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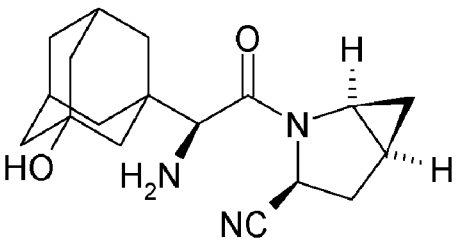
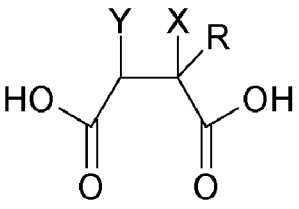
[Continued on next page]

(54) Title: NOVEL SALTS OF SAXAGRLIPTIN WITH ORGANIC DI-ACIDS



formula I



formula II

(57) Abstract: The present invention refers to a crystalline compound comprising a mixture of a compound of formula (I) (INN:Saxagliptin) and an organic C-4diacid of formula (II), wherein R represents H or OH and X and Y represent either both H or form a bond with each other, the resulting double bond being in Z-configuration, with the proviso that R represents H if X and Y represent a bond, or a hydrate thereof, wherein the molar ratio of the compound of formula (I) to the organic C4-di-acid of formula (II) is of from 1:0.8 to 1:1.2, as well as a process for obtaining the same.

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Novel salts of saxagliptin with organic di-acids

The present invention relates to novel salts of saxagliptin with organic di-acids. The present invention also relates to methods of making the novel salts of saxagliptin with organic di-acids.

Saxagliptin (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and its hydrochloride salt is an orally active reversible dipepdidyl peptidase-4 (DPP4) inhibitor, which is used as a therapeutic agent for treatment of type-2 diabetes mellitus, obesity or related diseases. It is disclosed for example in US 6,395,767, example 60.

Specific crystal forms of saxagliptin free base and specific acid addition salts including saxagliptin hydrochloride polymorphs, a fumarate (2:1), a tartrate, a benzoate, a trifluoroacetate, a bromide, an iodide, an ammoniumsulfate complex and a nitrate are disclosed in WO 2008/131149.

Some of the salts of saxagliptin disclosed in WO 2008/131149 are pharmaceutically not acceptable, while the free base is susceptible to intramolecular cyclysation.

Saxagliptin is marketed in a form wherein the base is formulated with an excess of hydrochloric acid. The formulation disclosed for example in US 2005/0266080 comprises a coated tablet formulation and a mix of saxagliptin hydrochloride polymorphs. As different polymorphs typically exhibit different properties with regard to solubility and dissolution kinetics, it can be expected to be difficult to produce a finished dosage form with reproducible dissolution properties based on such a mix of polymorphs. Moreover, the saxagliptin hydrochloride polymorphs, while in general showing good solubility in water, are quite prone to conversion to a number of different distinct hydrates upon exposure to environments differing in relative humidity, making it hard to control the polymorphic state during pharmaceutical processing.

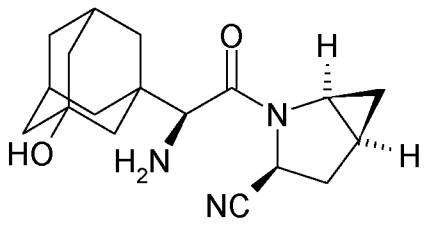
The above mentioned patent application US2005/0266080 also describes a capsule formulation of the benzoate hydrate as showing insufficient stability. In addition the benzoate salt is described to have a limited solubility of less than 15 g/l in water.

The disclosed salts of saxagliptin are all hydrated forms having relatively high water content. High-water content forms can have certain drawbacks, in particular compounds that are prone to hydrolysis like saxagliptin can show decreased chemical stability when present in such forms. Moreover, from a galenical perspective, bulk quantities of active pharmaceutical ingredients having high water contents tend to clog or stick together, thus sometimes having poor processing behavior in the formulation processes for the production of pharmaceutical compositions.

Thus, an improved salt form of saxagliptin with both good processability, good polymorphic stability and good solubility would be desirable.

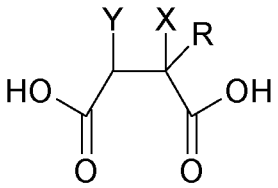
It is therefore an objective of the present invention to provide a novel pharmaceutically acceptable salt of saxagliptin with good solubility/dissolution properties. It is also an objective of the present invention to provide saxagliptin in a form of a salt having a good chemical and/or physical stability and/or good processability, both during its preparation as an active pharmaceutical ingredient as well as in the preparation of pharmaceutical compositions containing saxagliptin. It is a further objective to provide crystalline salts of saxagliption that are accessible in a reproducible manner and constant quality in inexpensive and well controlled production processes.

The technical problem underlying the present invention is solved by a crystalline compound comprising a mixture of a compound of formula I (INN: Saxagliptin)



formula I

and an organic C4-diacid of formula II,



formula II,

wherein R represents H or OH and X and Y represent either both H or form a bond with each other, the resulting double bond being in Z-configuration, with the proviso that R represents H if X and Y represent a bond, or a hydrate thereof, wherein the molar ratio of the compound of formula I to the organic C4-diacid of formula II is of from 1:0.8 to 1:1.2.

The crystalline compound comprising saxagliptin (compound of formula I) and the organic C4-diacid of formula II may be a salt. Saxagliptin may be a protonated cation, for example saxagliptin protonated at the nitrogen atom of the primary amino group and the counterion may be a respective monocarboxylate anion. However, as empirical formula the crystalline compound comprises saxagliptin and the organic C4-diacid in the denoted molar ratio.

In a preferred embodiment the molar ratio of the compound of formula I to the organic C4-diacid of formula II is of from 1:0.9 to 1:1.1 and most preferred is 1:1.

Preferably, the organic acid of formula II is selected from the group consisting of maleic acid, malic acid, L-malic acid, D-malic acid and succinic acid.

In the context of the present invention the following abbreviations apply unless explicitly stated otherwise:

DVS:	Dynamic (water) vapor sorption
DSC:	Differential scanning calorimetry
KF:	Karl Fischer titration
XRPD:	Powder X-ray diffraction or X-ray powder diffraction
r.h.:	relative humidity
TG-FTIR:	Thermogravimetry coupled with FT-infrared spectroscopy

The crystalline compound of the invention preferably is an essentially anhydrous form having a water content of below 1 wt-% at 50% relative humidity (20°C) as determined by the Karl Fischer method. This contrasts to the prior art hydrates and is surprising and unexpected in view of the prior art saxagliptin fumarate and saxagliptin tartrate salts, which are hydrates having a higher water content at 50% r.h. at 20°C.

