

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

13 December 2018 (13.12.2018)



WIPO | PCT



(10) International Publication Number

WO 2018/225085 A1

(51) International Patent Classification:

A61K 9/14 (2006.01)

A61P 3/00 (2006.01)

A61K 31/4025 (2006.01)

MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/IN2018/050362

(22) International Filing Date:

05 June 2018 (05.06.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201721019661

05 June 2017 (05.06.2017)

IN

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(71) Applicant: CIPLA LIMITED [IN/IN]; Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra 400013 (IN).

(72) Inventors: CHENNURU, Ramanaiah; Velagala ponnuru (Vi) (Po), Sulluru peta (Md), Nellore(Dt), Andhra Pradesh 524121 (IN). PATHI, Srinivas Laxminarayan; No. 530, 7th Cross, 4th main, III Block, HBR Layout, Bangalore, Karnataka 560043 (IN). PULLELA, Venkata Srinivas; 402, block-II, Bildens Paradise 5th main, Malleshpalya, Bangalore, Karnataka 560075 (IN). RAO, Dharmaraj Ramachandra; 4/403, Garden Enclave, Pokhran Road 2, Thane (West), Maharashtra 400601 (IN). MALHOTRA, Geena; 3403 Springs, Island City Centre, Next to Wadala Telephone Exchange, G. D Ambekar Marg, Dadar (East), Mumbai, Maharashtra 400014 (IN).

(74) Agent: NAIR, Gopakumar G.; Gopakumar Nair Associates, "Shivmangal", 3rd Floor, Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai, Maharashtra 400101 (IN).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

(54) Title: STABLE SOLID DISPERSIONS OF ELIGLUSTAT HEMITARTRATE

(57) Abstract: A pharmaceutical composition comprising eliglustat hemitartrate dissolved and/or dispersed in a pharmaceutical carrier selected from the group consisting of polymers of cellulose derivatives, cyclodextrins and lactose monohydrate to form a solid dispersion at ambient temperature having improved bioavailability.



WO 2018/225085 A1

“STABLE SOLID DISPERSIONS OF ELIGLUSTAT HEMITARTRATE”

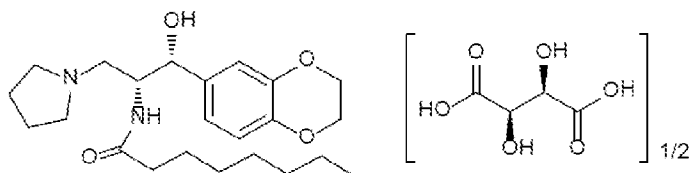
Technical field of the invention

The present invention relates to stable solid dispersions of eliglustat hemitartrate and process for preparation thereof. The invention further provides process for preparation of pure eliglustat hemitartrate in amorphous form.

Background of the invention

Eliglustat, chemically known as N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)octanamide, glucosylceramide synthase inhibitor.

Eliglustat is marketed under brand name Cerdelga in form of hemitartrate salt. Eliglustat has following structural formula as eliglustat hemitartrate salt.



US7196205 discloses a process for the preparation of Eliglustat.

US2013137743 discloses preparation of crystalline eliglustat hemitartrate.

WO2016001885 discloses preparation of a solid dispersion comprising an amorphous form of eliglustat hemitartrate and dispersing agents namely hydroxypropyl methyl cellulose (HPMC), Polyvinyl pyrrolidone (PVP), Colloidal silicon dioxide.

WO2016166170 discloses process of preparation of crystalline eliglustat hydrochloride.

In view of the above discussed prior art references, it is evident that eliglustat or salts exhibits different polymorphic forms under differential conditions that include solvent, moisture, temperature, time and drying conditions and thus the
5 bioavailability of the same also varies with polymorphic modification.

It is known that solid amorphous dispersions comprising a low-solubility drug in a polymer can increase the maximum concentration of drug that will dissolve in an aqueous solution in in vitro tests, or that will dissolve in body fluids such as those
10 present in the gastrointestinal (GI) tract in in Vivo tests, and, in turn, enhance the bioavailability of the drug. Solid dispersions of a drug in a matrix such as a polymer- can be prepared, for example, by forming a homogeneous solution or melt of the drug in matrix material, followed by solidifying the mixture by cooling or removal of solvent. Such solid dispersions of crystalline drugs have been known for more
15 than two decades, and often show enhanced bioavailability when administered orally relative to compositions comprising undispersed crystalline drug.

