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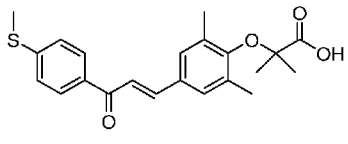
(54) Title: SOLID FORMS OF ELAFIBRANOR AND PROCESS OF PREPARATION THEREOF

(57) Abstract: The present invention relates to solid forms of elafibranor of Formula I, and process of preparation thereof, wherein said solid forms includes amorphous, crystalline, solid dispersion and premix with pharmaceutically acceptable polymer and/or carrier.



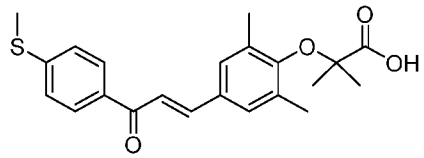
Formula I

WO 2020/115628 A1

SOLID FORMS OF ELAFIBRANOR AND PROCESS OF PREPARATION THEREOF

FIELD OF THE INVENTION

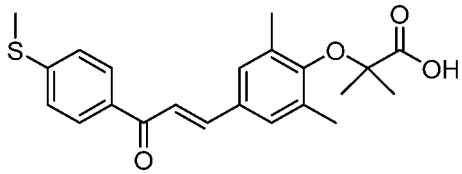
The present invention relates to solid forms of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof, methods for their preparation and pharmaceutical compositions thereof.



Formula I

BACKGROUND OF THE INVENTION

Elafibranor of formula I is chemically known as (E)-2-(2,6-dimethyl-4-(3-(4-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenoxy)-2-methylpropanoic acid and is disclosed in WO2004/005233A1.



Formula I

Elafibranor is also known as GFT-505, and is clinically used to treat Nonalcoholic Steatohepatitis (NASH. GFT-505 is an agonist of peroxisome proliferator-activated receptor-alpha (PPARA) and receptor-delta (PPARD).

WO 2018/133705A1 discloses anhydrous forms (CS1, CS5), hydrate form (CS2) and acetic acid solvate form (CS6) of Elafibranor.

Although there are few literatures known for crystallization of elafibranor, however there is always a need to develop a new polymorph and a process that can produce the said form of the product which has good stability, good process ability and other favourable properties with respect to Formulation.

Based on aforesaid, the present invention is focussed towards the development of new crystalline forms and amorphous form of elafibranor by employing simple, low cost and less time consuming processes, wherein the physicochemical stability and the dissolution characteristics of the solid form is improved, and wherein said Elafibranor is rendered more suitable for use in a pharmaceutical composition.

OBJECT OF THE INVENTION

The main object of the present invention is to provide novel solid forms of elafibranor free base, isomer or pharmaceutically acceptable salt thereof which possesses good stability, good processability and other favourable properties.

Another object of the present invention is to provide an amorphous form of elafibranor of free base, isomer or pharmaceutically acceptable salt thereof and process thereof.

Another object of the present invention is to provide a process for the preparation of stable amorphous form of elafibranor free base, isomer or pharmaceutically acceptable salt thereof, wherein said amorphous form is stable for atleast six months at 40°C and 75% RH and can be formulated easily for administering to patients.

Another object of the present invention is to provide novel crystalline forms of elafibranor free base, designated as MK-1, MK-2, and MK-3 through simple and cost effective processes that is reproducible at large scale production.

Another object of the present invention is to provide an amorphous solid dispersion of elafibranor or its salt with atleast one pharmaceutical acceptable polymer and/or excipient.

Another object of the present invention is to provide a process for the preparation of amorphous solid dispersion of elafibranor free base, isomer or pharmaceutically acceptable salt thereof with atleast one pharmaceutically acceptable excipient or polymer.

Another object of the present invention is to provide a premix of elafibranor or its salt with atleast one pharmaceutical acceptable polymer and/or excipient.

Another object of the present invention is to provide a process for the preparation of a premix of elafibranor, isomer, or salt thereof.

Another object of the present invention is to provide a pharmaceutical composition comprising solid form of elafibranor, isomer or its pharmaceutically acceptable salts.

SUMMARY OF THE INVENTION

In the main aspect, the present invention provides an amorphous form of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof.

In one another aspect, the present invention provides a process for the preparation of amorphous form of elafibranor free base, comprising the steps:

a) dissolving Elafibranor in suitable solvent,
b) stirring the reaction mixture to get the clear solution: and
c) isolating the amorphous form of Elafibranor of Formula I.

In one another aspect, the present invention provides a process for the preparation of amorphous form of elafibranor free base, comprising the steps:

a) dissolving Elafibranor in organic solvent,
b) stirring the reaction mixture to get the clear solution,
c) distilling the solvent to get the oil;
d) adding cyclohexane to the reaction mixture; and
e) isolating the amorphous form of Elafibranor of Formula I.

In another aspect, the present invention provides crystalline forms MK-1, MK-2 and MK-3 of elafibranor free base, characterized by their X-ray (powder) diffraction (XRD), Differential Scanning calorimetry (DSC) and Thermogravimetric analysis (TGA).

In one another aspect, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) at 9.34, 9.86, 10.72, 11.88, 12.25, 14.29, 15.85, 16.06, 16.52, 16.94, 17.54, 18.42, 18.72, 19.25, 19.79, 20.45, 20.92, 21.50, 22.62, 23.20, 24.01, 24.49, 24.97, 25.09, 25.68, 26.21, 26.74, 27.71, 28.13,

28.41, 29.26, 29.52, 30.00, 30.23, 30.50, 30.90, 31.54, 31.97, 32.50, 33.45, 34.03, 34.25, 34.83, 35.60, 36.16, 37.26, 37.61, and 38.16 ±0.2.

In another aspect, the present invention provides a crystalline Form MK-2 of elafibranor free base characterized by its XRD pattern having peaks (2θ values) at 6.81, 7.45, 8.21, 9.32, 10.64, 11.55, 12.22, 13.68, 14.27, 15.02, 15.38, 16.50, 17.08, 18.93, 20.08, 20.57, 21.36, 21.86, 23.68, 24.68, 25.30, 26.10, 26.85, 27.57, 28.14, 28.96, 29.57, 30.23, 30.93, 31.99, 32.60, 33.64, 34.05, 35.08, 35.76, 36.37, 36.98, 37.77, 38.52 and 39.34 ±0.2.

In one another aspect, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) at 7.74, 8.22, 10.30, 10.66, 10.98, 11.56, 12.55, 13.10, 13.34, 14.19, 15.04, 15.48, 15.93, 16.47, 17.14, 17.76, 18.35, 18.93, 19.74, 20.65, 21.70, 22.82, 23.86, 25.30, 25.83, 26.78, 27.33, 28.85, 29.54, 30.65, 32.48 and 34.21 ±0.2.

In further aspect, the present invention provides a process of preparation of crystalline forms of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof comprising the steps of:

a) adding elafibranor in an organic solvent;
b) optionally heating the solution below 100°C to get solution;
c) adding anti solvent to get crystals; and
d) drying the crystals to get crystalline form of elafibranor.

In one another aspect, the present invention provides a process for the preparation crystalline form MK-1 of elafibranor free base, comprising the steps:

a) dissolving crude elafibranor in 1,4-dioxane at room temperature;
b) adding petroleum benzine to the solution obtained in step (a); and
c) isolating elafibranor crystalline Form MK-1.