Preferably, the present invention relates to a crystalline compound having a water content of below 0.8 wt-%, more preferably below 0.5 wt-% when allowed to equilibrate by storage at 50% r.h. at 20°C.

In another embodiment processes are provided for forming the novel crystalline compound comprising saxagliptin as set out above.

In a preferred embodiment the organic acid is maleic acid and the crystalline compound has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 7.5°, 14.3°, 15.5°, 16.8° and 22.5°, referred to as form A.

In a further preferred embodiment form A has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 6.9°, 7.5°, 9.1°, 11.2°, 14.3°, 15.1°, 15.5°, 16.8°, 17.9°, 18.4°, 19.1°, 20.8°, 21.2° and 22.5°.

Typically such an X-ray powder diffractogram (XRPD) is measured with copper K-alpha radiation. An X-ray powder diffractogram of a sample of the crystalline maleate salt of saxagliptin (form A) is shown in figure 1 and the present invention,

in a preferred embodiment, relates to a crystalline salt of saxagliptin of the first aspect displaying a XRPD pattern which is substantially in accordance with figure 1.

Alternatively the crystalline maleate salt (form A) of the invention can be described by a FT-Raman spectrum comprising peaks at wave numbers of 3054, 2928, 2856, 2242, 1701, 1618, 1433, 1366, 1177, 888, 696 and 651 ± 2 cm^{-1}. An FT Raman spectrum of a sample of the crystalline maleate salt (form A) of the first aspect is shown in figure 2 and the present invention, in a preferred embodiment, relates to crystalline maleate salt (form A) of the first aspect characterized by an FT Raman spectrum substantially in accordance with figure 2.

A sample of the crystalline maleate salt (form A) of the present invention revealed a molar ratio of the compound of formula I and maleic acid of about 1:1 (determined by ^{1}H-NMR).

The crystalline maleate salt of the present invention (form A) preferably has a low water content of below 0.5 wt-% (determined by Karl Fischer titration), more preferably of below 0.2 wt-%, and one measured sample provided a water value of 0.15 wt-%. Investigation of the crystalline maleate salt (form A) of the present invention by dynamic vapor sorption showed a negligible mass increase up to a relative humidity of about 60%.

The crystalline saxagliptin maleate salt of the first aspect can be prepared by an efficient crystallization process from typical class 3 solvents (according to ICH Q6a) such as esters, e.g. ethyl acetate or isopropyl acetate, ketones, e.g. acetone or methyl ethyl ketone, or alcohols, e.g. 1- or 2-propanol or ethanol. Furthermore, it has advantageous properties with respect to drying as the thermogravimetric analysis shows a release of only small amounts of water and organic solvent of less than 2 % (m/m), although the produced sample was dried under very mild conditions. Therefore, it is expected that the required specifications for residual solvent content according to the ICH guidelines can be reached with short drying times at rather low temperature, which is an advantage in comparison to e.g. saxagliptin free base monohydrate where a

small range of a humidity level has to be maintained during drying, as disclosed in Organic Process Research & Development 2009, 13,1169-1176. Such mild drying conditions reduce the risk of impurity formation upon drying of saxagliptin substantially. The aqueous solubility of the maleate salt of the present invention was determined to be about 196 g per liter at a resulting pH of about 4, which is more than 13 -fold higher than that of the known benzoate salt which is approximately 15 g/l.

In another embodiment the acid is L-malic acid and the crystalline compound has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 6.3°, 10.2°, 15.7°, 19.1° and 20.5°, referred to as form B.

In a further preferred embodiment form B has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 6.3°, 10.2°, 10.9°, 12.7°, 14.1°, 14.4°, 15.7°, 17.3°, 18.6°, 19.1°, 19.5°, 20.5° and 22.0°. The crystalline L-malate salt of saxagliptin (form B) can be further characterized by a XRPD pattern being substantially in accordance with figure 3.

Alternatively the crystalline L-malate salt (form B) of the invention can be described by an FT-Raman spectrum comprising peaks at wavenumbers of 3064, 2928, 2853, 2242, 1745, 1643, 1436, 1194, 802, 697 and 556 ± 2 cm^{-1}. Crystalline saxagliptin L-malate (form B) of the present invention can be further characterized by an FT Raman spectrum substantially in accordance with figure 4.

A sample of the crystalline L-malate salt (form B) of the present invention revealed a molar ratio of the compound of formula I and malic acid of about 1:1 (determined by ^{1}H-NMR).

Investigation of the novel malate salt (form B) by dynamic vapor sorption (DVS) reveals an increase of mass of about 0.7% between 50 and 85 % relative humidity. Therefore the salt is classified as being slightly hygroscopic.

The preferred form of the crystalline L-malate salt is essentially free of organic solvent.

The crystalline forms of the malate salt may contain H_2O and/or organic solvent. The TG-FTIR investigation of one produced sample of form B shows a small loss of about 0.9 wt-% upon heating to 180°C which is attributable to small amounts of H_2O and ethyl acetate.

Therefore, it is expected that the required specifications for residual solvent content according to the ICH guidelines can be reached with short drying times at rather low temperature, which is an advantage in comparison to e.g. saxagliptin free base monohydrate where a small range of a humidity level has to be maintained during drying, as disclosed in Organic Process Research & Development 2009, 13,1169-1176.

The aqueous solubility of form B was determined to be about 191 g per liter at a resulting pH of about 4 which is more than 10 -fold higher than that of the known benzoate salt which is approximately 15 g/l.

In a further preferred embodiment the organic acid is succinic acid and the crystalline compound has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 14.6°, 19.2°, 20.3°, 21.3° and 22.7°, referred to as form C.

In a further preferred embodiment form C has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 6.7°, 7.8°, 9.2°, 13.5°, 14.1°, 14.6°, 15.9°, 17.2°, 18.2°, 19.2°, 20.3°, 21.3°, 22.7° and 24.1°. The crystalline succinate salt of saxagliptin (form C) can be further characterized by a XRPD pattern substantially in accordance with figure 5.

Alternatively, form C can be described by an FT-Raman spectrum comprising peaks at wavenumbers of 3096, 2931, 2855, 2241, 1668, 1437, 1181, 1031, 960 and 699 ± 2 cm^{-1}. Crystalline saxagliptin succinate (form C) of the present

invention can be further characterized by an FT Raman spectrum substantially in accordance with figure 6.