A major problem with current solid dispersions of drugs is that while the dispersions may show enhanced bioavailability of the low-solubility drug if administered
20 shortly after preparation, however, bioavailability typically decreases over a period of time upon storage due to changed environment in the solid dispersion. Such solid dispersions are often physically unstable in that the drug present in the dispersion reverts to the crystalline form upon storage-particularly at elevated temperature and humidity. Accordingly, the dispersion cannot be used to provide proper dosing of
25 the drug because the bioavailability of the drug changes over time.

Further, amorphous dispersions of drugs tend to convert to crystalline forms over time, which can lead to improper dosing due to differences of the solubility of crystalline drug material compared to amorphous drug material.

What is therefore desired is a composition comprising a stable dispersion of eliglustat hemitartrate in a polymer that provides superior bioavailability, together with improved stability of the dispersion in typical storage environments, particularly for dispersions where the drug is present in concentrations above its
5 equilibrium value.

Objectives of the invention

Accordingly, the object of the present invention is to provide a stable solid dispersion of eliglustat hemitartrate and processes for the preparation thereof.

10

Another object of the present invention is to provide a pharmaceutical composition comprising stable solid dispersion of eliglustat hemitartrate.

Yet another object of the present invention is to provide a process for the
15 preparation of pure amorphous form of eliglustat hemitartrate.

Summary of the invention

The present invention provides a novel pharmaceutical solid dispersion and the process for its preparation whereby water insoluble drugs are combined with a
20 carrier.

Accordingly, in a first aspect, the present invention provides a solid dispersion comprising an eliglustat hemitartrate and one or more pharmaceutically acceptable carrier s and compositions thereof.

25

According to the second aspect, the present invention provides processes for the preparation of a solid dispersion comprising an eliglustat hemitartrate and one or more pharmaceutically acceptable carrier polymers.

30 The novel solid dispersions of the present invention are characterized by unique XRD and DSC patterns.

According to the third aspect, the present invention provides a novel process for the preparation of pure amorphous form of eliglustat hemitartrate.

The amorphous form of eliglustat hemitartrate prepared according to the present invention is characterized by unique XRD patterns.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows modulated differential scanning calorimetry (DSC) of a solid dispersion of Eliglustat hemitartrate with lactose monohydrate prepared according to Example 1.

Figure 2 shows powder X-ray power diffraction ("PXRD") pattern of a solid dispersion of Eliglustat hemitartrate with lactose monohydrate prepared according to Example 1.

Figure 3 depicts powder X-ray power diffraction ("PXRD") pattern of a solid dispersion of Eliglustat hemitartrate with HPMC-phthalate prepared according to Example 3.

Figure 4 shows modulated differential scanning calorimetry (DSC) of a solid dispersion of Eliglustat hemitartrate with HPMC-phthalate prepared according to Example 3.

Figure 5 shows powder X-ray power diffraction ("PXRD") pattern of a solid dispersion of Eliglustat hemitartrate with Enteract HPMCAS prepared according to Example 4.

Figure 6 shows modulated differential scanning calorimetry (DSC) of a solid dispersion of Eliglustat hemitartrate with Enteract HPMCAS prepared according to Example 4.

Figure 7 depicts powder X-ray power diffraction ("PXRD") pattern of a solid dispersion of Eliglustat hemitartrate with beta-cyclodextrin prepared according to Example 5.

- 5 Figure 8 depicts powder X-ray power diffraction ("PXRD") pattern of pure amorphous form of eliglustat hemitartrate prepared according to Example 6.

Detailed description of the inventions

The invention will now be described in more detail in connection with certain
10 preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The present invention describes a stable solid dispersion comprising eliglustat hemitartrate and one or more pharmaceutically acceptable carrier s.