In one another aspect, the present invention provides a process for the preparation crystalline form MK-2 of elafibranor free base, comprising,

a) dissolving crude elafibranor in 1,4-dioxane at room temperature;
b) adding n-hexane to the solution obtained in step (a); and

c) isolating elafibranor crystalline Form MK-2.

In one another aspect, the present invention provides a process for the preparation crystalline form MK-3 of elafibranor free base, comprising,

a) adding crude elafibranor in methanol at room temperature;
b) heating the solution to get clear solution;
c) adding cyclohexane to the solution obtained in step (b); and
d) isolating elafibranor crystalline Form MK-3.

In another aspect, the present invention provides an amorphous solid dispersion of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof, with atleast one pharmaceutically acceptable carrier or polymer.

In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof, comprising the steps of:

a) providing a solution of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier to the solution obtained in step a); and

c) isolating to get amorphous solid dispersion of Elafibranor free base, isomer, or pharmaceutical acceptable salt thereof.

In another aspect, the present invention provides a stable solid dispersion of elafibranor of Formula I comprising elafibranor free base with atleast one pharmaceutically acceptable carrier.

In another aspect, the present invention provides a stable solid dispersion of elafibranor salt comprising elafibranor salt along with atleast one pharmaceutically acceptable carrier.

In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of elafibranor free base comprising the steps of:

a) providing a solution of amorphous form of elafibranor free base in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier; and

c) removing the solvent and isolating to get amorphous solid dispersion of elafibranor free base.

In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of elafibranor salt comprising the steps of:

a) providing a solution of amorphous form of elafibranor salt in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier; and

c) removing the solvent and isolating to get amorphous solid dispersion of elafibranor salt.

In another aspect, the present invention provides a process for the preparation of a stable solid dispersion of elafibranor, isomer, or salt thereof, comprising the steps of:

a) providing a solution of crystalline form of elafibranor, isomer, or salt thereof, in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier or polymer; and

c) removing the solvent and isolating to get solid dispersion of elafibranor, isomer, or salt threreof.

In another aspect, the present invention provides a premix of elafibranor or its salt with atleast one pharmaceutical acceptable polymer and/or excipient.

In another aspect, the present invention provides a process for the preparation of a premix of elafibranor, isomer, or salt thereof, comprising the steps of:

a) adding elafibranor, isomer, or salt thereof, to atleast one pharmaceutically acceptable carrier to get a solid mass;
b) optionally adding solvent to get a solution; and
c) isolating the premix of elafibranor, isomer, or salt thereof, either by removal of solvent from solution of step b) or by isolating the solid mass of step a).

In another aspect, the present invention provides a process for the preparation of a premix of elafibranor isomer, or salt thereof, wherein said process comprises grinding of elafibranor or its salts with atleast one pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

Details of the drawings:

Fig. 1, which represents the X-ray (powder) diffraction (XRD) pattern of the crystalline Form MK-1 of elafibranor.

Fig. 2, which represents the Differential Scanning calorimetry (DSC) of the crystalline Form MK-1 of elafibranor.

Fig. 3, which represents the Thermogravimetric analysis (TGA) of the crystalline Form MK-1 of elafibranor.

Fig. 4, which represents the X-ray (powder) diffraction pattern of the crystalline Form MK-2 of elafibranor.

Fig. 5, which represents the Differential Scanning calorimetry (DSC) of the Crystalline Form MK-2 of elafibranor.

Fig. 6, which represents the Thermogravimetric analysis (TGA) of the Crystalline Form MK-2 of elafibranor.

Fig. 7, which represents the X-ray (powder) diffraction pattern of the Crystalline Form MK-3 of elafibranor.

Fig. 8, which represents the Differential Scanning calorimetry (DSC) of the Crystalline Form MK-3 of elafibranor.

Fig. 9, which represents the Thermogravimetric analysis (TGA) of the Crystalline Form MK-3 of elafibranor.

Fig. 10 which represents the X-ray (powder) diffraction (XRD) pattern of the amorphous form of elafibranor.

The term “Elafibranor” is used herein to describe salts, or solvates, hydrates of Elafibranor.

The terms “amorphous form of elafibranor free base or a salt thereof" and “amorphous elafibranor free base or a salt thereof” indicate that the elafibranor free base or a salt thereof is present in substantially amorphous state and is substantially free from crystalline form. It may be present in the form of solid dispersion, adsorbate or pharmaceutical composition. "Substantially pure amorphous” denotes that atleast 90%, preferably atleast 95%, more preferably atleast 99% of the elafibranor or a salt thereof is amorphous. In other words, “substantially free from crystalline form” preferably means that the amorphous form does

not contain detectable amounts, of crystalline portions of elafibranor free base or a salt thereof e.g. measurable upon X-ray powder diffraction analysis and/or Differential scanning calorimetry , and preferably the crystalline form is less than about 5% w/w of the amorphous form.

"Solid dispersion" as used herein refers to the dispersion of one or more active ingredients in an inert polymer or carrier, where the active ingredients could exist in finely crystalline, solubilized or amorphous state. Solid dispersion consists of two or more components, generally a polymer or carrier and drug optionally along with stabilizing agent (and/or surfactant or other additives). The most important role of the added polymer in solid dispersion is to reduce the molecular mobility of the drug to avoid the phase separation and re-crystallization of drug during storage. The resulting solid dispersions may have increased solubility. The increase in solubility of the drug in solid dispersion is mainly because drug remains in amorphous form which is associated with a higher energy state as compared to crystalline counterpart and due to that it requires very less external energy to dissolve. A solid dispersion is a molecular dispersion of a compound, particularly a drug substance within a polymer or carrier. Formation of a molecular dispersion provides a means of reducing the particle size to nearly molecular levels (i.e. there are no particles). As the polymer dissolves, the drug is exposed to the dissolution media as fine particles that are amorphous, which can dissolve and be absorbed more rapidly than larger particles. Further, the term "stable solid dispersion" as used in the context of the present invention, denotes a state where most of the Elafibranor or a salt thereof, preferably 90%, 95% or all of the Elafibranor or a salt thereof of the solid dispersion, is homogeneously molecularly dispersed in a solid polymer/ carrier matrix. In a preferred embodiment, in the solid dispersion according to the present invention no chemical bonds can be detected between the API and the polymer. In order to arrive at such a solid dispersion, preferably solid solution, it is required to have a substantial amount of API dissolved in a suitable solvent at least at one time point during preparation of said solid dispersion.

The term "premix" is used herein to describe combinations of Elafibranor or its salt and at least one pharmaceutically acceptable excipient/polymer, wherein individual particles of the components cannot be distinguished using techniques such as optical microscopy. In embodiments, the drug is considered as being uniformly or non-uniformly distributed over

surfaces of excipient particles. In other embodiments, the premixes are considered to be in the nature of molecular dispersions, or solid solutions. Simple mixtures of powdered ingredients will not constitute premixes.

The term "excipient" or "pharmaceutically acceptable excipient" means a component of a pharmaceutical product that is not an active ingredient, and includes but not limited to filler, diluent, disintegrants, glidants, stabilizers, surface active agents etc. The excipients that are useful in preparing a pharmaceutical composition are generally safe, non-toxic and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as well as human pharmaceutical use. One excipient can perform more than one function.