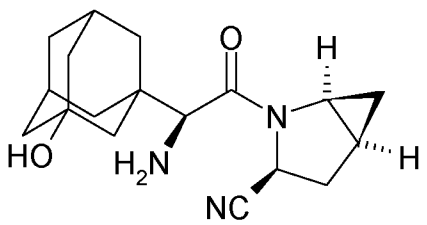
A sample of the crystalline succinate salt (form C) of the present invention revealed a molar ratio of the compound of formula I and succinic acid of about 1:1 (determined by ^{1}HNMR).

Investigation of the succinate salt (form C) of the present invention by dynamic vapor sorption reveals an increase of mass of about 0.4% (starting at a relative humidity of about 50% relative humidity up to 85% relative humidity). The succinate salt (form C) of this invention is only slightly hygroscopic.

The aqueous solubility was determined to be about 216 g per liter at a resulting pH of about 4.5, which is more than 10 -fold higher than that of the known benzoate salt which is approximately 15 g/l.

The present invention further refers to a process for obtaining the crystalline compound comprising the steps of:

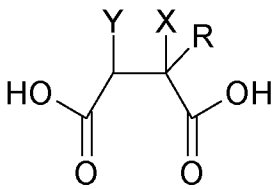
a) providing a compound of formula I (INN: Saxagliptin)



formula I

in a suitable solvent or a mixture of solvents;

b) adding an organic C4-diacid of formula II,



formula II,

wherein R represents H or OH and X and Y represent either both H or form a bond with each other, the resulting double bond being in Z-configuration, with

the proviso that R represents H if X and Y represent a bond to the mixture of step a)

c) optionally concentrating the composition of step b)

d) crystallizing

e) optionally equilibrating the obtained suspension of step d) and

f) isolating the obtained precipitate.

In step b) neat organic C4-diacid of formula II or organic C4-diacid of formula II in a suitable solvent may be added to the mixture of step a). Suitable solvents are for instance polar and/or protic solvents like ethanol, isopropanol, acetone, water or mixtures thereof. The solution of the C4-diacid of formula II in the solvent is preferably a saturated or nearly saturated solution of the respective acid.

Preferably, in step b) the organic acid of formula II is selected from the group consisting of maleic acid, malic acid, L-malic acid, D-malic acid and succinic acid.

In a further preferred embodiment the molar ratio of the compound of formula I in step a) and the acid of formula II of step b) is in the range of from 1:0.5 to 1:2, even more preferred of from 1:0.5 to 1:1.2, preferably of from 1:0.5 to 1:1.1 and most preferred is 1:1.

The process further may comprise step g) of slurrying the isolated precipitate of step f) in a further suitable solvent or mixture of solvents being preferably acetonitril, ethylacetate and/or 2-propanol and h) isolating the obtained precipitate.

Preferably, in step c) a part of the solvent is removed by for instance distillation or evaporation under reduced pressure or in a flow of a carrier gas like N_2.

Optionally, in step c) the entire solvent is removed by for instance distillation or evaporation under reduced pressure or in a flow of a carrier gas like N_2 and the residue is dissolved in a suitable solvent or mixture of solvents and water.

The solvent may be selected from the group consisting of C2-C4 alcohols, a C3-C6 ketone, an ether or an acetic ester C1-C4 alkylester, acetonitrile, a hydrocarbon or mixtures thereof.

In step d), e) and/or g) the obtained mixture may be stirred. Step d), e) and/or g) may be carried out at a temperature of from 10°C to 30°C. Suspension equilibration in step e) and/or slurrying in step g) are preferably carried out at a temperature from 10 °C to 30 °C and most preferred at ambient temperature. Step e) and/or g) are typically carried out for one day. Optionally, samples may be recovered from the suspension and analyzed by XRPD. Filtration is performed when the XRPD analysis indicates that the desired form is obtained in a reasonable purity.

Optionally, in step d), e) and/or g) seed crystals are added. Said seed crystals preferably are the desired form of the crystalline compound of the present invention which is to be obtained.

A process for the preparation of the novel crystalline salts of saxagliptin with organic acid is also subject of the invention.

The crystalline maleate salt (form A) of the invention may be prepared by combining saxagliptin free base with maleic acid in a suitable solvent. The molar ratio of saxagliptin to maleic acid is not critical; typically 0.9 equivalents of maleic acid to about 2 equivalents of maleic acid are used. Preferably 1 to 1.5 equivalents of maleic acid is employed, even more preferably one equivalent of maleic acid is used. Suitable solvents include esters, e.g. ethylacetate, alcohols, ketones, or nitriles, e.g. acetonitrile or mixtures thereof.

If desirable, the solution or suspension may be concentrated in order to induce crystallization or in order to complete crystallization. A preferred temperature for the crystallization step is from about 10° to about 70°C, preferred is ambient temperature of about 15 to 40°C. The obtained crystals may be isolated in usual manner, e.g. by filtration and drying in vacuo.

The crystalline L-malate salt (form B) of the invention may be prepared by combining saxagliptin free base with L-malic acid in a suitable solvent. The molar ratio of saxagliptin to L-malic acid is not critical; typically 0.9 equivalents of L-malic acid to about 2 equivalents of L-malic acid are used. Preferably 1 to 1.5 equivalents of L-malic acid is employed, even more preferably one equivalent of L-malic acid is used. Suitable solvents include esters, e.g. preferably ethyl-acetate, alcohols, ketones, or nitriles, e.g. preferably acetonitrile or mixtures thereof. If desirable the solution or suspension may be concentrated in order to induce crystallization or in order to complete crystallization. A preferred temperature for the crystallization step is from about 10° to about 70°C, preferred is ambient temperature of about 15 to 40°C. The obtained crystals may be isolated in usual manner, e.g. by filtration and drying in vacuo.

The crystalline succinate salt (form C) of the invention may be prepared by combining saxagliptin free base with succinic acid in a suitable solvent. The molar ratio of saxagliptin to succinic acid is not critical; typically 0.9 equivalents of succinic acid to about 1.5 equivalents of succinic acid are used. Preferably 1 to 1.2 equivalents of succinic acid is employed, even more preferably one equivalent of succinic acid is used. Suitable solvents include alcohols, e.g. isopropanol, esters, ketones, or nitriles, e.g. preferable acetonitrile or mixtures thereof. If desirable the solution or suspension may be concentrated in order to induce crystallization or in order to complete crystallization. A preferred temperature for the crystallization step is from about 10° to about 70°C, preferred is ambient temperature of about 15 to 40°C. The obtained crystals may be isolated in usual manner, e.g. by filtration and drying in vacuo.

The novel salts of the invention are stable, e.g. the maleate salt shows no increase in the content of the cyclic amidine impurity disclosed for example in US 2005/0266080 designated as cis-cyclic amidine (CA) when kept dry and when stored in closed vial at 60°C for 7 days.