15

A solid dispersion is a pharmaceutical formulation which may be defined as “a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting the two (fusion), dissolving them in a solvent, or a combination of approaches, i.e., a quasi melting-solvent method”. In the present
20 context, the term “solid dispersion denotes a drug or active ingredient or substance dispersed on a particulate level in an inert vehicle, carrier, diluent or matrix in the solid state, i.e. usually a fine particulate dispersion.

A solid dispersion as such is not physically stable and the amorphous drug present
25 in the dispersion tends to recrystallize over time. This is especially true where the concentration of the drug in the polymer is greater than its equilibrium value or supersaturated. Such dispersions may be considered a supersaturated solid solution. Such supersaturated solid solutions are not thermodynamically stable. Over time it is believed that such solid dispersions will separate into a mixture of two or more
30 phases, one phase enriched in drug and the other phase enriched in

polymer. The drug-rich phase generally contains crystalline or amorphous drug and the other phase generally contains a solid solution of the drug and polymer in which the drug is at a lower concentration (than the drug-rich phase) and may be at or near equilibrium concentration in the polymer. Drug within the drug-rich phase may be crystalline or amorphous. Further, over time, the amorphous drug within the drug-rich phase that has separated from the polymer may also tend to crystallize. Separation of a drug-rich phase generally results in a decrease in bioavailability, because the bioavailability of the amorphous or crystalline form of a low-solubility drug is usually much less than its bioavailability in an amorphous drug dispersion in polymer. Thus, over time, the bioavailability of the drug in solid dispersions tends to decrease as increasing amounts of the drug separate as either amorphous or crystalline drug.

However, it has been determined by the present invention that the dispersions can be made physically stable over a relatively long period of time, i.e., up to several months or even years. Thus, by increasing the glass transition temperature (T_g) of the solid dispersion, the mobility of the drug may be decreased and hence its ability to form relatively pure domains, be they amorphous or crystalline, may be inhibited. In cases where amorphous drug-rich domains form, the drug present in such domains generally crystallizes rapidly relative to its rate of crystallization in the original dispersion. Further, by initially creating substantially homogenous dispersions, that is, dispersions wherein the drug is not present in drug-rich domains, the drug tends to be stabilized by the polymer and is not present in relatively pure drug domains that tend to be susceptible to crystallization.

25

The solid dispersions of the present invention comprise a low-solubility drug eliglustat hemitartrate and at least one polymer. At least a major portion of the drug in the dispersion is present in the amorphous, rather than the crystalline state. By “amorphous” is meant simply that the drug is in a non-crystalline state. As used herein, the term “a major portion” of the drug means that at least 60% of the drug once dispersed in the dispersion is in the amorphous form, rather than the crystalline

30

form. Preferably, the drug in the dispersion is substantially amorphous. As used herein, substantially amorphous means that the amount of the drug in crystalline form does not exceed 20%. More preferably, the drug in the dispersion is "almost completely amorphous" meaning that the amount of drug in the crystalline form does not exceed 10% as measured by using various techniques such as Hot Stage Microscopy (HSM), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) optionally in combination with Energy Dispersive X-ray (EDX), and X-ray powder diffraction (XRD).

10 Methods for preparing solid dispersions are known in the art and typically comprise the steps of dissolving the compound and the polymer in a common solvent and evaporating the solvent. In a preferred embodiment, the active ingredient is fully dissolved in the polymer to form a solid solution at ambient temperature.

15 Methods for evaporating the solvent include but not limited to the rotary evaporation, spray drying, lyophilisation, freeze drying and thin film evaporation. Other techniques may be used such as solvent controlled precipitation, pH controlled precipitation, supercritical fluid technology and hot melt extrusion. To aid the process the melt may be extruded with any necessary additional excipient
20 such as a plasticiser, including super critical fluids.

In general the process for preparing solid dispersions according to the present invention comprises steps of:

- a. treating eliglustat hemitartrate with a pharmaceutical carrier selected from
25 the group consisting of polymers of cellulose derivatives, cyclodextrins and lactose monohydrate in an alcoholic solvent, water or mixture thereof at room temperature to reflux temperature of the solvent;
- b. removing the solvent from the reaction mixture to obtain a residue; and
- c. isolating the solid dispersion consisting of amorphous eliglustat
30 hemitartrate dispersed in the pharmaceutical carrier.