The terms “pharmaceutically acceptable salt” or “salt” are used interchangeably in the context of the present invention. “Pharmaceutically acceptable salts” or “salts” as used in the context of the present invention refers to inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid salt, carbonate salts; organic acids such as succinic acid, formic acids, acetic acid, diphenyl acetic acid, palmoic acid, triphenylacetic acid, caprylic acid, dichloroacetic acid, trifluoro acetic acid, propionic acid, butyric acid, lactic acid, citric acid, gluconic acid, mandelic acid, tartaric acid, malic acid, adipic acid, aspartic acid, fumaric acid, glutamic acid, maleic acid, malonic acid, benzoic acid, *p*-chlorobenzoic acid, dibenzoyl tartaric acid, oxalic acid, nicotinic acid, *o*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, 1-hydroxy-naphthalene-2-carboxylic acid, hydroxynaphthalene-2-carboxylic acid, ethanesulfonic acid, ethane-1,2-disulfonic acid, 2-hydroxyethane sulfonic acid, methanesulfonic acid, (+)-camphor-10-sulfonic acid, benzenesulfonic acid, naphthalene-2-sulfonic acid, p-toluenesulfonic acid and the like. The inorganic salts may further includes alkali metal and alkaline earth metal salts such as sodium, potassium, barium, lithium, calcium, magnesium, rhodium, zinc, cesium, selenium, and the like or, benethamine, benzathine, diethanolamine, ethanolamine, 4-(2-hydroxy-ethyl)morpholine, 1-(2-hydroxyethyl)pyrrolidine, N-methyl glucamine, piperazine, triethanol amine or tromethamine and the like.

An “alcohol” as used in the context of the present invention, is an organic compound containing a carbon bound to a hydroxyl group. Alcohol includes, but are not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol,

hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, phenol, glycerol, or the like.

The present invention is focussed towards the development of amorphous and crystalline forms of elafibranor free base or pharmaceutical acceptable salt thereof by employing simple, low cost and less time consuming process wherein the crystalline forms so obtained possesses good stability, good processability and other favourable properties.

Accordingly, in main embodiment, the present invention provides an amorphous form of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof.

In another embodiment, the present invention provides a process for the preparation of amorphous form of elafibranor free base, comprising the steps:

a) dissolving Elafibranor in alcoholic solvent,
b) stirring the reaction mixture to get the clear solution,
c) distilling the solvent to get the oil;
d) adding anti-solvent to the reaction mixture; and
e) isolating the amorphous form of Elafibranor of Formula I.

In another embodiment, the present invention provides a process for the preparation of amorphous form of elafibranor free base, comprising the steps:

a) dissolving Elafibranor in methanol,
b) stirring the reaction mixture to get the clear solution,
c) distilling the solvent to get the oil;
d) adding cyclohexane to the reaction mixture; and
e) isolating the amorphous form of Elafibranor of Formula I.

In another embodiment, the present invention provides a process of preparation of crystalline form of elafibranor free base or pharmaceutical acceptable salt thereof comprising the steps of:

a) adding crude elafibranor in an organic solvent;

b) optionally heating the solution below 100°C to get the homogenous solution;
c) adding anti solvent to get crystals; and
d) isolating elafibranor crystalline form.

In further embodiment, the elafibranor used in step a) is prepared by any of the conventional methods known in the prior arts.

In a preferred embodiment, the elafibranor used in step a) is either a crude mass, or an amorphous form or any of the crystalline forms.

In another embodiment, the organic solvent used to dissolve elafibranor in step a) is selected from the group comprising of ketones such as methyl isobutyl ketone, acetone and the like; alcohol such as ethanol, methanol, n-propanol, butanol, isobutanol and tert-butanol; acetates such as ethyl acetate, propyl acetate, n-pentyl acetate, isopropyl acetate, butyl acetate and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like, and preferably the organic solvent is selected from methyl isobutyl ketone, methanol, ethyl acetate, 1,4-dioxane, and mixture thereof.

In another embodiment, the another solvent used as anti-solvent in steps b) or step c) is selected from the group comprising of organic and inorganic solvents such as n-heptane, cyclohexane, n-hexane, petroleum benzine, water, and mixture thereof.

In another embodiment, the present invention is to provide a process for the preparation of stable amorphous form of elafibranor free base, isomer or pharmaceutically acceptable salt thereof, wherein said amorphous form is stable for atleast six months at 40°C and 75% RH and can be formulated easily for administering to patients.

As used herein, the term stable amorphous includes amorphous elafibranor that after exposure to 40°C °C/75% RH for a period of six months or 25°C /60% RH., for a period of at least 12 months contains less than about 0.5% (wt/wt) total impurities and doesn't change to any other solid forms.

In another embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) at 9.34, 9.86, 10.72, 11.88, 12.25, 14.29, 15.85, 16.06, 16.52, 16.94, 17.54, 18.42, 18.72, 19.25, 19.79, 20.45, 20.92, 21.50, 22.62, 23.20, 24.01, 24.49, 24.97, 25.09, 25.68, 26.21, 26.74, 27.71, 28.13, 28.41, 29.26, 29.52, 30.00, 30.23, 30.50, 30.90, 31.54, 31.97, 32.50, 33.45, 34.03, 34.25, 34.83, 35.60, 36.16, 37.26, 37.61, and 38.16 ±0.2.

In another embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) at 9.34, 10.72, 14.29, 17.54, 18.72, 20.45, 24.01, 25.68, and 26.21±0.2.

In other embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its XRD pattern as depicted in Fig-1.

In other embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its DSC having endothermic peaks at 158.13°C and 262.85° C.

In other embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its DSC as depicted in Fig-2.

In other embodiment, the present invention provides a crystalline Form MK-1 of elafibranor free base, characterized by its TGA corresponding to a weight loss of about 2.77 % w/w as depicted in Fig-3.

In another embodiment the present invention provides a process for the preparation of Form MK-1 of elafibranor free base, comprising,

a) dissolving crude elafibranor in 1,4-dioxane at room temperature;
b) adding petroleum benzine to the solution obtained in step (a); and
c) isolating elafibranor crystalline Form MK-1.

In other embodiment, the present invention provides a crystalline Form MK-2 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) 6.81, 7.45, 8.21, 9.32, 10.64, 11.55, 12.22, 13.68, 14.27, 15.02, 15.38, 16.50, 17.08, 18.93, 20.08, 20.57, 21.36,

21.86, 23.68, 24.68, 25.30, 26.10, 26.85, 27.57, 28.14, 28.96, 29.57, 30.23, 30.93, 31.99, 32.60, 33.64, 34.05, 35.08, 35.76, 36.37, 36.98, 37.77, 38.82 and 39.34 ±0.2.

In other embodiment, the present invention provides a crystalline Form MK-2 of elafibranor free base characterized by its XRD pattern as depicted in Fig-4.

In other embodiment, the present invention provides a crystalline Form MK-2 of elafibranor free base, characterized by its DSC having endothermic peaks at 148.15°C, 158.97°C and 265.44°C.

In other embodiment, the present invention provides a crystalline Form MK-2 of elafibranor free base, characterized by its DSC as depicted in Fig-5.

In other embodiment, the present invention provides a crystalline Form MK-2 of elafibranor free base, characterized by its TGA curve corresponding to a weight loss of about 0.904 % w/w as depicted in Fig-6.

In another embodiment the present invention provides process for the preparation of crystalline Form MK-2 of elafibranor free base, comprising,

d) dissolving crude elafibranor in 1,4-dioxane at room temperature;
e) adding n-hexane to the solution obtained in step (a); and
f) isolating elafibranor crystalline Form MK-2.