Therefore the present invention also relates to pharmaceutical compositions comprising the crystalline salts of the invention.

It is preferred that the pharmaceutical composition comprising the crystalline compound of the invention show a high chemical and physical stability. In an even more preferred aspect of the invention the crystalline compounds are formulated in their anhydrous form (i.e., neither as a hydrate nor as a solvate) and the formulated crystalline compounds do not undergo any phase change during formulation and during their shelf-life which is at least 180 days, preferably at least 2 years.

The equilibrium relative humidity of the pharmaceutical compositions comprising the crystalline anhydrous compounds of the invention is measured by determining the relative humidity in % in the air of the test sample, e.g. a pharmaceutical composition of the invention comprising the crystalline compound, after establishment of a humidity equilibrium in a closed system at a constant temperature.

The pharmaceutical composition of the invention comprising the novel anhydrous crystalline forms of the invention are preferably stored in a relatively dry environment, and preferably it is to be assured that the storage environment remains relatively dry during the lifetime of the pharmaceutical composition.

The invention therefore also relates to a container comprising the crystalline compound of the invention which container is able to keep the equilibrium relative humidity of the composition at below 70%, preferably of below 60%, preferably from about 20% to about 60%.

The novel crystalline compound of the present invention may be used alone or in combination with one or more types of antidiabetic agents (employed to treat diabetes and related diseases) and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate dosage form or by injection.

The other types of antidiabetic agents which optionally employed in combination with the novel crystal forms of the compound of formula I are more antidiabetic agents or antihyperglycemic, hypolipidemic or lipid-modulating agents including

insulin secretagogues or other antidiabetic agents preferably having a mechanism different from DPP4 inhibition and may include biguanidines, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, SGLT2 inhibitors, PAR α/γ dual antagonists, aP" inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin and/or glucagons-like peptide-1 (GLP-1) or mimetics thereof or SIRT activators or mimics thereof. In carrying out the method of the invention, a pharmaceutical composition will be employed containing the novel crystalline salts of the compound of formula I, with or without another antidiabetic agent and/or other therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, the administration by an oral route in the form of tablets, capsules, granules or powders. The dose for adults is preferably between 1 mg to 1000 mg per day, preferably between 5 and 100 mg per day, which can be administered in a single dose or in the individual doses from 1-4 times a day.

A typical tablet contains one or more excipients such as bulking agents, optionally a binder and a disintegrant. Examples of bulking agents include cellulose derivatives, such as microcrystalline cellulose, lactose, sucrose, starch, pre-gelatinized starch, dextrose, mannitol, fructose, xylitol, sorbitol, corn starch, inorganic salts such as calcium salts, e.g. calcium carbonate, calcium phosphate, dicalcium phosphate, dextrin or dextrates, maltodextrin compressible sugars and/or other known bulking agents or fillers.

Examples of binders suitable for use include hydroxypropyl cellulose, PVP, starch, hydroxypropylmethyl cellulose, cellulose acetate as well as a wax binder such as carnauba wax, polyethylenes or other conventional binding agents or mixtures thereof.

Examples of disintegrants include croscarmellose sodium, crospovidone, starch, low substituted hydroxypropyl cellulose as well as other conventional disintegrants.

The lubricant optionally present include for example magnesium stearate, zinc stearate, calcium sterarate, talc, carnauba wax, stearic acid, palmitinic acid, sodium laurylsulfate or hydrogenated vegetable oils and fats or other known lubricants or mixtures thereof.

Tablets may be coated including a tablet core and a inner seal coating layer coated on the tablet core, a second coating layer containing the crystals of the present invention coated on the inner seal coating on the tablet core and optionally an outer protective coating layer coated on the second coating layer of the tablet as e.g. disclosed in US 2005/0266080.

Typical capsules for oral administration contain the novel crystalline compound of the invention contain e.g., lactose, crosscarmelose, magnesium stearate or e.g. sodium stearyl fumarate.

Solubility determination:
The aqueous solubility was determined by suspending the corresponding salt in water. The suspensions were shaken for 24 hours at 25°C and 500 rpm. After filtration the solution was investigated by HPLC using the following method:

HPLC Apparatus:	TSP HPLC (UV3000, AS3000, P4000, SCM1000 Soft.Version 4.1) or Agilent 1100 Series (UV/Vis detector)
Column:	CC06 (Penomenex Luna C18; 150x4.60 mm 3 µm) or equivalent
Mobile phase A:	0.49 g of sulfamic acid (SAS), 1000 g of H_2O
Mobile phase B:	0.49 g of sulfamic acid (SAS), 300 g of H_2O, 587 g of acetonitril

Gradient:

t [min]	0	18	20	21
% B	5	95	5	5

Flow:	0.8 ml/min
Injection volume:	10µm
Wavelength:	220 nm

DVS:

Dynamic (water) vapor sorption is a method well known in the art to monitor the adsorption of water on a solid material. Therefore, DVS is a suitable method to determine the hygroscopic nature of a pharmaceutical active ingredient.

DVS was performed with a Surface Measurement Systems Ltd. DVS-1 water sorption analyzer or with SPS11-100n moisture sorption instrument form Projekt Meßtechnik, Ulm, Germany. Program: The relative humidity was kept at starting value of 50% for two hours, then continuously scanned from 50% to 0 %, kept constant at 0% for four hours, and then scanned to 96% relative humidity, and kept constant for four hours, then r.h. was scanned back to 50% and kept there for two hours. The scanning change rate of relative humidity was 5% per hour. The temperature was 25 ± 0.1 °C.

Raman Spectroscopy:

FT- Raman spectroscopy was performed using a Bruker RFS100 (Nd:YAG 1064 nm exitation, 300 mW laser power, Ge detector, 64 scans, range 25-3500 cm^{-1}, 2 cm^{-1} resolution).

DSC:

Differential scanning calorimetry is a well known method in the art that measures the heat flow through a sample upon heating at a defined rate. It is a suitable method to determine the melting temperatures, the glass transition temperature, or other thermal events such as phase conversions or thermal decomposition.

DSC was performed using a Perkin Elmer DSC 7. Measurements were performed in closed Au crucibles, at heating rates or 10 or 20°C min^{-1}, range -50°C to 250°C.

