii) removing the solvent or mixture of solvent to form an agglomerate (a),
(iii) mixing agglomerate (a) with optionally filler (b), disintegrant (c) and optionally excipients (d),
(iv) optionally dry-granulating the mixture of step (iii),
(v) optionally adding further excipient (d) to the mixture of step (iii) or the granulates of step (iv),
(vi) processing the composition of step (v) into a dosage form, and
(vii) optionally film-coating the dosage form.

Preferably, in step (iii) no filler is added.

Detailed Description of the invention

In the following, explanations with regard to the pharmaceutical composition of the present invention are given. These explanations can also apply to the processes for manufacturing the pharmaceutical dosage form of the present invention and to the use of the present invention.

The agglomerate (a) contains the compounds (a1) and (a2).

In the context of this invention, compound (a1) is odanacatib, which is represented by the above Formula (I). Further, compound (a1) may refer to pharmaceutically acceptable salts, hydrates, solvates, polymorphs, stereoisomers, like enantiomers, and mixtures thereof. For example, the invention also refers to enantiomers of pharmaceutical acceptable salts of the compound according to Formula (I), to solvates of salts or hydrates of polymorphs, or the like.

In a preferred embodiment of the invention odanacatib is referred to as odanacatib in form of the free base.

In an alternative preferred embodiment odanacatib is referred to pharmaceutically acceptable salts thereof, preferably pharmaceutically acceptable acid addition salts. The acids, which can be used to prepare the pharmaceutically acceptable acid addition salts, are preferably those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

In a particularly preferred embodiment of the invention, the pharmaceutical composition comprises odanacatib as the sole pharmaceutically active agent. In another preferred embodiment the pharmaceutical composition of the invention can comprise odanacatib in combination with further pharmaceutically active agent(s).

In a preferred embodiment, the pharmaceutical composition of the present invention can comprise 5 to 25 wt.% odanacatib, preferably 7 to 20 wt.%, more preferably 8 to 17 wt.% and still more preferably 9 to 15 wt.% odanacatib, based upon the total weight of the pharmaceutical composition and based on the weight of odanacatib in form of the free base, i.e. as shown in formula (I) above.

In a preferred embodiment, the pharmaceutical composition of the present invention can comprise 25 to 150 mg, more preferably 30 to 120 mg odanacatib. In particular, the present composition can comprise 25 mg odanacatib. Alternatively particularly preferred, the present composition can comprise 50 mg odanacatib. Alternatively particularly preferred, the present composition can comprise 100 mg odanacatib.

Compound (a2) preferably is a release modifying polymer, which more preferably is pH-dependent. It can be regarded as partially esterified derivative of hydroxypropyl methyl cellulose, wherein the acid with which the esterification has been conducted and the degree of esterified groups depend on the corresponding substance.

Compound (a2) is selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropylmethylcelluose acetate phthalate, hydroxyproylmethylcellulose acetate trimellitate, hydroxypropyl-methylcelluose acetate succinate and mixtures thereof.

In a preferred embodiment the pharmaceutical composition of the present invention can preferably comprise 20 to 80 wt.%, more preferably 35 to 75 wt.% and more preferably 40 to 70 wt.% compound (a2), based upon the total weight of the pharmaceutical composition.

In the present agglomerate (a) the compound (a2) can preferably be described as providing a scaffold (matrix) for embedding the active ingredient and to form a physical barrier, which hinders the odanacatib from being released immediately from the dosage form. Thus, the compound (a2) material may have the effect that the active ingredient can be released from the scaffold in a continuous manner. The release of the drug from the matrix can be dissolution-controlled as well as diffusion-controlled mechanisms. In this first embodiment the compound (a2) can function as matrix-forming material.

Compound (a2) can preferably be suitable as release-controlling agent.

Usually, compound (a2) is a substance, which is able to provide modified-release properties, preferably due to the limited solubility, more preferably due to the limited solubility in aqueous conditions at pH 5.0. Preferably, the compound (a2) can have a water solubility of less than 33 mg/l at a temperature of 25 °C, at a pH of 5.0, more preferably of less than 22 mg/l, still more preferably of less than 11 mg/l, especially from 0.01 to 5 mg/l. The water solubility can be determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6. The pH-value can be determined according to Ph. Eur. 6.0, Chapter 2.2.3. The pH value of the aqueous medium usually can be achieved by addition of HCl (or NaOH), if necessary.

Within the present application, the term "modified release" can generally be used as defined by the USP. Preferably, modified-release dosage forms can be those whose drug-release characteristics accomplish therapeutic or convenience objectives not offered by immediate release forms. Generally, immediate-release (IR) forms are reported to release at least 70 % of the drug within 1 hour or less. The term "modified release" can comprise delayed release, prolonged release, sustained release, extended release and/or controlled release.

Delayed release is reported to indicate that odanacatib is not released immediately after administration but at a later time, preferably less than 10 % are released within two hours after administration.

Prolonged release is reported to indicate that odanacatib is provided for absorption over a longer period of time than in case of IR forms, preferably for about 2 to 24 hours, in particular for 3 to 12 hours.

Sustained release is reported to indicate an initial release of odanacatib, sufficient to provide a therapeutic dose soon after administration, preferably within two hours after administration, and then a gradual release after an extended period of time, preferably for about 3 to 18 hours, in particular for 4 to 8 hours.

Extended release is reported to indicate an odanacatib release, so that plasma concentrations are maintained at a therapeutic level for a time period of between 6 and 36 hours, preferably between 8 and 24 hours.