In one another embodiment, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its XRD pattern having peaks (2θ values) at 7.74, 8.22, 10.30, 10.66, 10.98, 11.56, 12.55, 13.10, 13.34, 14.19, 15.04, 15.48, 15.93, 16.47, 17.14, 17.76, 18.35, 18.93, 19.74, 20.65, 21.70, 22.82, 23.86, 25.3025.83, 26.78, 27.33, 28.85, 29.5430.65, 32.48 and 34.21 ±0.2.

In other embodiment, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its XRD pattern as depicted in Fig-7.

In other embodiment, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its DSC having endothermic peaks at 146.97°C, 155.41°C and 273.35°C.

In other embodiment, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its DSC as depicted in Fig-8.

In other embodiment, the present invention provides a crystalline Form MK-3 of elafibranor free base, characterized by its TGA corresponding to a weight loss of about 0.125 % w/w as depicted in Fig-9.

In another embodiment the present invention provides a process for the preparation of crystalline Form MK-3 of elafibranor free base or pharmaceutical acceptable salt thereof, comprising,

a) adding elafibranor in methanol at room temperature;
b) heating the solution to get clear solution;
c) adding cyclohexane to the solution obtained in step (b); and
d) isolating elafibranor crystalline Form MK-3.

In further embodiment, the present invention further relates to a composition comprising crystalline form MK-1 or MK-2 or MK-3 of elafibranor free base.

In another embodiment, the present invention provides the crystalline forms of elafibranor free base or pharmaceutical acceptable salt thereof that is characterized by particle size distribution wherein, d_{90} is 0.1µm to 200µm.

In another embodiment, the present invention provides the crystalline forms of elafibranor free base or pharmaceutical acceptable salt thereof that is characterized by particle size distribution wherein, d_{90} is 2.0 µm to 150µm.

In a preferred embodiment, the crystalline forms of elafibranor may be isolated from the reaction mixture by purification, centrifugation, crystallization, filtration, extraction or evaporation.

In one more embodiment, the present invention provides an amorphous form of elafibranor, characterized by XRD pattern as depicted in Fig-10.

In another embodiment, the present invention provides an amorphous solid dispersion of elafibranor free base, isomer or salt thereof, with atleast one pharmaceutically acceptable carrier or polymer.

In another embodiment, the present invention provides a process for the preparation of an amorphous solid dispersion of elafibranor salt comprising the steps of:

a) providing a solution of amorphous form of elafibranor salt in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier; and

c) removing the solvent and isolating to get amorphous solid dispersion of elafibranor salt.

In further embodiment, the suitable solvent used in step a) is selected from water or water miscible solvents.

In another embodiment, the elafibranor and the pharmaceutically acceptable carriers may be dissolved either in the same solvent or they may be dissolved in different solvents and then combined to form a mixture. In embodiments, the solid dispersion described herein comprises amorphous or crystalline elafibranor or its salt, and the carrier present in weight ratios ranging from about 1:99 to about 99:1. Preferably, the ratio is about 50:50. In some embodiments, the solid dispersion described herein comprises one or more pharmaceutically acceptable carrier or polymer.

In another embodiment, the suitable solvent used for preparing solid dispersion of elafibranor, isomer, or a salt thereof, is selected from, but not limited to, the group comprising of alcohol such as methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, polyethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, phenol, glycerol and the like; halogenated solvent such as

dichloromethane, chlorobenzene, tetrachloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform and the like; ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diethyl ketone, methyl t-butyl ketone and the like; ester solvent such as methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, propenyl acetate, t-butyl acetate, isobutyl acetate, n-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate and the like; hydrocarbon solvent such as toluene, xylene, heptane, cyvlohexane and the like, ether such as tetrahydrofuran, methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole and the like; nitrile such as acetonitrile, propionitrile, butanenitrile and the like; water; and mixture thereof.

In another embodiment, elafibranor or a salt thereof as used for preparing amorphous solid dispersion, can be either crystalline, amorphous or mixture in nature.

In another embodiment, the present application provides a pharmaceutical composition comprising a stable solid dispersion of elafibranor or salt thereof together with atleast one pharmaceutically acceptable excipient

In an embodiment, the present application provides a stable solid dispersion of elafibranor free base, or pharmaceutically acceptable salt thereof, with less than 5% of crystallinity, preferably with less than 1% crystallinity and more preferably with less than 0.5% crystallinity as per X-ray diffraction analysis.

In one another embodiment, the present invention provides a premix of elafibranor or its salt with atleast one pharmaceutical acceptable polymer and/or excipient.

In one another embodiment, the present invention provides a process for the preparation of a premix of elafibranor, isomer or pharmaceutically acceptable salt thereof, comprising the steps of:

a) adding elafibranor, isomer, or pharmaceutically acceptable salt thereof, to atleast one pharmaceutically acceptable polymer to get a solid mass;

b) optionally adding solvent to get a solution; and

c) isolating the premix of elafibranor, isomer or pharmaceutically acceptable salt either by removal of solvent from solution of step b) or by isolating the solid mass of step a).

In another embodiment, the present invention provides a process for the preparation of a premix of elafibranor isomer, or salt thereof, wherein said process comprises grinding of elafibranor or its salts with atleast one pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a pharmaceutical composition comprising a premix of elafibranor, isomer, or a salt thereof, together with atleast one pharmaceutically acceptable excipient.

In another embodiment, elafibranor or a salt thereof as used for preparing premix, can be either crystalline, amorphous or mixture in nature.

In preferred embodiments, removal of solvent at any stage of preparation of amorphous form/ solid dispersion/ premix of elafibranor or its salt may include, but not limited to, solvent evaporation under atmospheric pressure or reduced pressure / vacuum such as a rotational distillation using Büchi® Rotavapor®, flash evaporation, rotational dying, agitated nutsche filter drying, spray drying, freeze drying, thin film drying, agitated thin film drying, rotary vacuum paddle dryer (RVPD), lyophilization, and the like. In preferred embodiment, the solvent may be removed under reduced pressures and at a temperature of less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C, less than about -60°C, less than about -80°C, or any other suitable temperatures.

In another embodiment, pharmaceutically acceptable carrier used for preparing solid dispersion may include, but not limited to, an inorganic oxide such as SiO_2, TiO_2, ZnO_2, ZnO, Al_2O_3 and zeolite; a water insoluble polymer is selected from the group consisting of cross-linked polyvinyl pyrrolidinone, cross-linked cellulose acetate phthalate, cross-linked hydroxypropyl methyl cellulose acetate succinate, microcrystalline cellulose, polyethylene glycol, polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone

copolymer, cross-linked carboxymethyl cellulose, sodium starch glycolat, and cross-linked styrene divinyl benzene or any other excipient at any aspect of present application. In an embodiment, atleast one pharmaceutically acceptable excipient may be selected from the group consisting of polyvinyl pyrrolidone, povidone K-30, povidone K-60, Povidone K-90, polyvinylpyrrolidone vinylacetate, co-povidone NF, polyvinylacetal diethylaminoacetate (AEA®), polyvinyl acetate phthalate, polysorbate 80, polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188), polyoxyethylene (40) stearate, polyethyene glycol monomethyl ether, polyethyene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit or Eudragit-RLPO), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), hydroxypropylmethyl cellulose, hydroxypropyl cellulose SSL (HPC-SSL), hydroxypropyl cellulose SL(HPC-SL), hydroxypropyl cellulose L (HPC-L), hydroxyethyl cellulose, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG)), gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxy methyl ethyl cellulose and the like; cyclodextrins, gelatins, hypromellose phthalates, sugars, polyhydric alcohols, and the like; water soluble sugar excipients, preferably having low hygroscopicity, which include, but are not limited to, mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrins, lactitol and the like; polyethylene oxides, polyoxyethylene derivatives, polyvinyl alcohols, propylene glycol derivatives and the like; organic amines such as alkyl amines (primary, secondary, and tertiary), aromatic amines, alicyclic amines, cyclic amines, aralkyl amines, hydroxylamine or its derivatives, hydrazine or its derivatives, and guanidine or its derivatives, or any other excipient at any aspect of present application. The use of mixtures of more than one of the pharmaceutical excipients to provide desired release profiles or for the enhancement of stability is within the scope of this invention. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, and mixtures are all within the scope of this invention without limitation. Solid dispersions of the present application also include the solid dispersions obtained by combining elafibranor or a salt thereof with a suitable non-polymeric excipient by employing techniques known in the art or procedures described or exemplified in any aspect of the instant application.