XRPD:

The measurements were carried out with a Bruker D8 Advance powder X-ray diffractometer using Cu Kα radiation in the Bragg-Brentano reflection geometry. Generally, the 2θ values are accurate within an error of ±0.1-0.2°. The relative peak intensities can vary considerably for different samples of the same

crystalline form because of different preferred orientations of the crystals. The samples were prepared without any special treatment other than the application of slight pressure to get a flat surface. Silicon single crystal sample holders of either 0.5 mm or 0.1 mm depth and 12 mm cavity diameter were used. The tube voltage and current were 40 kV and 40 mA, respectively. The X-ray diffractometer is equipped with a LynxEye detector. A variable divergence slight was used with a 3° window. The step size was 0.02 °2θ with a step time of 37 seconds. The samples were rotated at 0.5 rps during the measurement.

TG-FTIR:

Thermogravimetry coupled with FT-infrared spectroscopy is a well known method that allows to monitor the mass loss of a given sample upon heating while identifiying the volatile substances by infrared spectroscopy. Therefore, TG-FTIR is a suitable methods to identify solvates or hydrates.

TG-FTIR was performed on a Netzsch Thermo-Microbalance TG 209, which is coupled to a Bruker FT-IR Spectrometer Vector 22. The measurements were carried out with aluminum crucibles with a micro pinhole under a nitrogen atmosphere and at a heating rate of 10 °C/min over the range 25-250 °C.

Examples

Example 1:

Preparation of saxagliptin maleate (form A)

150 mg of (1*S*, 3S, 5S)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile hemihydrate were dissolved in 6 ml of ethyl acetate. A solution of 53.7 mg of maleic acid in 4ml of ethyl acetate was added. A turbid solution was obtained. The turbid solution was filtered and evaporated under gentle nitrogen stream to dryness during about 16 hours. Thereafter the product was investigated by powder X-ray diffraction and Raman spectroscopy. The obtained XRPD pattern corresponds to the pattern of figure 1 and the FT-Raman spectrum corresponds to the spectrum shown in figure 2.

Example 2:

Preparation of saxagliptin maleate (form A)

A solution of 116 mg of maleic acid in 4 ml of ethyl acetate was added to a solution of 330 mg of (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile in 4 ml of ethyl acetate. A suspension was obtained. The suspension was stirred for 30 min at ambient temperature; the crystals were then isolated by filtration and drying in vacuo for 2 hours at room temperature. Thereafter the product was investigated by powder X-ray diffraction and Raman spectroscopy. The obtained XRPD pattern corresponds to the pattern of figure 1 and the values given in table 1 and the FT-Raman spectrum corresponds to the spectrum shown in figure 2.

Vapor sorption of the sample was performed as described above starting at a relative humidity of 50% to a relative humidity of 70%. A negligible mass increase was observed up to a relative humidity of about 60%. A mass increase of about 2.2 % was observed from about 65% to 70% relative humidity. A water content of 2.5% was found by KF. A sample was stored in a desiccator at 63% relative humidity for 24 hours : H2O by KF : 0.45%

Table 1: XRPD peaks of saxagliptin maleate (form A) at 2-theta angles ±0.2

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
6.9	12.9	m
7.6	11.7	s
9.1	9.7	m
11.2	7.9	w
13.9	6.4	w
14.3	6.2	vs
14.6	6.1	w
15.1	5.85	s
15.5	5.72	s
16.8	5.28	s
17.9	4.96	m

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
18.4	4.83	m
18.6	4.76	w
19.1	4.65	m
19.9	4.49	w
20.8	4.28	m
21.2	4.19	M
21.9	4.06	vw
22.3	3.99	m
22.5	3.95	s
24.3	3.67	w
25.8	3.45	m
26.3	3.39	w
26.7	3.33	w
30.5	2.93	w

where vs means very strong, s means strong, m means medium, w means weak, and vw means very weak intensity.

A sample of the maleate salt (water content by KF 0.15%) was stored in a sealed container at 60°C for 7 days and no increase of cis-cyclic amidine impurity was found after the stress test when using the same HPLC method as for solubility determination which is provided above.

Example 3:

Preparation of saxagliptin L-malate (form B)

134 mg of L-malic acid were dissolved by heating the suspension in 5 ml ethyl acetate.

The solution was then added to a solution of 330 mg of (1*S*, 3S, 5S)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile in 6 ml of ethyl acetate. A suspension was obtained which was stirred for 24 hours at ambient temperature. 2 ml of acetonitrile was then added to the suspension and the crystalline suspension was stirred for 5 days, one day in a closed vial and 4 days in an open vial allowing to evaporate some of the

solvent. The suspension was then filtered and the crystals were dried in vacuo at ambient temperature for 2 hours. The obtained XRPD pattern corresponds to the pattern of figure 3 and the FT-Raman spectrum corresponds to the spectrum shown in figure 4. Karl Fischer titration revealed a water content of 0.22%. A sample of the L-malate salt was stored in a desiccator at about 60% relative humidity for 24 hours and a water content of 0.45% by KF was found.

Table 2: XRPD peaks of saxagliptin L-malate (form B) at 2-theta angles ±0.2

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
6.3	14.0	vs
6.7	13.2	vw
8.4	10.5	w
10.2	8.7	s
10.9	8.1	m
11.8	7.5	w
12.3	7.2	vw
12.7	7.0	w
13.35	6.6	vw
14.1	6.3	m
14.4	6.1	w
14.7	6.0	w
15.4	5.74	m
15.7	5.66	vs
17.0	5.22	vw
17.3	5.11	s
17.7	5.01	m
18.0	4.94	w
18.3	4.84	w
18.6	4.77	s
19.1	4.65	vs
19.5	4.54	m
19.9	4.49	w
20.5	4.33	s

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
21.5	4.13	w
22.0	4.04	m
23.5	3.79	w
23.9	3.72	w
24.3	3.66	w
24.7	3.60	w
25.6	3.48	w
26.4	3.37	w
29.5	3.02	w

Example 4:

Preparation of saxagliptin succinate (form C)

A solution of 118 mg of succinic acid in 10 ml of acetonitrile was added to a solution of 330 mg of (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile in 4ml of acetonitrile. A suspension was obtained. The suspension was stirred for 24 hours at ambient temperature. The crystals were then isolated by filtration and dried in vacuo for approximately 2 hours at room temperature. The obtained XRPD pattern corresponds to the pattern of figure 5 and the FT-Raman spectrum corresponds to the spectrum shown in figure 6.

The water content by KF was 0.11%. A sample was stored in a desiccator at about 60% relative humidity for 24 hours and a water content of 0.24% by KF was found.