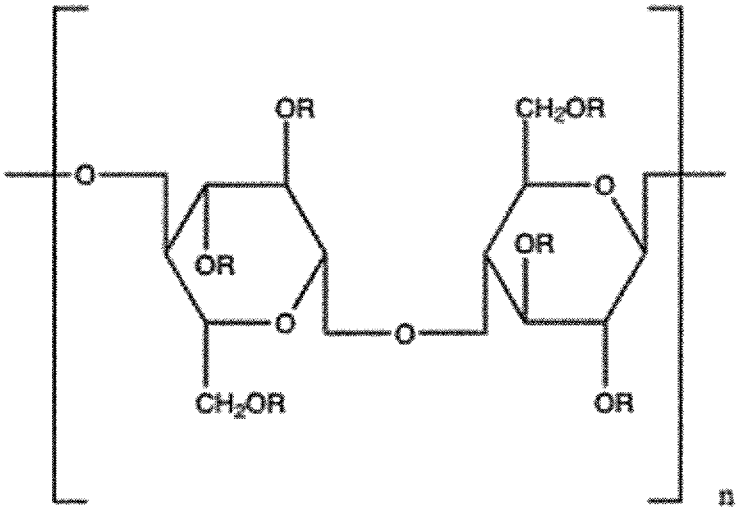
Controlled-release dosage forms are reported to release odanacatib at a constant rate and provide plasma concentrations that remain essentially invariant within a certain time period.

In a preferred embodiment, the pharmaceutical composition of the present invention can be a pharmaceutical composition showing sustained release properties.

Within this application the release profiles are generally determined according to USP 31-NF26 release method, apparatus 2 (paddles) with 50 rpm. The measurements are carried out at 37°C, in 750 ml 0.1 N HCl (pH 1.2); pH change after 2 hours to pH 6.8 by addition of 250 ml 0.2M Na_3PO_4.

It is further preferred that the weight ratio of odanacatib (a1) and compound (a2) can be from 1 : 3 to 1: 10, more preferably from 1 : 3.5 to 1 : 8, in particular from 1 : 4 to 1 : 7.

In a particularly preferred embodiment of the present invention, compound (a2) can be hydroxypropylmethylcellulose acetate succinate, which is referred to in the following as HPMC-AS. HPMC-AS is reported to be a partially esterified derivate of HPMC and to have the following chemical structure represented by formula (II),



formula (II),

wherein R is selected form H, CH_3, $CH_2CH(CH_3)OH$, $COCH_3$, $COCH_2CH_2COOH$, $CH_2CH(CH_3)OCOCH_3$ and $CH_2CH(CH_3)OCOCH_2CH_2COOH$. In a preferred embodiment HPMC-AS can contain acetyl groups from 2 to 16%, more preferably from 4 to 14%, in particular from 5 to13 %. In a preferred embodiment HPMC-AS can contain succinoyl groups from 4 to 28%, more preferably from 5 to 20%, in particular from 6 to 17 %.

The ratio of acetyl to succinoyl substitution can be from 8 : 15 to 13 : 5. It is particularly preferred that the ratio of acetyl to succinoyl substitution can be from 11 : 7 to 13 : 5.

As indicated above, HPMC-AS can preferably be described as providing a scaffold (matrix) for embedding the active ingredient and to form a physical barrier, which hinders the active ingredient from being immediately released from the dosage form. Thus, HPMC-AS may have the effect that the active ingredient can be released from the scaffold in a continuous manner. Release of the drug from the matrix can be dissolution-controlled as well as diffusion-controlled mechanisms. In this embodiment HPMC-AS can function as matrix-forming material.

In a preferred embodiment, HPMC-AS can have a weight average molecular weight ranging from 5000 to 300000 g/mol, preferably from 8000 to 150000 g/mol, more preferably from 10000 to 100000 g/mol. Furthermore, a 2 % w/w solution of HPMC-

AS in water at pH 7.0 preferably can have a viscosity of more than 2 mPas, more preferably of more than 5 mPas, particularly more than 8 mPas and up to 850 mPas when measured at 25 °C. The viscosity can be determined according to Ph. Eur. 6.0, Chapter 2.2.10. In the above definition the term "solution" may also refer to a partial solution (in case that the polymer does not dissolve completely in the solution). The weight average molecular weight can preferably be determined by gel electrophoresis.

The present pharmaceutical composition may further comprise filler (b). Fillers can be used to increase the bulk volume and weight of a low-dose drug to a limit at which a pharmaceutical dosage can be formed. Fillers may fulfil several requirements, such as being chemically inert, non-hygroscopic and biocompatible. Examples of fillers are microcrystalline cellulose, dextrose, lactose, sucrose, glucose, mannitol, calcium carbonate, cellulose and others.

In the present invention, filler (b) can be present in amounts of 0 to 30 wt.%, preferably of 0 to 20 wt.%, in particular of 0 to 5 wt.% based on the total weight of the pharmaceutical composition. In an alternative, particularly preferred embodiment the present composition does not comprise (b) filler. In other words, in a preferred embodiment the present composition is filler free.

The pharmaceutical composition of the present invention further comprises disintegrant (c). Disintegrants are reported to be compounds which can enhance the ability of the intermediate to break into smaller fragments when in contact with a liquid, preferably water.