In another embodiment, the present invention provides stable amorphous form of elafibranor or a salt thereof, its stable solid dispersion comprising elafibranor or a salt thereof, wherein

said elafibranor or a salt thereof is having a chemical purity of atleast 99% by HPLC or atleast 99.5% by HPLC or atleast 99.9% by HPLC.

In another embodiment, the amorphous solid dispersion of elafibranor or salt thereof, obtained by the process of the present invention is characterized by particle size distribution of less than about 300µm, preferably less than about 200µm and most preferably about 100µm.

In another embodiment, the amorphous form of elafibranor or salt thereof, obtained by the process of the present invention is characterized by particle size distribution of less than about 300µm, preferably less than about 200µm and most preferably about 100µm.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

EXAMPLES

Example-1: Form MK-1 of Elafibranor

Charged 1,4-dioxane (5.0 ml) and elafibranor (1.7 g) in a 100 ml 4-necked round bottom flask at 20-25°C. Stirred the reaction mass for 10-15 minutes at 20-25°C. Charged 20 ml petroleum benzine slowly in the above round bottom flask at 20-25°C. Reaction mixture was stirred for 4-5 hours at 20-25°C. Filtered the reaction mass at 20-25°C and washed with 2 ml petroleum benzine at 20-25°C. Material was dried under vacuum for 10-12 hour at 40-45°C to obtain the crystalline Form MK-1 of elafibranor.

Yield: 1.35 gm

Example-2: Form MK-2 of Elafibranor

Charged 1,4-dioxane (5.0 ml) and elafibranor (1.0 g) in a 100 ml 4-necked round bottom flask at 20-25°C. Stirred the reaction mass for 10-15 minutes at 20-25°C. Charged 20 ml n-hexane slowly in the above round bottom flask at 20-25°C. Reaction mixture was stirred for 4-5 hours at 20-25°C. Filtered the reaction mass at 20-25°C and washed with 2 ml n-hexane

at 20-25°C. Material was dried under vacuum for 10-12 hour at 40-45°C to obtain the crystalline Form MK-2 of elafibranor.

Yield: 0.90 gm

Example-3: Form MK-3 of elafibranor

Charged Methanol (5.0 ml) and elafibranor (1.0 g) in a 100 ml 4-necked round bottom flask at 20-25°C. Stirred the reaction mass for 10-15 minutes at 20-25°C and raised the temperature up to 60-65°C. Charged 20 ml cyclohexane slowly in the above reaction mixture at 60-65°C. Cooled the reaction mixture at 20-25°C and stirred for 4-5 hours at 20-25°C. Filtered the reaction mixture at 20-25°C and washed with 2 ml cyclohexane at 20-25°C. Material was dried under vacuum for 20-25 to obtain the crystalline Form MK-3 of elafibranor.

Yield: 0.85 gm

Example-4: Amorphous form of Elafibranor

Charged methanol (10.0 ml) and elafibranor (2.0 g) in a 100 ml 4-neck round bottom flask at 20-25°C. Stirred the reaction mass for 10-15 minutes at 20-25°C. Reaction mixture was heated at 60-65°C. After getting the clear of solution, reaction mixture was stirred for 1-2 hours at 60-65°C. Distilled out methanol at 60-65°C. Charged 20 ml cyclohexane slowly in the above round bottom flask at 60-65°C. Reaction mixture was cooled to 20-25°C and stirred for 4-5 hours at 20-25°C. Filtered the reaction mass at 20-25°C and washed with 4 ml cyclohexane at 20-25°C. Dried the material under vacuum for 20-25 hour at 40-45°C.

Yield: 1.80 gm

Example-5 Preparation of solid dispersion of Elafibranor with HPMC

120mg of Elafibranor and 80mg of hydroxypropyl methyl cellulose were dissolved in dimethylsulfoxide and stirred until clear solution is obtained. The clear solution was evaporated under reduced pressure to obtain the solid dispersion of elafibranor with hydroxypropyl methylcellulose.

Example-6: Preparation of solid dispersion of Elafibranor free base with HPC (Hydroxypropyl cellulose)

A mixture of Elafibranor free base (1.0 g) and HPC (1.0 g) was dissolved in methanol (25 mL) at 25°C and filtered the solution to make it particle free. The solvent was evaporated in rotavapour under reduced pressure at 50°C to obtain title compound.

Example 7: Preparation of solid dispersion of Elafibranor free base with more than one pharmaceutically acceptable carrier

To a mixture of hydroxypropylmethylcellulose (1g), low-substituted hydroxypropylcellulose (3 g) and lactose (5 g) is added a solution of elafibranor (1 g) in absolute ethanol and after stirring, the ethanol is evaporated in vacuo to provide a solid dispersion.

Example 8: To the solid dispersion (598 g) obtained in Example 7 is added magnesium stearate (2 g) and the mixture is molded into tablets each weighing 180 mg in the conventional manner.

Example-9: Preparation of Stable solid dispersion of Elafibranor with PVP K-90

A mixture of Elafibranor (0.5 g) and PVP K-90 (0.5 g) was dissolved in ethanol (25 mL) at 25°C and filtered the solution to make it particle free. The solvent was evaporated in rotavapour under reduced pressure at 50°C to obtain title compound.

Example 10: Ball mill mixed-grinding method

Using a ball mill (SPEX Industries), a mixture of elafibranor (2 g), hydroxypropylmethylcellulose (10 g) and crystalline cellulose (15 g) is mix-ground for 4 hours to provide a solid dispersion.

CLAIMS:

1. A stable amorphous form of elafibranor.

2. A process for preparing stable amorphous form of elafibranor of Formula I, comprising the steps:
   a) dissolving Elafibranor in alcoholic solvent,
   b) stirring the reaction mixture to get the clear solution,
   c) distilling the solvent to get the residue;
   d) adding anti-solvent to the reaction mixture; and
   e) isolating the amorphous form of Elafibranor of Formula I.

3. A process for preparing stable amorphous form of elafibranor of Formula I, comprising the steps:
   a) dissolving Elafibranor in methanol,
   b) stirring the reaction mixture to get the clear solution,
   c) distilling the solvent to get the residue;
   d) adding cyclohexane to the reaction mixture; and
   e) isolating the amorphous form of Elafibranor of Formula I.

4. A crystalline form MK-1 of elafibranor of Formula I characterized by a powder X-ray diffraction diffractogram pattern having peaks at 9.34, 10.72, 11.88, 12.25, 14.29, 15.85, 16.06, 16.52, , 17.54, 19.25, 19.79, 20.45, 24.01, 24.49 and 24.97 ±0.2.