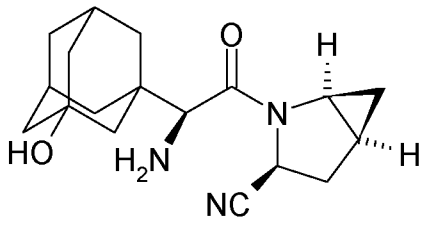
Table 3: XRPD peaks of saxagliptin succinate (form C) at 2-theta angles

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
6.7	13.2	s
7.8	11.4	w
9.2	9.6	m
13.5	6.6	m
14.1	6.3	s

Angle [°2θ]	D-spacing [Å]	Qualitative Intensity
14.6	6.1	vs
15.1	5.87	m
15.6	5.67	w
15.9	5.59	vs
17.2	5.16	s
18.2	4.87	s
18.4	4.81	s
18.7	4.74	s
19.2	4.63	vs
20.3	4.38	vs
21.3	4.16	s
22.4	3.96	m
22.7	3.92	s
23.2	3.83	m
24.1	3.70	m
26.0	3.43	w
26.2	3.40	w
26.5	3.36	m
26.9	3.31	m
27.2	3.28	m
27.6	3.23	m
27.9	3.20	w
28.1	3.17	w
28.5	3.13	s
29.4	3.04	w
29.7	3.00	vw
30.7	2.90	w
31.1	2.87	w
39.8	2.26	m

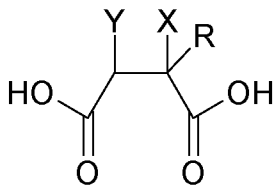
Claims

1. A crystalline compound comprising a mixture of a compound of formula I (INN: Saxagliptin)



formula I

and an organic C_4-diacid of formula II,



formula II,

wherein R represents H or OH and X and Y represent either both H or form a bond with each other, the resulting double bond being in Z-configuration, with the proviso that R represents H if X and Y represent a bond, or a hydrate thereof, wherein the molar ratio of the compound of formula I to the organic C_4-diacid of formula II is of from 1:0.8 to 1:1.2.

2. The crystalline compound according to claim 1, wherein the organic acid of formula II is selected from the group consisting of maleic acid, malic acid, L-malic acid, D-malic acid and succinic acid.

3. The crystalline compound according to at least on of the claims 1 or 2, characterized in that the organic acid is maleic acid and has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 7.5°, 14.3°, 15.5°, 16.8° and 22.5°.

4. The crystalline compound according to at least one of the claims 1 to 3, characterized in that the organic acid is maleic acid and has a Raman spectrum comprising peaks at 3054, 2928, 2856, 2242, 1701, 1618, 1433, 1366, 1177, 888, 696 and 651 ± 2 cm^{-1}.

5. The crystalline compound according to at least on of the claims 1 or 2, characterized in that the organic acid is L-malic acid and has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 6.3°, 10.2°, 15.7°, 19.1° and 20.5°.

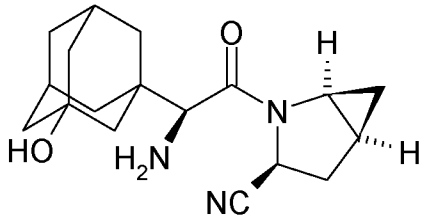
6. The crystalline compound according to at least one of the claims 1, 2 and 5, characterized in that the organic acid is L-malic acid and has a Raman spectrum comprising peaks at 3064, 2928, 2853, 2242, 1745, 1643, 1436, 1194, 802, 697 and 556 ± 2 cm^{-1}.

7. The crystalline compound according to at least on of the claims 1 or 2, characterized in that the organic acid is succinic acid and has an XRPD pattern with at least one characteristic peak (expressed in 2θ ± 0.2° 2θ (CuKα radiation)) at 14.6°, 19.2°, 20.3°, 21.3° and 22.7°.

8. The crystalline compound according to at least one of the claims 1, 2 and 7, characterized in that the organic acid is succinic acid and has a Raman spectrum comprising peaks at 3096, 2931, 2855, 2241, 1668, 1437, 1181, 1031, 960 and 699 ± 2 cm^{-1}.

9. A process for obtaining the crystalline compound according to at least one of the claims 1 to 8 comprising the steps of:

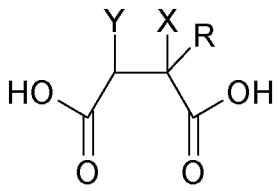
a) providing a compound of formula I (INN: Saxagliptin)



formula I

in a suitable solvent or a mixture of solvents

b) adding an organic C_4-diacid of formula II,



formula II,

wherein R represents H or OH and X and Y represent either both H or form a bond with each other, the resulting double bond being in Z-configuration, with the proviso that R represents H if X and Y represent a bond to the mixture of step a)

c) optionally concentrating the composition of step b)

d) crystallizing

e) optionally equilibrating the obtained suspension of step d) and

f) isolating the obtained precipitate.

10. The process according to claim 9, characterized in that in step b) the organic acid of formula II is selected from the group consisting of maleic acid, malic acid, L-malic acid, D-malic acid and succinic acid.

11. The process according to claim 9 or 10, characterized in that the molar ratio of the compound of formula I in step a) and the acid of formula II of step b) is in the range of from 1:0.5 to 1:2.

12. The process according to at least one of the claims 9 to 11, further comprising step g) of slurrying the isolated precipitate of step f) in a further

suitable solvent or mixture of solvents being preferably acetonitril, ethylacetate and/or 2-propanol and h) isolating the obtained precipitate.

13. The process according to at least one of the claims 9 to 12, characterized in that in step c) the entire solvent is removed and the residue is dissolved in a suitable solvent or mixture of solvents and water.

14. The process according to at least one of the claims 9 to 13, characterized in that the solvent is selected from the group consisting of C2-C4 alcohols, a C3-C6 ketone, an ether or an acetic ester C_1-C_4 alkylester, acetonitril, a hydrocarbon or mixtures thereof.

15. The process according to at least one of the claims 9 to 14, characterized in that in step d), e) and/or g) seed crystals are added.

16. A pharmaceutical composition comprising the crystalline compound according to at least one of the claims 1 to 8 and optionally one or more pharmaceutically acceptable excipients.