Preferred disintegrants are cross-linked carboxymethyl cellulose sodium (croscarmellose sodium) cross-linked polyvinylpyrrolidone (for example Kollidon® Cl), sodium starch glycolate (for example Explotab®), swelling polysaccharide, for example soy polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, protein, for example formaldehyde-casein, sodium bicarbonate or mixtures thereof. In a more preferred embodiment the disintegrant is croscarmellose sodium. In an alternatively more preferred embodiment the disintegrant is cross-linked polyvinylpyrrolidone. In a

further, alternatively more preferred embodiment the disintegrant is a mixture of croscarmellose sodium and cross-linked polyvinylpyrrolidone.

Disintegrant (c) can be present in amounts of 15 to 70 wt.%. In a preferred embodiment, the disintegrant can be present from 17 to 60 wt.%, more preferably from 18 to 55 wt.%, in particular from 20 to 52 wt.% or 25 to 50 wt.%, based on the total weight of the pharmaceutical composition of the present invention.

The pharmaceutical composition of the present invention can further comprise at least one excipient (d), selected from lubricants (d1), surfactants (d2), glidants (d3), anti-sticking agents (d4), plasticizers (d5) and mixtures thereof.

The function of lubricants (d1) is reported to ensure that tablet formation and ejection can occur with low friction between the solid and the wall. The lubricant is preferably a stearate or fatty acid, more preferably an earth alkali metal stearate, such as magnesium stearate. The lubricant can be present in an amount of 0 to 3 wt.%, preferably of 0.1 to 2.7 wt.%, more preferably of 0.25 to 2.3 wt.%, based on the total weight of the pharmaceutical composition. Lubricants generally can increase the powder flowability.

In a preferred embodiment of this invention, a lubricant (d1) may be used. In a preferred embodiment of the present invention magnesium stearate can be used as lubricant (d1).

Surfactants (d2) can be regarded as substances lowering the interfacial tension between two phases, thus enabling or supporting the formation of dispersions or working as solubilizer. Common surfactants are alkylsulfates (for example sodium lauryl sulfate), alkyltrimethylammonium salts, alcohol ethoxylates and the like. Surfactants can be used in an amount of 0 to 5wt.%, preferably of 0.25 to 4.25 wt.%, more preferred 0.5 to 3.5wt.%, based on the total weight of the pharmaceutical composition.

In a preferred embodiment of this invention, a surfactant (d2) may be used. In a preferred embodiment of the present invention sodium lauryl sulfate can be used as surfactant (d2).

Glidants (d3) are reported to be substances used to improve the flowability. Examples of glidants are talc and fumed or colloidal silica (for example Aerosil®). Preferably, the glidant (d3) can be present in an amount of 0 to 2.5 wt.%, preferably 0.1 to 2.25 wt.%, more preferably 0.25 to 2.05 wt.%, based on the total weight of the pharmaceutical composition. In a preferred embodiment of the present invention silicon dioxide can be used as a glidant (d3). Preferably, the silicon dioxide has a specific surface area of 50 to 400 m^2/g, measured by gas adsorption according to Ph. Eur. 6.0, Chapter 2.9.26, multipoint method, volumetric determination.

In a preferred embodiment of this invention, a lubricant (d3) may be used. In a preferred embodiment of the present invention fumed silica (Carb o Sil) can be used as glidant (d3).

Generally, anti-sticking agents (d4) are reported to be substances to prevent the adhesion of the tableting mass to the compression mould. Further anti-sticking agents may increase the brightness of a tablet. The anti-sticking agent can be for example talcum, magnesium stearate, paraffin and the like. Further, the anti sticking agent (d5) may be present in amounts of 0 to 5wt.%, based on the total weight of the pharmaceutical composition.

Plasticizers (d5) usually are reported to be compounds capable of lowering the glass transition temperature (T_g) of a non-erodible material, preferably of lowering T_g from 1 to 50 °C. Plasticizers (d5) can be low molecular weight compounds (having a molecular weight of 50 to 500 g/mol) and can comprise at least one hydrophilic group. Examples of suitable plasticizers are dibutyl sebacetate (DBS), Myvacet® (acetylated monoglycerides), triacetin (GTA), citric acid esters, like acetyltriethyl citrate (ATEC) or triethyl citrate (TEC), propylene glycol, dibutyl phthalate, diethyl phthalate, or mixtures thereof.

Regarding the above-mentioned pharmaceutically acceptable excipients, the application generally refers to "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", edited by H. P. Fiedler, 5th Edition, Editio Cantor Verlag, 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.

In this regard it is generally noted that due to the nature of pharmaceutical excipients, it cannot be excluded that a certain compound meets the requirements of more than one of the components (d1) to (d5). However, to enable an unambiguous distinction, it is preferred in the present application that one and the same pharmaceutical compound be only used as one of the compounds (d1) to (d5). For example, if magnesium stearate is used as lubricant (d1) it is not additionally used as anti-sticking agent (d4), even though magnesium stearate also exhibits a certain anti-sticking effect.

Another preferred embodiment the pharmaceutical composition of the present invention is in the form of a tablet, preferably a matrix tablet.