5. A crystalline form MK-1 of Elafibranor of Formula I as claimed in claim 4, is further characterized by a powder X-ray diffraction diffractogram pattern having peaks at 9.34, 9.86, 10.72, 11.88, 12.25, 14.29, 15.85, 16.06, 16.52, 16.94, 17.54, 18.42, 18.72, 19.25, 19.79, 20.45, 20.92, 21.50, 22.62, 23.20, 24.01, 24.49, 24.97, 25.09, 25.68, 26.21, 26.74, 27.71, 28.13, 28.41, 29.26, 29.52, 30.00, 30.23, 30.50, 30.90, 31.54, 31.97, 32.50, 33.45, 34.03, 34.25, 34.83, 35.60, 36.16, 37.26, 37.61, and 38.16 ±0.2.

6. The crystalline form MK-1 of Elafibranor of Formula I as claimed in claim 5 characterized by atleast one of:

a) an X-ray powder diffraction (XRD) pattern as depicted in Fig. 1,
b) DSC with endotherms peak at 158.13°C with onset at about 156.41, or
c) a weight loss of about 2.77% w/w, as measured by a Thermo gravimetric analysis (TGA).

7. A process for preparing crystalline form MK-1 of elafibranor of Formula I, comprising the steps:
a) dissolving elafibranor of Formula I in 1,4-dioxane,
b) adding petroleum benzine to the reaction mixture, and
c) isolating the crystalline form MK-1 of elafibranor of Formula I.

8. A process for preparing crystalline form MK-2 of elafibranor of Formula I, comprising the steps:
a) dissolving elafibranor in 1,4-dioxane at room temperature;
b) adding n-hexane to the solution obtained in step (a); and
d) isolating elafibranor crystalline Form MK-2 of elafibranor of Formula I.

9. A process for preparing crystalline form MK-3 of elafibranor of Formula I, comprising the steps:
a) adding elafibranor in methanol at room temperature;
b) heating the solution to get clear solution;
c) adding cyclohexane to the solution obtained in step (b); and
d) isolating elafibranor crystalline Form MK-3 of elafibranor of Formula I.

10. Amorphous solid dispersion of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof, with atleast one pharmaceutically acceptable carrier or polymer.

11. A process for the preparation of an amorphous solid dispersion of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof, comprising the steps of:
a) providing a solution of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier to the solution obtained in step a); and

c) isolating to get amorphous solid dispersion of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof.

12. A process for the preparation of solid dispersion comprising elafibranor free base, isomer, or pharmaceutical acceptable salt thereof and one or more pharmaceutically acceptable carriers, comprising the steps of:

a) providing a solution of elafibranor free base, isomer, or pharmaceutical acceptable salt thereof in a suitable solvent;

b) adding atleast one pharmaceutically acceptable carrier to the solution obtained in step a); and

c) isolating to get amorphous solid dispersion of Elafibranor free base, isomer, or pharmaceutical acceptable salt thereof.

13. A pharmaceutical composition comprising elafibranor and atleast one pharmaceutically acceptable excipients.

14. A premix of elafibranor or its salt with atleast one pharmaceutical acceptable polymer and/or excipient.

15. A process for the preparation of a premix of elafibranor, isomer, or salt thereof, comprising the steps of:

a) adding elafibranor, isomer, or salt thereof, to atleast one pharmaceutically acceptable carrier to get a solid mass;

b) optionally adding solvent to get a solution; and

c) isolating the premix of elafibranor, isomer, or salt thereof, either by removal of solvent from solution of step b) or by isolating the solid mass of step a).

16. Elafibranor free base or pharmaceutical acceptable salt characterized by particle size distribution wherein, d_{90} is 0.1µm to 300µm.