Within the scope of the present invention is eliglustat hemitartrate in any physical form (crystals, amorphous powder, any possible polymorphs, any possible solvates including the hydrate, anhydrate, complexes thereof etc.). Included is also any analogue, derivative or active metabolite of eliglustat hemitartrate,
5 pharmaceutically acceptable salts, solvates, complexes and prodrugs thereof.

When referring to a solid dispersion we do not exclude the possibility that a proportion of the eliglustat hemitartrate may be dissolved within the polymer used, the exact proportion, if any, will depend upon the physical properties of the
10 eliglustat hemitartrate and the polymer selected.

Polymers of cellulose derivatives which are suitable for use in the dispersions of the present invention are particularly selected to increase the glass transition temperature (T_g) of the solid dispersion thereby providing the stability to the solid
15 dispersion. The polymer should have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. pH 1-8). Virtually any such polymer which is inert should be suitable. By "inert" is merely meant not undesirably-reactive or bioactive, yet still capable of positively affecting the drug's bioavailability. The polymer also should be biologically inert or non-toxic in the sense that it is
20 acceptable for oral administration to a mammal such as a human. The amount of the polymer present in the dispersion may range from about 20 wt % to about 99 wt % of the dispersion. A preferred class of polymers is cellulose derivatives are cellulosic esters and ethers thereof, as well as mixed esters and ethers, including both so-called "enteric" and "non-enteric" polymers.

25

Preferred examples of cellulosic polymer useful in the solid dispersions of the subject invention include those that possess both a carboxylic acid functional aromatic substituent and an alkylate substituent. Exemplary polymers include but are not limited to: cellulose acetate phthalate, methyl cellulose acetate phthalate,
30 ethyl cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate

phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methylcellulose acetate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate, trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate-pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

Even more preferred are those cellulosics with both ester-linked phthalate or trimellitate groups and an alkylate group. Exemplary polymers of this class include: cellulose acetate phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMC phthalate), hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, hydroxypropyl methyl cellulose trimellitate, cellulose acetate trimellitate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, and cellulose acetate isophthalate.

25

Most preferred polymers are cellulose acetate phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMC phthalate), cellulose acetate terephthalate, cellulose acetate isophthalate, and cellulose acetate trimellitate.

30

Suitable water soluble carriers include polymers such as polyethylene glycol, poloxamers, polyoxyethylene stearates, poly-s-caprolactone, polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon(R) VA64), poly-methacrylic polymers (Eudragit(R) RS, Eudragit(R) RL, Eudragit(R) NE, Eudragit(R) E) and
5 polyvinylalcohol (PVA), methyl cellulose, and poly (ethylene oxide) (PEO), methylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, Xanthan gums and mixtures thereof.

10 In a preferred embodiment, suitable cyclodextrins according to the invention are selected from α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin.

Spray-dried solutions and the resulting dispersions may also contain various additives which are miscible with the eliglustat hemitartrate /pharmaceutical carrier
15 melt mixture, that aid in the stability, dissolution, tableting, or processing of the dispersion. Examples of such additives include: surfactants, pH-controlling substances (e.g., acids, bases, buffers), fillers, disintegrators, or binders. Such additives may be added directly to the spray-drying solution such that the additive is dissolved or suspended in the solution as a slurry. Alternatively, such additives
20 may be added following the spraying process to aid in forming the final dosage form.

In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable additives is selected from the group consisting of silica
25 acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof, magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

Suitable organic solvents that can be used for the preparation of solid dispersions
30 according to the invention include pharmaceutical acceptable solvent in which the active substance is soluble. The solvents which can be used include but are not

limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers such as diethyl ether, dimethyl ether, di-isopropyl ether, methyl-t-butyl ether, 1,4-dioxane and the like; hydrocarbons such as toluene, xylene, cyclohexane, hexane, heptane and the like; water and/ or mixtures thereof.