The present pharmaceutical composition preferably comprises

- 5 to 20 wt.% odanacatib, preferably 8 to 17 wt.% odanacatib, more preferably 9 to 15 wt.% odanacatib (a1),
- 20 to 80 wt.% of compound (a2), preferably 35 to 75 wt.% of compound (a2), more preferably 40 to 70 wt.% of compound (a2), wherein compound (a2) is selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethyl-cellulose trimellitate, hydroxypropylmethylcelluose acetate phthalate, hydroxy-propylmethylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures thereof,
- 0 to 30 wt.% filler, preferably 0 to 20 wt.% filler, more preferably 0 to 5 wt.% filler (b), in particular, essentially filler free,
- 15 to 70 wt.% disintegrant, preferably 17 to 60 wt.% disintegrant, more preferably 18 to 55 wt.% disintegrant (c),
- 0 to 3 wt.% lubricant, preferably 0.1 to 2.7 wt.% lubricant, more preferably 0.25 to 2.3 wt.% lubricant (d1)
- 0 to 5 wt.% surfactant, preferably 0.25 to 4.25 wt.% surfactant, more preferably 0.5 to 3.5 wt.% surfactant (d2)

- 0 to 2.5 wt.% glidant, preferably 0.1 to 2.25 wt.% glidant, more preferably 0.25 to 2.05 wt.% glidant (d3),

wherein all weight percent are based on the total weight of the composition.

In a further preferred embodiment the composition of the present invention comprises

- (a1) 5 to 20 wt.% odanacatib,
- (a2) 20 to 80 wt.% of the compound selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropyl-methylcelluose acetate phthalate, hydroxyproylmethylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures therefrom,
- (b) 0 to 30 wt.% filler,
- (c) 15 to 70 wt.% disintegrant,
- (d1) 0 to 3 wt.% lubricant,
- (d2) 0 to 5 wt.% surfactant,
- (d3) 0 to 2.5 wt.% glidant.

In a preferred the composition is can be present in form of a tablet.

In a further preferred embodiment of the present invention the hardness of the tablet is from 40 to 350 N, more preferred from 50 to 325 N, still more preferred from 75 to 300 N, in particular from 85 to 275 N, wherein the hardness is measured according to Ph. Eur. 6.0, Chapter 2.9.8.

In addition, the tablets preferably can have a friability of less than 5%, particularly preferably less than 2%, especially less than 1%, in particular 0.5 to 0.9. The friability is determined in accordance with Ph. Eur., 7.7, chapter 2.9.7.

Further, the tablets of the invention preferably have a content uniformity, i.e. a content of active agent(s), which lies within the concentration of 90 to 110%, preferably of 95 to 105%, especially preferred of 98 to 102% of the average content of the active agents(s). The "content uniformity" is determined with a test in accordance with Ph. Eur., 6.0, Chapter 2.9.6. According to that test, the content of the active agents of each individual tablet out of 20 tablets must lie between 90 and 110%, preferably between 95 and 105%, especially between 98 and 102% of the average content of the active agents(s).

Therefore, the content of the active drugs in each tablet of the invention differs from the average content of the active agent by at most 10%, preferably by at most 5% and especially by at most 2%.

Hardness, friability and content uniformity are determined from an uncoated tablet.

In another preferred embodiment the tablet according the present invention is film-coated with a coating (e).

In the present invention, the following three types of film-coatings are possible

- film-coating without effecting the release of the active ingredient (preferred),
- gastric juice resistant film-coatings,
- retard coatings.

Film-coatings that do not affect the release of the active ingredient are preferred. In gastric juice resistant coatings the solubility depends on the pH of the surrounding. Retard coatings are usually non-soluble (preferably having a water-solubility at 25 °C of less than 10 mg/ml).

Generally, film-coatings can be prepared by using cellulose derivatives, poly(meth)-acrylate, polyvinylpyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers such as carrageenan.

Preferred examples of coatings (e), which do not affect the release of the active ingredient can be those including poly(meth)acrylate, methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP) and mixtures thereof. These polymers can have a median molecular weight of 10,000 to 150,000 g/mol.

Examples of gastric juice resistant coatings can comprise cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP) and polyvinyl acetate phthalate (PVAP). Examples of retard coatings can comprise ethyl cellulose (EC,

commercially available e.g. as Surelease®) and poly(meth)acrylate (commercially available e.g. as Eudragit® RL or RS and L/S).

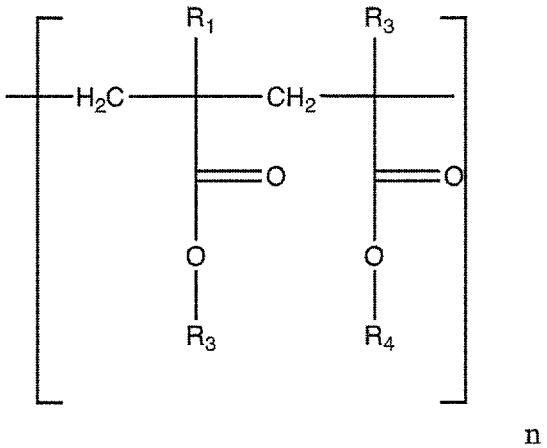
The coating (e) can be free of active ingredient. However, it is also possible that the coating can contain active ingredient (odanacatib). In such a case, that amount of active ingredient would function as an initial dose. In such a case the coating (e) preferably can comprise 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of odanacatib, based on the total amount of odanacatib contained in the tablet. In this application, the coating preferably is a coating which does not affect the release of odanacatib.

In case the film coating does not contain odanacatib (which is preferred), it can have a thickness of 2 μm to 100 μm, preferably from 20 to 60 μm. In case of a coating containing odanacatib, the thickness of the coating usually is 10 μm to 2 μm, preferably 50 to 500 μm.

The preferred coating (e) may comprise

(e1) film-forming agent;
(e2) lubricant;
(e3) surfactant;
(e4) glidant;
(e5) pigment; and/or
(e6) water.