Figure 1

Powder X-ray pattern of saxagliptin maleate (form A)

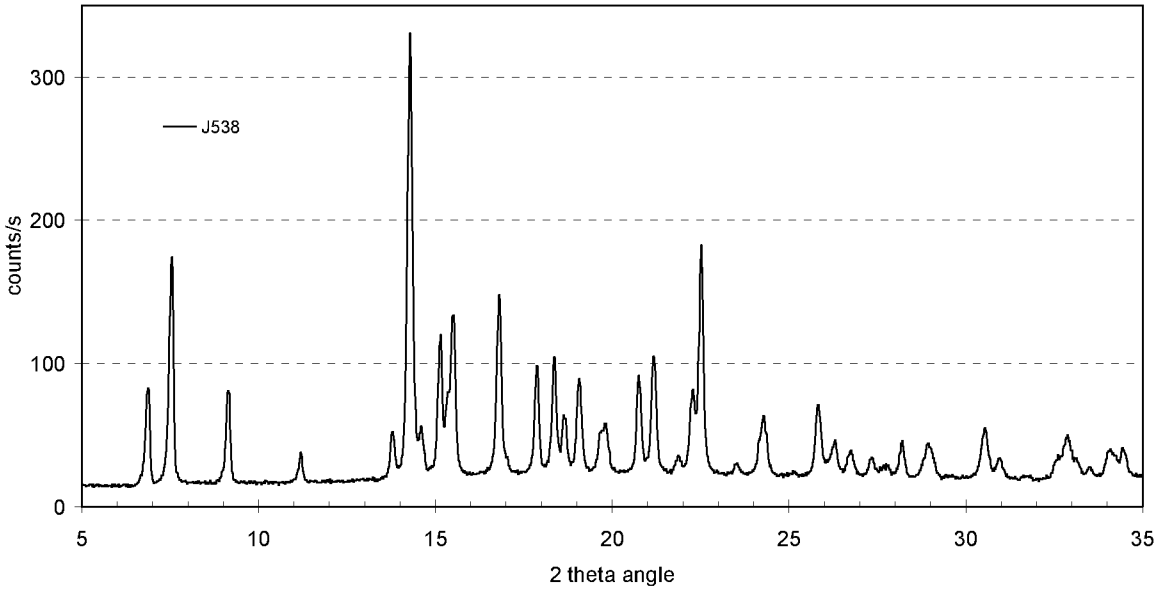


Figure 2

Raman spectrum of saxagliptin maleate (form A)

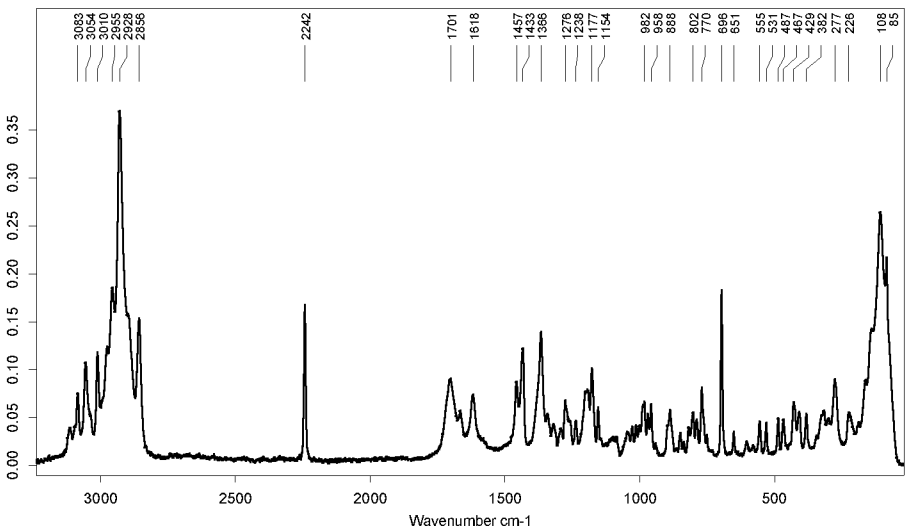


Figure 3

Powder X-ray pattern of saxagliptin L-malate (form B)

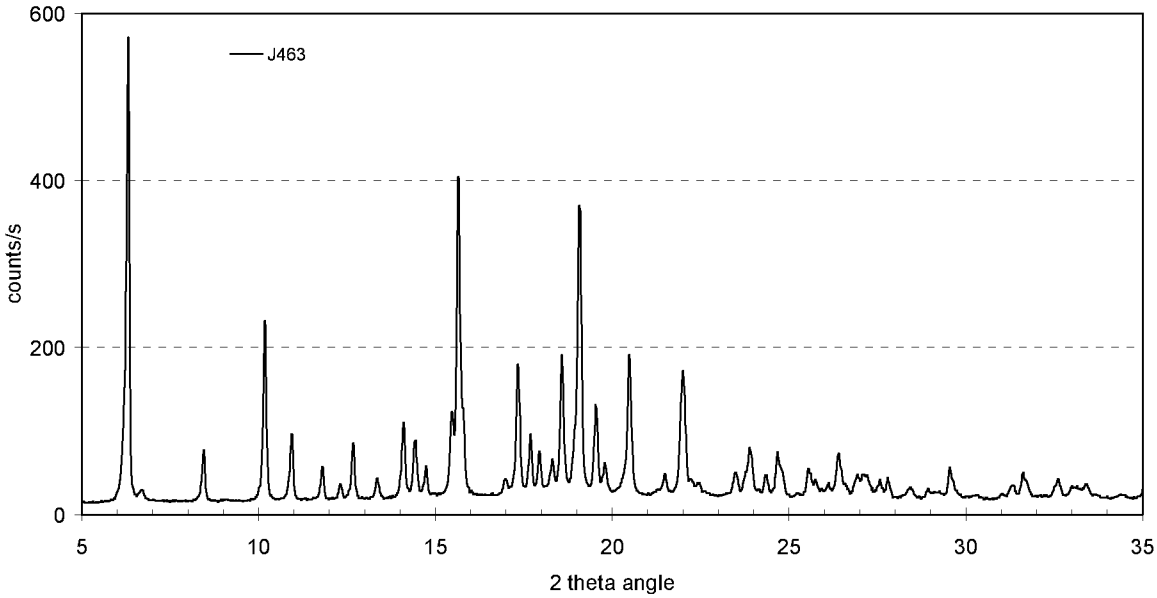


Figure 4

Raman spectrum of saxagliptin L-malate (form B)