- 10 The recovered product may optionally be further dried. Drying may be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, rotatory dryer, and the like. Drying may be carried out at temperatures from about 25°C to about 90°C with or without vacuum and in the presence or absence of an inert atmosphere like nitrogen, argon, neon, and helium.
- 15 Drying may be carried out for a desired time period to achieve the desired product purity. Drying times from about 1 to about 15 hours, or longer, are frequently adequate.

Accordingly, in the first aspect the present application provides a stable solid dispersion of eliglustat hemitartrate with lactose monohydrate.

The stable solid dispersion of eliglustat hemitartrate with lactose monohydrate of the present invention may be prepared as follows,

- a. treating eliglustat hemitartrate with lactose monohydrate in mixture of an alcoholic solvent and water;
- b. heating reaction mixture to obtain an oily mass; and
- c. drying to isolate the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the lactose monohydrate.

In an embodiment, a solid dispersion of eliglustat hemitartrate with lactose monohydrate is further characterized by a differential scanning calorimetry curve depicted in Figure 1.

- 5 In an embodiment, a solid dispersion of eliglustat hemitartrate with lactose monohydrate is characterized by XRD as depicted in Figure 2.

Accordingly, in the second aspect the present application provides a stable solid dispersion of eliglustat hemitartrate with hydroxypropyl methylcellulose phthalate (HPMC phthalate).
10

The stable solid dispersion of eliglustat hemitartrate with HPMC phthalate of the present invention may be prepared as follows,

- 15 a. treating eliglustat hemitartrate with HPMC phthalate in an alcoholic solvent;
b. heating reaction mixture to obtain an oily mass;
c. optionally evaporating the solvent; and
d. drying to isolate the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the HPMC phthalate.

20

In an embodiment, a solid dispersion of eliglustat hemitartrate with HPMC phthalate is characterized by XRD as depicted in Figure 3.

In an embodiment, a solid dispersion of eliglustat hemitartrate with HPMC phthalate is further characterized by a differential scanning calorimetry curve depicted in Figure 4.
25

Accordingly, in the third aspect the present application provides a stable solid dispersion of eliglustat hemitartrate with Enteract HPMCAS.

30

The stable solid dispersion of eliglustat hemitartrate with Enteract HPMCAS of the present invention may be prepared as follows,

- a. treating eliglustat hemitartrate with Enteract HPMCAS in an alcoholic solvent;
- 5 b. evaporating the solvent; and
- c. isolating the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the Enteract HPMCAS.

10 In an embodiment, a solid dispersion of eliglustat hemitartrate with Enteract HPMCAS is characterized by XRD as depicted in Figure 5.

In an embodiment, a solid dispersion of eliglustat hemitartrate with Enteract HPMCAS is further characterized by a differential scanning calorimetry curve depicted in Figure 6.

15

Accordingly, in the fourth aspect the present application provides a stable solid dispersion of eliglustat hemitartrate with β - Cyclodextrin.

20 The stable solid dispersion of eliglustat hemitartrate with β - Cyclodextrin of the present invention may be prepared as follows,

- a. treating eliglustat hemitartrate with β - Cyclodextrin in an mixture of an alcoholic solvent and water;
- b. evaporating the solvent;
- c. optionally treating with Syloid; and
- 25 d. isolating the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the β - Cyclodextrin and Syloid.

In an embodiment, a solid dispersion of eliglustat hemitartrate with β - Cyclodextrin is characterized by XRD as depicted in Figure 7.

30

Accordingly the invention provides a stable solid dispersion comprising amorphous eliglustat hemitartrate dispersed in pharmaceutical carrier selected from the group consisting of hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), β -cyclodextrin and lactose monohydrate.

The solid dispersions of the present invention were found to have greater stability, flow properties, dissolution properties.

In a preferred embodiment, the solid dispersions of the present invention can be formulated into pharmaceutical composition with the help of one or more suitable pharmaceutical carriers, in the form of capsules, tablets, pills, powders or granules. The composition comprising the solid dispersion provides enhanced bioavailability of the drug.