Since in a preferred embodiment the solubility of the coating should be based on a pH-dependent binder, a polymeth(acrylate) polymer can preferably be contained as a film-forming agent (e1). Such a preferred polymeth(acrylate) polymer can dissolve readily in acidic media of pH < 5 via salt formation and, therefore, does not affect further tablet disintegration and release behaviour. A preferred polymeth(acrylate) polymer (for example Eudragit® E PO) can have the following chemical structure represented by formula (III)



formula (III),

wherein R_1 and R_2 are CH_3, R_3 is $(CH_2)_2N(CH_3)_2$, and R_4 is CH_3 or C_4H_9. The molecular weight is from 20000 to 300000 g/mol, more preferred from 30000 to 150000 g/mol and particularly from 35000 to 80000 g/mol.

The preferred coating (e) according to an embodiment of the present invention can comprise, along with the film-forming agent (e1), e.g. stearic acid as lubricant (e2) for plasticizing and dissolving the polymer, sodium lauryl sulfate as a surfactant (e3) for wetting and dispersing, talc as glidant (e4), iron oxide yellow and/or titanium oxide as pigment(s) (e5) and, optionally, purified water.

In a further embodiment of the subject invention the pharmaceutical composition is a modified release pharmaceutical composition.

Accordingly, in a further preferred embodiment the modified release pharmaceutical composition can relate to a tablet, in which 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of the total amount of the odanacatib contained in the tablet can be present as initial doses having immediate release, and 55 to 99 wt.%, preferably 65 to 95 wt.%, most preferably 70 to 90 wt.% of the active ingredient can be present in the tablet as a modified-release composition.

In a preferred embodiment the total weight of the tablet of the present invention is more than 50 mg, e.g. more than 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 180 mg, 200 mg or

250 mg. In a preferred embodiment the total weight of the tablet of the present invention is less than 800 mg, e.g. less than 750 mg, 700 mg, 650 mg, 600 mg, 550 mg, 500 mg, 450 mg, 400 mg, 350 mg or 300 mg. All combinations thereof are further preferred, e.g. from 200 to 600 mg.

In a preferred embodiment the tablet of the present invention has a ratio of tablet height to tablet weight from 0.002 to 0.06 mm/mg, preferably from 0.01 to 0.03 mm/mg.

An embodiment of a further subject of the invention relates to a process for manufacturing a dosage form containing the above-mentioned-pharmaceutical composition comprising the steps of

(i) dissolving components (a1) and (a2) in a solvent or a mixture of solvents,
(ii) removing the solvent or the mixture of solvents from the solution of step (i) to form an agglomerate (a),
(iii) blending agglomerate (a) with optionally filler (b), disintegrant (c) and optionally excipients (d),
(iv) optionally compacting the mixture from step (III) and granulating said compacted mixture
(v) processing the mixture from step (iii) or the granulated mixture composition of step (iv) into a dosage form, and
(vi) optionally film-coating the dosage form.

Preferably in step (iii) no filler is added.

In step (i) odanacatib (a1) and compound (a2) selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropylmethylcelluose acetate phthalate, hydroxyproylmethylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures therefrom are dissolved, preferably completely dissolved, in a solvent or mixture of solvents. The dissolving process can preferably be done accompanied by stirring, for example for one minute to one hour. Suitable solvents are, for example, water, alcohol (for example methanol, ethanol, isopropanol), dimethyl sulphoxide (DMSO), acetone, butanol, ethyl

acetate, heptane, pentanol, chlorinated solvent (for example dichlormethane, chloroform) or mixtures thereof. Preferably, the solvent can be acetone.

In the subsequent step (ii), the solvent or mixture of solvents is removed. The removal of the mixture of solvents may, for example, be achieved by raising the temperature (for example 50 to 150 °C) and/or by reducing the pressure (for example 0.001 to 0.9 bar).

In a preferred embodiment, the solution from step (i) is spray-dried in step (ii). The spray-drying can be carried out in a spray tower. As an example, a Büchi MiniSpray Dryer B-191 is suitable (Büchi Labortechnik GmbH, Germany). Preferably an inlet temperature of 50 °C to 150 °C, more preferably 70 °C to 130 °C, is chosen. The amount of air is, for example, 10 to 100 litres/hour, and the aspirator preferably runs at 80 to 100 %.

After the solvent has been removed, the mixture obtained in step (ii) can be granulated, where applicable, in optional step (iia). The granulation may preferably also take place during removal of the solvent, i.e. steps (ii) and (iia) may be performed simultaneously.

Steps (ii) and (iia) can preferably be performed in a fluidised bed granulator, such as a Glatt GPCG 3 (Glatt GmbH, Germany). Work is preferably performed with air inlet temperatures of 60 °C to 80 °C, with product temperatures of 30 °C to 40 °C and with a spray pressure of 1 to 1.5 bar.

In step (iii) agglomerate (a) can be blended with filler (b), disintegrant (c) and optionally excipients (d). The components filler (b), disintegrant (c) and optionally further excipient(s) (d) refer to the components as described above. All of said components can preferably be sieved before blending. In a preferred embodiment the sieve has a mesh size of 600 to 1400 µm, preferably of 800 to 1250 µm. In a preferred embodiment further excipients (d) refer to lubricant (d1) surfactant (d2) and glidant (d3).

In another preferred embodiment in step (iii) a part of filler (b), disintegrant (c) and optionally further excipient(s) (d), preferably sieved, is added to the agglomerate (a)

from step (ii) and subsequently blended. Subsequently, a further part of filler (b), disintegrant (c) and optionally further excipients(s) (d), preferably sieved, is added to the resulting blend and another blending is conducted. This procedure can be repeated, depending on the number of parts into which filler (b), disintegrant (c) and optionally further (s) excipient(s) (d).