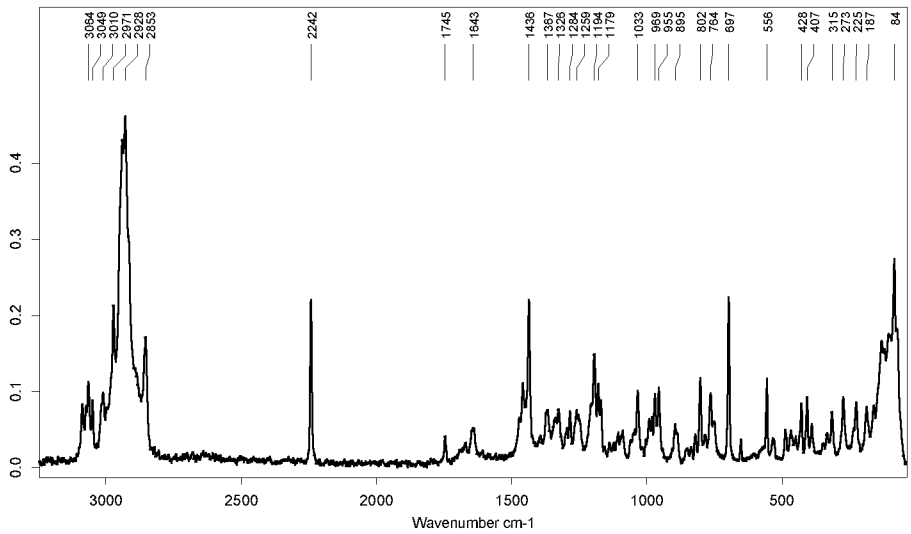


Figure 5

Powder X-ray pattern of saxagliptin succinate (form C)

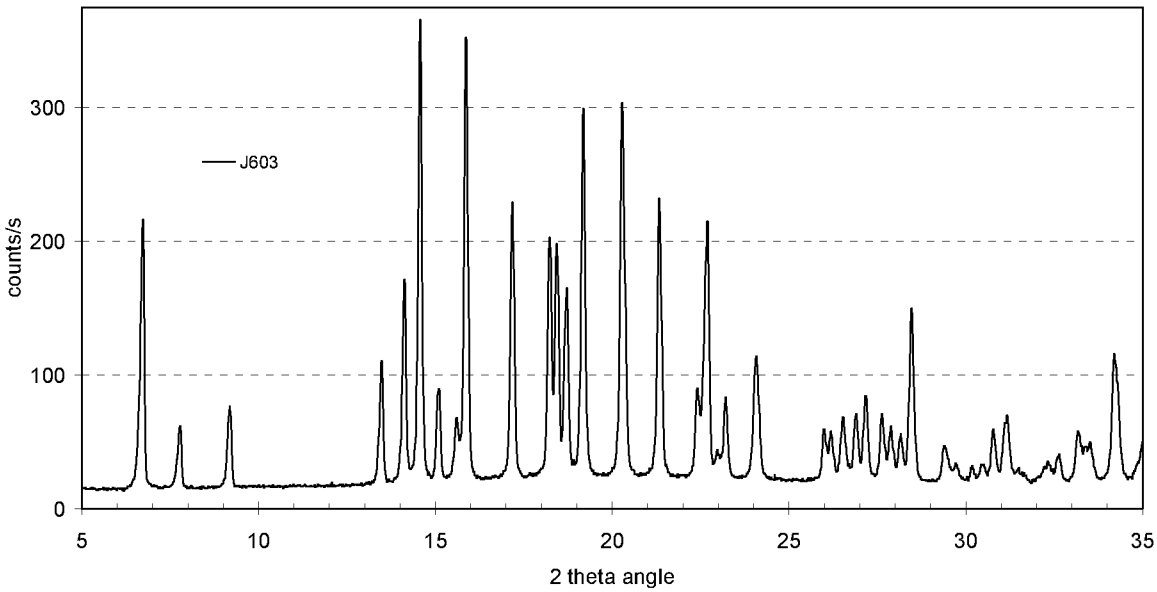
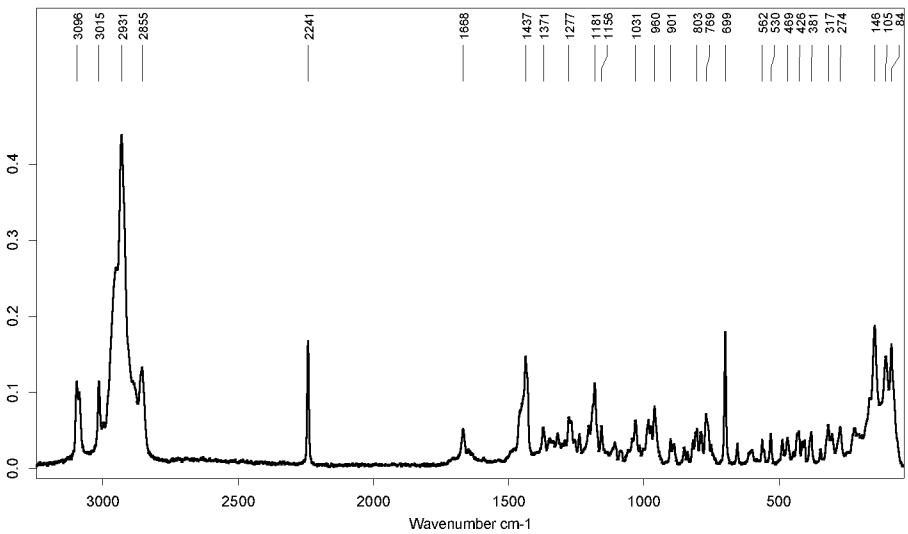


Figure 6

Raman spectrum of saxagliptin succinate (form C)



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/063423

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/52 A61K31/403 A61P3/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/131149 A2 (SQUIBB BRISTOL MYERS CO [US]; GOUGOUTAS JACK Z [US]; MALLEY MARY F [US) 30 October 2008 (2008-10-30) cited in the application claims 1, 4, 8; examples 6, 8; tables 17, 18, 23, 24	1-16
A	US 6 395 767 B2 (ROBL JEFFREY A [US] ET AL) 28 May 2002 (2002-05-28) cited in the application the whole document	1-16

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[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 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	Date of mailing of the international search report
25 August 2011	31/08/2011

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	Lécaillon, Jennifer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/063423

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/063423

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGE S M ET AL: "PHARMACEUTICALS SALTS", JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION, WASHINGTON, US LNKD-DOI:10.1002/JPS.2600660104, vol. 66, no. 1, 1 January 1977 (1977-01-01), pages 1-19, XP000562636, ISSN: 0022-3549 page 5, line 15 - column 1, line 19 -----	1-16

1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 4(completely); 1, 2, 9-16(partially)

A crystalline compound comprising a mixture of a compound of formula (I) and an organic C4-diacid of formula (II) as defined in present claim 1 wherein X and Y represent a double bond and R is H, a process for the preparation of said compound and a pharmaceutical composition comprising it.

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2. claims: 5-8(completely); 1, 2, 9-16(partially)

A crystalline compound comprising a mixture of a compound of formula (I) and an organic C4-diacid of formula (II) as defined in present claim 1 wherein X and Y both represent H and R is H or OH, a process for the preparation of said compound and a pharmaceutical composition comprising it.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/063423

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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