15

According to the fifth aspect, the present application provides a process for the preparation of pure amorphous form of eliglustat hemitartrate comprises steps of:

- a. treating eliglustat hemitartrate with a solvent;
- b. heating reaction mixture to obtain an oily mass; and
- c. drying to isolate pure amorphous eliglustat hemitartrate.

20

In an embodiment an amorphous form of eliglustat hemitartrate is characterized by XRD as depicted in Figure 8.

The solvents which can be used include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers such as diethyl ether,

30

dimethyl ether, di-isopropyl ether, 1,4-dioxane and the like; hydrocarbons such as toluene, xylene and the like; and any mixtures of two or more thereof.

The pure amorphous form of eliglustat hemitartrate obtained by the present invention was found to have improved yield and of improved purity.

The pure amorphous form of eliglustat hemitartrate obtained according to the present invention was found to be substantially free from crystalline forms of eliglustat hemitartrate. "Substantially free" from other forms of eliglustat hemitartrate shall be understood to mean that the polymorphs of eliglustat hemitartrate contain less than 10%, preferably less than 5%, of any other forms of eliglustat hemitartrate and less than 1% of other impurities, water or solvates. Thus, the amorphous form of eliglustat hemitartrate prepared according to the present invention contains less than 11% total impurities, preferably less than 6% total impurities. In a particularly preferred embodiment, the amorphous form of eliglustat hemitartrate prepared according to the present invention contains less than 1% total impurities.

The solid dispersions as well as amorphous form of the present invention may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules.

According to another aspect, the invention provides a method of treating Gaucher's disease in a subject which method comprises administering therapeutically effective amounts of a pharmaceutical composition comprising solid dispersion of amorphous eliglustat hemitartrate dispersed in a pharmaceutical carrier selected from the group consisting of hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), β -cyclodextrin and lactose monohydrate along with one or more suitable pharmaceutical carriers, in the form of capsules, tablets, pills, powders or granules.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

5

Examples;-**Example 1**

Process to prepare Eliglustat hemitartrate solid dispersion with lactose monohydrate:

10

Suspended Eliglustat hemitartrate (3g) and Lactose monohydrate (1.128g) in 500 ml of Methanol: Water (9:1 v/v) at room temperature. The reaction mixture was heated to obtain an oily mass. Dried in the vacuum tray dryer at 60°C for overnight, resulted the title compound. The DSC and PXRD of the Eliglustat hemitartrate solid dispersion with lactose monohydrate are depicted in Figs 1 and 2 respectively.

15

Example 2

Process to prepare Eliglustat hemitartrate solid dispersion with HPMC-phthalate:

Suspended Eliglustat hemitartrate (0.5g) and HPMC-Pthalate (0.5g) in 30ml of Methanol at room temperature. The reaction mixture was heated to obtain an oily mass. Dried in the vacuum tray dryer for overnight, resulted the title compound.

20

Example 3

Process to prepare Eliglustat hemitartrate solid dispersion with HPMC-phthalate: Suspended Eliglustat hemi tartrate (8g) and HPMC-phthalate (8g) (1:1 wt/wt) in 400 ml of Methanol (25v) at room temperature. The temperature of the reaction mass was increased to 55°C to get a clear solution. The solution was clarified and the solvent evaporated completely using rota vapour, to result the titled compound. The PXRD and DSC of the Eliglustat hemitartrate solid dispersion with HPMC-phthalate are depicted in Figs 3 and 4 respectively.

30

Example 4**Process to prepare Eliglustat hemi tartrate solid dispersion with Enteract HPMCAS:**

Suspended Eliglustat hemi tartrate (9g) and Enteract HPMCAS (9g) (1:1 wt/wt) in
5 540 ml of Methanol (30v) at room temperature. The temperature of the reaction
mass was increased to 55°C to get a clear solution. The solution was clarified and
the solvent evaporated completely using buchi rotavapour, to result the titled
compound. The PXRD and DSC of the Eliglustat hemitartrate solid dispersion with
HPMCAS are depicted in Figs 5 and 6 respectively.