Blending can be carried out with conventional mixing devices, e.g. in a free-fall mixer like Turbula® T10B (Bachofen AG, Switzerland). Blending can be carried out e.g. for 1 minute to 30 minutes, preferably for 2 minutes to less than 10 minutes.

In optional step (iv) the mixture from step (iii) can preferably be compacted. Here, it is preferred that the compaction is carried out as dry-compacting. Thus, the compaction is preferably performed in the absence of solvents, especially in the absence of organic solvents.

The compaction can be carried out with the corresponding devices and parameters as known in art, for example with a roller compactor.

It is preferred to compact the mixture of step (iii) in a tablet press Korsch EKO to obtain the compacted mixture in form of a tablet. Preferably, a compaction force from 10 to 80, more preferably from 15 to 75, even more preferably from 20 to 70, can be applied.

Further, the resulting compacted mixture can be granulated. The granulation can be performed by using processes known in the state of the art.

In a preferred embodiment, the granulation is performed by milling the compacted mixture through a screen. The mesh width of the screen usually is 0.1 to 4 mm, preferably 0.2 to 2 mm, more preferably 0.4 to 2 mm, especially 0.6 to 1.5 mm.

In step (v) the mixture resulting from step (iii) or, optionally, the granulates from step (iv) can be further processed into a dosage form. For this purpose, said mixture or said granulates can, for example, be filled into sachets or capsules.

In a preferred embodiment, step (v) can include compressing the mixture resulting from step (iii) or, optionally, the granulates from step (iv) and, optionally, further excipient(s) (d), such as lubricant (d1), into tablets.

The compression of the mixture resulting from step (iii) or optionally the granulates from step (iv) can preferably be a direct compression. This direct compression step can preferably be carried out on a rotary press, for example on a Fette® 102i (Fette GmbH, Germany) or a Riva® piccola (Riva, Argentina). If a rotary press is applied, the main compaction force can range from 1 to 50 kN, preferably from 2 to 40 kN, more preferably from 3 to 30 kN.

In optional step (vi) the dosage form, preferably a tablet, can preferably be film-coated. The film-coating (e) can be applied preferably by spraying a coating solution onto the tablets and then drying the tablets. The coating solution may comprise the above-mentioned excipients, whereby a solid content of about 15% is preferred.

Further, as described before, the applied film coating preferably should not affect the tablet disintegration and release behaviour. The thickness of the coating ranges from 0.01 μm to 2 mm, preferably from 50 to 500 μm.

The coating process in optional step (vi) can be carried out in a continuous process in a pan coater or a fluid bed dryer. The coating process can preferably be carried out on a pan coater, for example on a Lödige LHC 25 (Lödige GmbH, Germany). If a pan coater is applied, the spray pressure can range from 0.8 to 2 bar, preferably from 1 to 1.5 bar. The product temperature can vary according to the applied polymer. The product temperature can be adjusted to 20 to 40 °C, preferably to 32 to 38 °C.

All explanations given above for the process of the present invention may also apply to the tablet of the present invention.

In a preferred embodiment, the pharmaceutical composition of the present invention can be suitable for administration once or twice per day, most preferably once per day.

Alternatively, the pharmaceutical composition of the present invention can be administered every second day, thrice a week, twice a week or once a week.

The present invention is illustrated by the following examples.

EXAMPLES

The following commercially available compounds were used in the examples below:

Example 1: Preparation of agglomerate containing odanacatib and HPMC AS

Odanacatib (15 wt.%) and HPMC (85 wt.%) were dissolved under stirring in acetone. The solution is subjected to a spray-drying process in a Büchi Mini Spray Drayer B-191, wherein the following parameters were used:

process step	time [min]	aspirator	temperature [°C]			spray nozzle			comments
		[%]	inlet air		exhaust air (Ist)	amount of air [L/h]	spray rate		
			(nominal)	(actual)			[%]	[g/min]	
warming	10	100	80	80		20			15 min pre-warming and flooding the system with nitrogen
product		100	80	80	60	20	10		product can easily be sprayed
		100	80	81	58	20	10		
Pump rate (enhanced)		100	83			20	15		

Example 2:

Odanacatib	50 mg (9.10 %)
HPMCAS	283.33 mg (51.57 %)
Cross-linked polyvinylpyrrolidone	200.00 mg (36.41%)
Sodium lauryl sulfate	7.50 mg (1.37 %)
Silicon dioxide	3.75 mg (0.68 %)
Magnesium stearate	4.65 mg (0.85 %)

Odanacatib and hydroxypropyl methylcellulose acetate succinate (HPMCAS-HF) were used to form an agglomerate according to Example 1. Cross-linked polyvinylpyrrolidone (Kollidon CL), sodium lauryl sulfate, silicon dioxide (carb o Sil) and magnesium stearate were added and the resulting mixture was blended together for 15 min in a tumble blender. The mixture was compressed on a Korsch EKO with 38 kN and subsequently milled through a 0.8mm screen. The final granulated blend was compressed on an eccentric press (Korsch EK0) to obtain tablets of 549.23 mg.