17. A stable amorphous form of elafibranor, wherein said elafibranor having a chemical purity of atleast 99%.

DRAWINGS

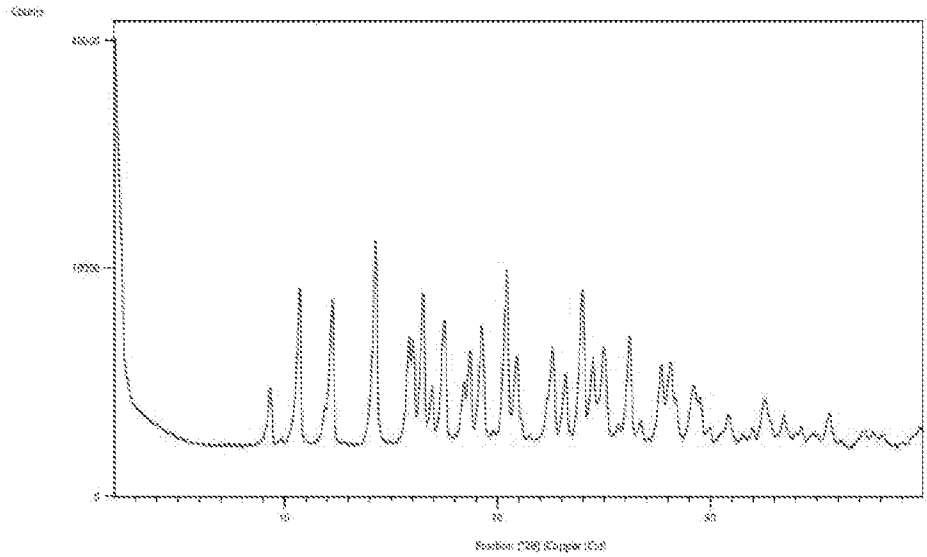


Fig.-1

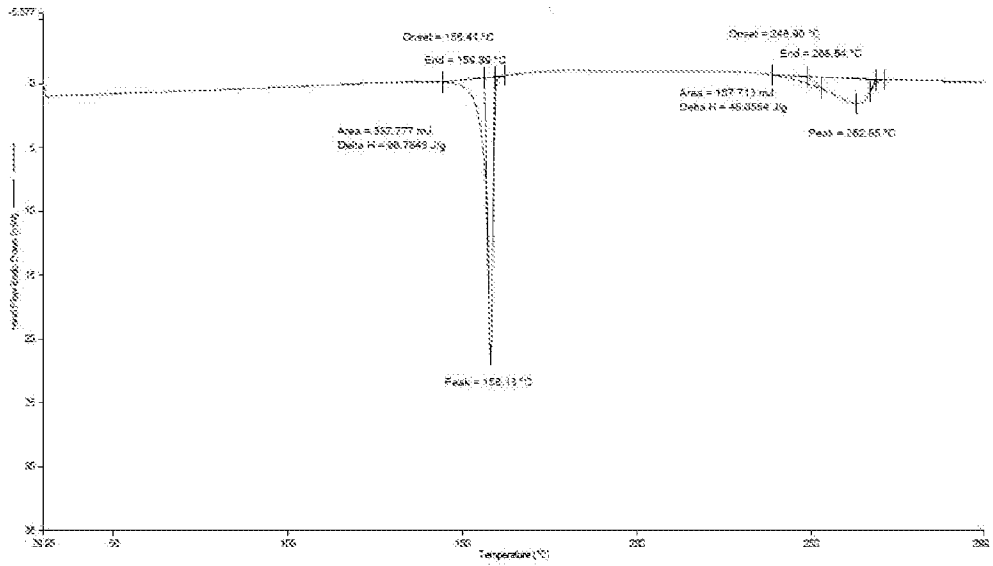


Fig.-2

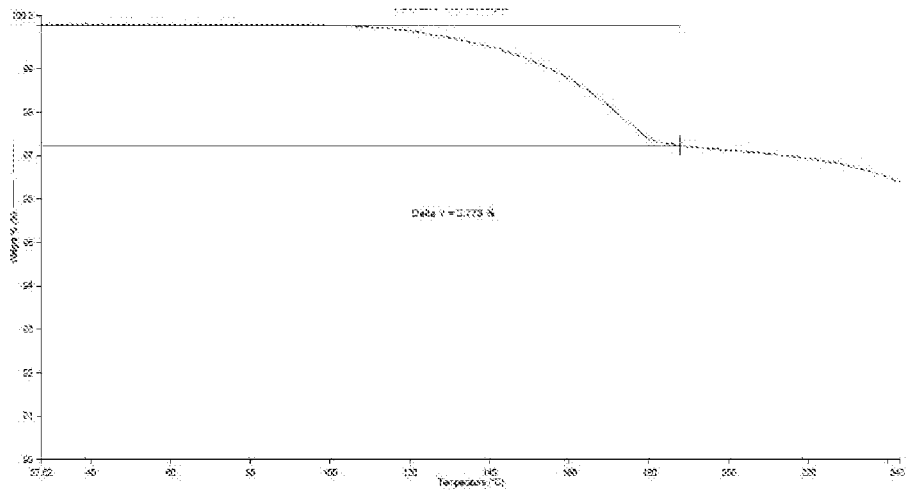


Fig.-3

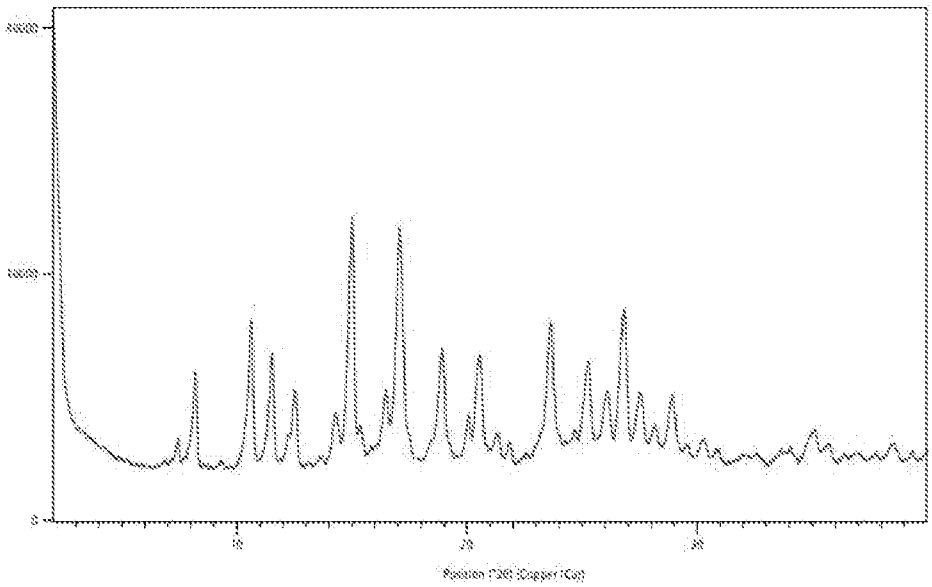
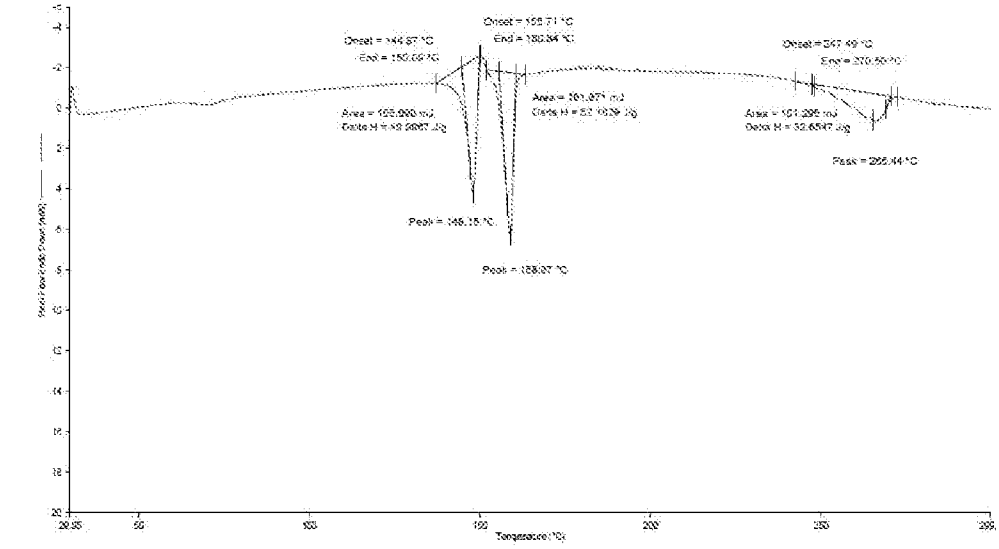


Fig.-4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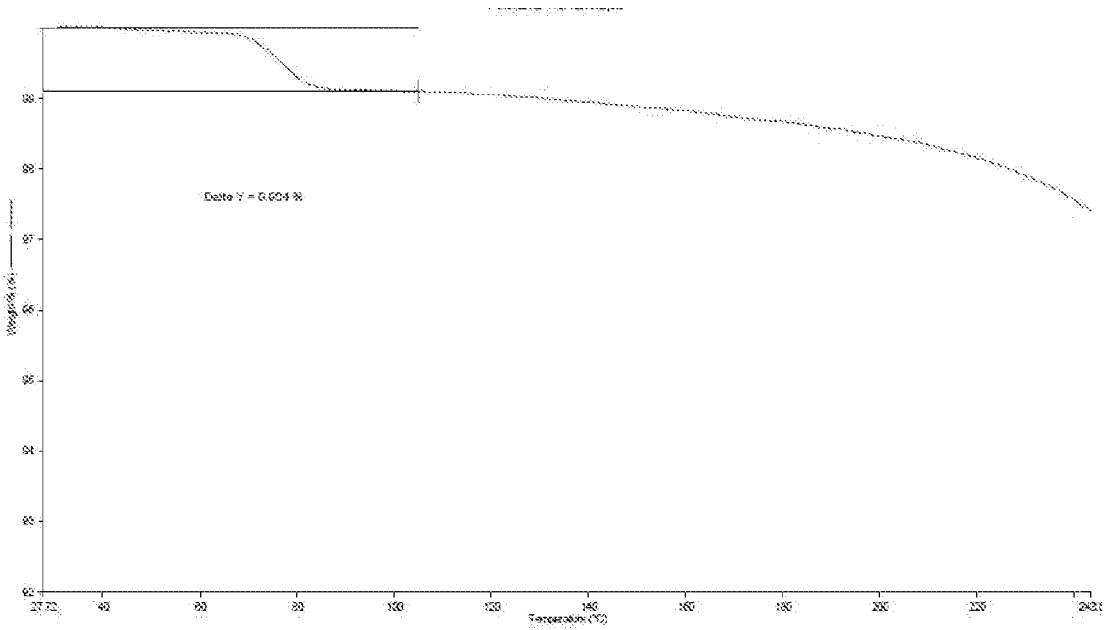
Peak = 266.44 °C
Temperature (°C)