Example 3:

Odanacatib	50 mg (10.88 %)
HPMCAS	283.33 mg (61.63 %)
Cross-linked carboxymethylcellulose sodium	95.00 mg (20.64 %)
Sodium lauryl sulfate	15.00 mg (3.26 %)
Silicon dioxide	7.50 mg (1.63 %)
Magnesium stearate	9.38 mg (2.04 %)

Odanacatib and hydroxypropyl methylcellulose acetate succinate (HPMCAS-HF) were used to form an agglomerate according to Example 1. Cross-linked carboxymethylcellulose sodium (croscarmellose sodium), sodium lauryl sulfate, silicon dioxide (Carb o Sil) and magnesium stearate were added and the resulting mixture was blended together for 15 min in a tumble blender. The mixture was compressed on a Korsch EKO with 38 kN and subsequently milled through a 0.8mm screen. The final

granulated blend was compressed on an eccentric press (Korsch EK0) to obtain tablets of 459.71 mg.

Reference Example:

For reference, Example 2 of WO 2009/140105 is prepared as follows.

Odanacatib	50 mg (6.67 %)
HPMCAS	283.33 mg (37.78 %)
α-Lactose monohydrate	339.79 mg (45.31%)
Cross-linked carboxymethylcellulose sodium	45.00 mg (6.00 %)
Sodium lauryl sulfate	15.00 mg (2.00 %)
Silicon dioxide	7.50 mg (1.00 %)
Magnesium stearate	9.38 mg (1.25 %)

Odanacatib and hydroxypropyl methylcellulose acetate succinate (HPMCAS-HF) were used to form an agglomerate according to Example 1. Cross-linked carboxymethylcellulose sodium (croscarmellose sodium), α-Lactose monohydrate (FlowLac), sodium lauryl sulfate, silicon dioxide (carb o Sil) and magnesium stearate were added and the resulting mixture was blended together for 15 min in a tumble blender. The mixture was compressed on a Korsch EKO with 38 kN and subsequently milled through a 0.8mm screen. The final granulated blend was compressed on an eccentric press (Korsch EK0) to obtain tablets of 750 mg.

As it can be seen from Figure 1, the composition of present Example 3 shows a dissolution profile being as good as the one of the Reference Example. However, compared to the composition of the Reference Example, having a weight of 750 mg and a corresponding size of the tablet, the composition of present Example 3 has significantly lower weight and, thus, can be swallowed more easily.

Claims

1. Pharmaceutical composition comprising

(a) agglomerate containing

(a1) odanacatib,

(a2) a compound selected from hydroxypropylmethylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropylmethylcelluose acetate phthalate, hydroxypropylmethylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures therefrom,

(b) 0 – 30 wt.% filler, and

(c) 15 - 70 wt.% disintegrant.

2. Pharmaceutical composition according to claim 1, wherein the weight ratio of odanacatib to compound (a2) polymer is from 1:3 to 1:10.

3. Pharmaceutical composition according to claim 1 or 2, wherein compound (a2) is hydroxypropylmethylcelluose acetate succinate.

4. Pharmaceutical composition according to any one of claims 1 to 3, wherein the filler is present from 0 to 5 wt.%.

5. Pharmaceutical composition according to any one of claims 1 to 4, wherein the disintegrant is present from 20 to 52 wt.%.

6. Pharmaceutical composition according to any one of claims 1 to 5, further comprising at least one further excipient (d).

7. Pharmaceutical composition according to claim 6, wherein the at least one further excipient is selected from lubricants (d1), surfactants (d2), glidants (d3), anti-sticking agents (d4), plasticizers (d5) and mixtures thereof.

8. Pharmaceutical composition according to any one of claims 1 to 7, comprising

(a1) 5 to 20 wt.% odanacatib,

(a2) 20 to 80 wt.% of the compound selected from hydroxypropyl-methylcelluose phthalate, hydroxyproylmethylcellulose trimellitate, hydroxypropyl-methylcelluose acetate phthalate, hydroxyproylmethylcellulose acetate trimellitate, hydroxypropylmethylcelluose acetate succinate and mixtures therefrom,

(b) 0 to 30 wt.% filler,

(c) 15 to 70 wt.% disintegrant,

(d1) 0 to 3 wt.% lubricant,

(d2) 0 to 5 wt.% surfactant,

(d3) 0 to 2.5 wt.% glidant.

9. Pharmaceutical composition according to any one of claims 1 to 8, wherein the pharmaceutical composition is in form of a tablet, and wherein the total weight of the tablet is from 200 to 600 mg.

10. Pharmaceutical composition according to claim 9, wherein the friability of the tablet is from 0 to 2 %.

11. A process for manufacturing a dosage form containing the composition according to any one of claims 1 to 8, comprising the steps of

(i) dissolving components (a1) and (a2) in a solvent or a mixture of solvents,

(ii) removing the solvent or the mixture of solvents from the solution of step (i) to form an agglomerate (a),

(iii) blending agglomerate (a) with filler (b), disintegrant (c) and optionally excipients (d),

(iv) optionally compacting the mixture from step (iii) and granulating said compacted mixture,

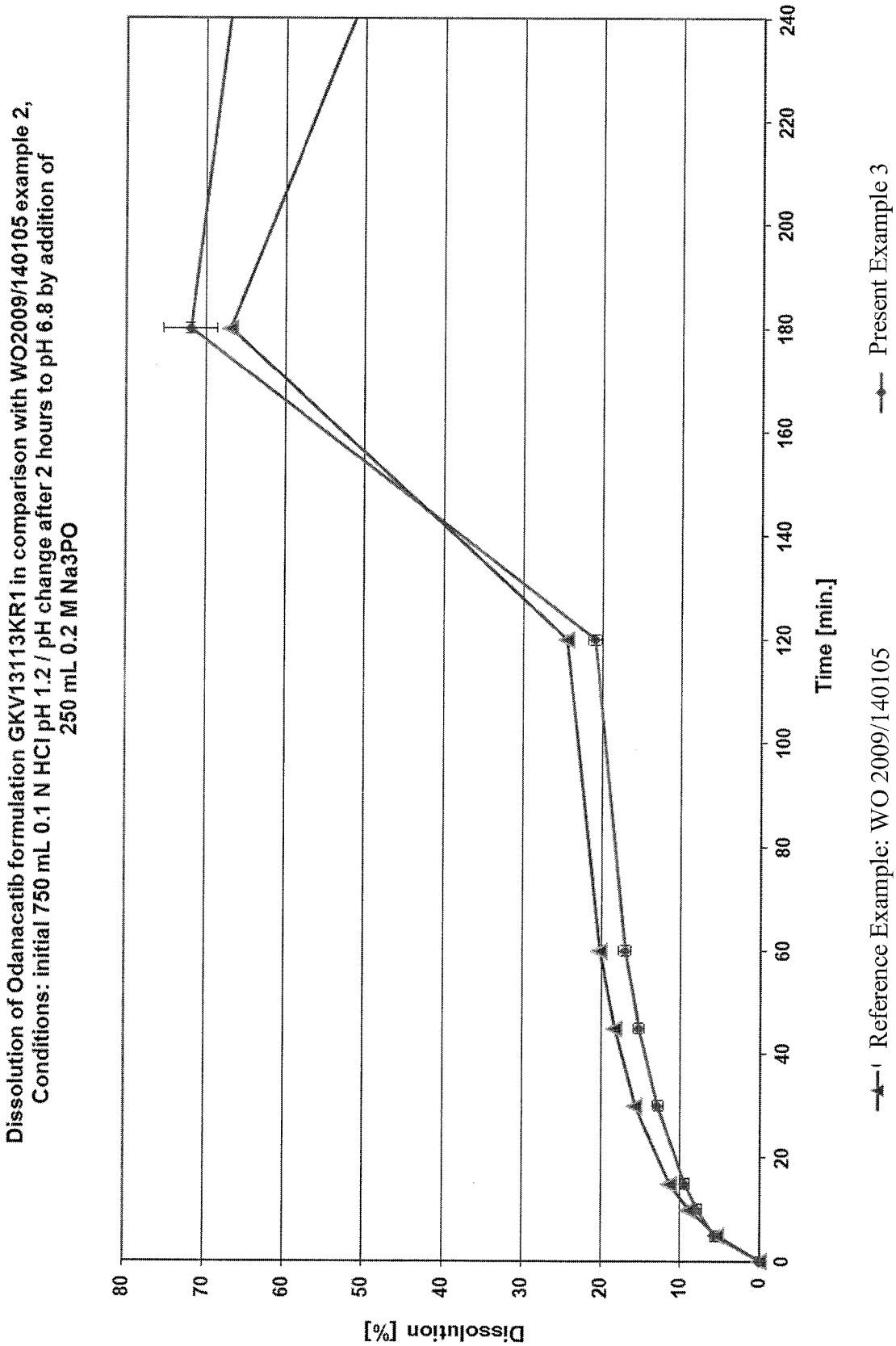
(v) processing the mixture from step (iii) or the granulated mixture composition of step (iv) into a dosage form, and

(vi) optionally film-coating the dosage form.

12. A process according to claim 11, wherein step (ii) is a spray-drying step.

13. A process according to claim 11 or 12, wherein step (v) involves compressing the mixture from step (iii) or the granulated mixture composition of step (iv) into tablets.

Figure 1


Dissolution of Odanacatib formulation GKV13113KR1 in comparison with WO2009/140105 example 2,
Conditions: initial 750 mL 0.1 N HCl pH 1.2 / pH change after 2 hours to pH 6.8 by addition of
250 mL 0.2 M Na3PO
Dissolution [%]
0
10
20
30
40
50
60
70
80
Time [min.]
0
20
40
60
80
100
120
140
160
180
200
220
240
Reference Example: WO 2009/140105
Present Example 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/073957

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/165 A61K31/277
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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/140105 A2 (MERCK & CO INC [US]; FAN HAIHONG [US]; MAHJOUR MAJID [US]; MOSER JUSTI) 19 November 2009 (2009-11-19) claim 5; examples 3,5,11	1-13
A	WO 2008/106059 A1 (MERCK & CO INC [US]; MERCK FROSST CANADA LTD [CA]; PARENT WAYNE [CA];) 4 September 2008 (2008-09-04) claim 1	1-13

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
9 December 2015	17/12/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kardas-Llorens, Eyüp

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LANGDAHL B ET AL: "Odanacatib in the treatment of postmenopausal women with low bone mineral density: five years of continued therapy in a phase 2 study", JOURNAL OF BONE AND MINERAL RESEARCH, BLACKWELL SCIENCE, INC, vol. 27, no. 11, 1 November 2012 (2012-11-01), pages 2251-2258, XP002701524, ISSN: 0884-0431, DOI: 10.1002/JBMR.1695 [retrieved on 2012-10-16] the whole document -----	1-13

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/073957

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009140105 A2	19-11-2009	EP 2291079 A2	09-03-2011
		US 2011065800 A1	17-03-2011
		US 2013217766 A1	22-08-2013
		WO 2009140105 A2	19-11-2009
WO 2008106059 A1	04-09-2008	EP 2132173 A1	16-12-2009
		US 2009318560 A1	24-12-2009
		WO 2008106059 A1	04-09-2008