Fig.-5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Temperature (°C)

Fig.-6

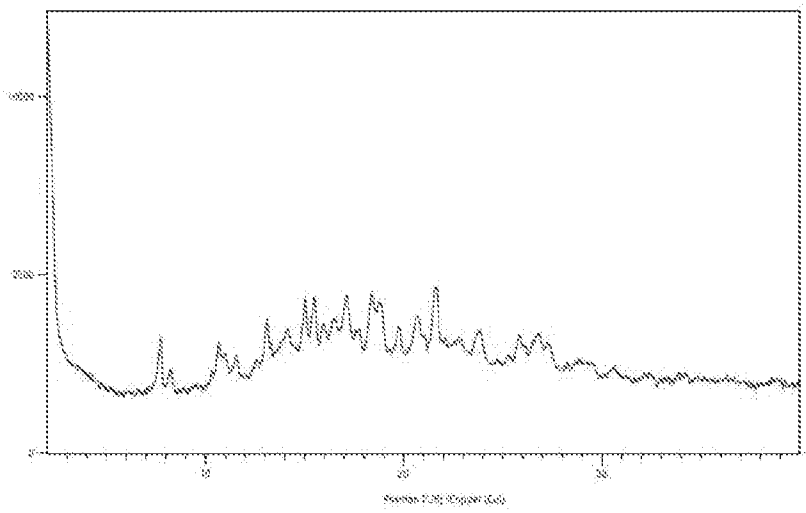
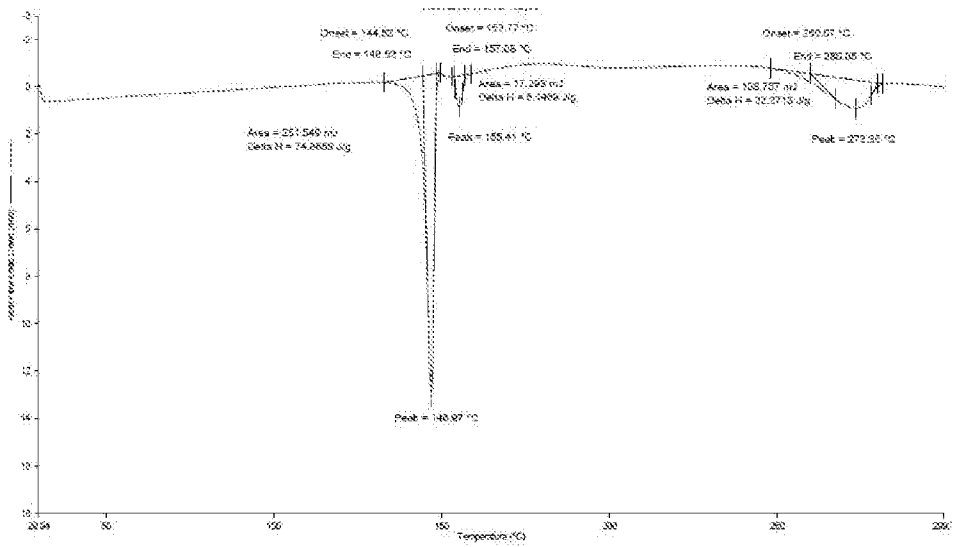


Fig.-7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Temperature (°C)

Fig.-8

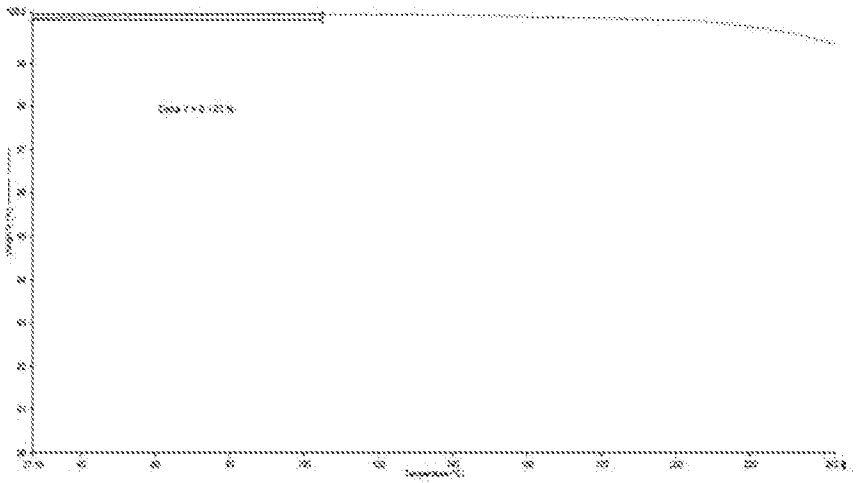

Fig.-9

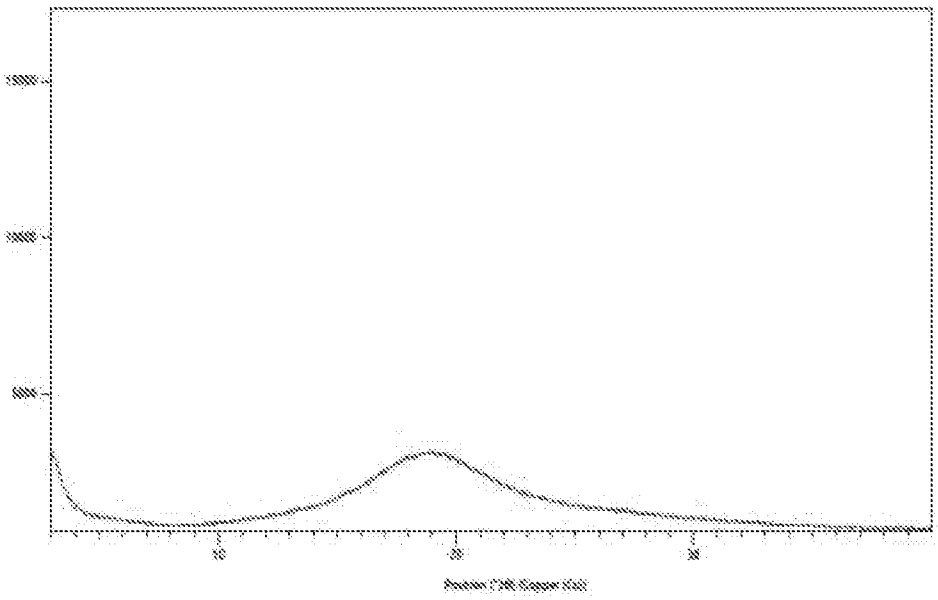

Fig. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/060341

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00,C07C323/52,C07C323/22,C07C67/30,A61P1/16 Version=2020.01

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, C07C, 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 practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2018060373 A1; (NASHPHARM [FR]); 05 April 2018. Formula 1, examples 1-3, figures 1, 8, summary	1, 10, 13, 16-17
A	Formula 1, examples 1-3, figures 1, 8, summary	2-9, 11-12, 14-15
	WO2004/005233 A1; (CAUMONT-BERTRAND KARINE [FR]; GENFIT [FR]; NAJIB JAMILA [FR]); 15 July 2004. Column 51, lines 35-67, method 5 , compound 29, claims	1, 10, 13, 16-17
A	Column 51, lines 35-67, method 5 , compound 29, claims	2-9, 11-12, 14-15
A	CN106674069 B; (SHANGHAI BOCIMED PHARMACEUTICAL CO LTD); 11 May 2017. Examples, claims	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
20-02-2020	20-02-2020
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