10

Example 5**Process to prepare Eliglustat hemi tartrate solid dispersion with Beta Cyclodextrin:**

Eliglustat hemitartrate (500mg) and Beta Cyclodextrin (500mg) were dissolved in
15 50ml of methanol : water mixture (0.6:0.4) at 65°C. The clear solution was
evaporated in a rotavapour at 65°C under vacuum to obtain the amorphous solid
dispersion. The obtained solid dispersion (600mg) was combined with Syloid
(300mg) by gently grinding the mixture in a mortar and pestle for 30 minutes. The
PXRD of the Eliglustat hemitartrate solid dispersion with Beta Cyclodextrin is
20 depicted in Figs 7 respectively.

Example 6**Pure amorphous form of Eliglustat hemi tartrate:**

Suspended Eliglustat hemitartrate (0.5g) in Methanol: Water (9:1 v/v) 50 ml at
25 room temperature. The reaction mixture was heated to obtain an oily mass. Dried
the mass in the vacuum tray dryer for overnight, resulted the title compound. The
PXRD of the pure amorphous form of Eliglustat hemitartrate is depicted in Figs 8.

We claim,

1. A process for preparing solid dispersions of eliglustat hemitartrate comprises steps of :
 - 5 a) treating eliglustat hemitartrate with a pharmaceutical carrier selected from the group consisting of polymers of cellulose derivatives, cyclodextrins and lactose monohydrate in an alcoholic solvent, water or mixture thereof at room temperature to reflux temperature of the solvent;
 - 10 b) removing the solvent from the reaction mixture to obtain a residue; and
 - c) isolating the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the pharmaceutical carrier.
2. The process as claimed in claim 1, wherein, the carrier is present in the dispersion in an amount of about 20 wt % to about 99 wt % of the dispersion.
3. The process as claimed in claim 1, wherein, the polymers of cellulose derivatives are its esters, ethers as well as mixed esters and ethers thereof.
- 20 4. The process as claimed in claim 3, wherein, the polymers of cellulose derivatives are selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMC phthalate), cellulose acetate terephthalate, cellulose acetate isophthalate, and cellulose acetate trimellitate.
5. The process as claimed in claim 4, wherein, the polymers of cellulose derivative is selected from hydroxypropyl cellulose acetate phthalate and hydroxypropyl methylcellulose acetate succinate (HPMCAS).
- 30 6. The process as claimed in claim 1, wherein, the cyclodextrin is selected from α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin.

7. The process as claimed in claim 1, wherein, the stable solid dispersion of eliglustat hemitartrate with lactose monohydrate is prepared by a process which comprises;
- 5 a) treating eliglustat hemitartrate with lactose monohydrate in mixture of an alcoholic solvent and water;
- b) heating reaction mixture to obtain an oily mass; and
- c) drying to isolate the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the lactose monohydrate.
8. The process as claimed in claim 1, wherein, the stable solid dispersion of eliglustat hemitartrate with HPMC phthalate is prepared by a process which comprises;
- 10 a) treating eliglustat hemitartrate with HPMC phthalate in an alcoholic solvent;
- b) heating reaction mixture to obtain an oily mass;
- 15 c) optionally evaporating the solvent; and
- d) drying to isolate the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the HPMC phthalate.
9. The process as claimed in claim 1, wherein, the stable solid dispersion of eliglustat hemitartrate with Enteract HPMCAS is prepared by a process which comprises;
- 20 a) treating eliglustat hemitartrate with Enteract HPMCAS in an alcoholic solvent;
- b) evaporating the solvent; and
- c) isolating the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the Enteract HPMCAS.
- 25 10. The process as claimed in claim 1, wherein, the stable solid dispersion of eliglustat hemitartrate with β - Cyclodextrin is prepared by a process which comprises;
- a) treating eliglustat hemitartrate with β - Cyclodextrin in an mixture of an alcoholic solvent and water;
- 30 b) evaporating the solvent;

- c) optionally treating with Syloid; and
 - d) isolating the solid dispersion consisting of amorphous eliglustat hemitartrate dispersed in the β -Cyclodextrin and Syloid.
- 5 11. The process as claimed in any one of the preceding claims, wherein, the alcoholic solvent is methanol.
- 10 12. A stable solid dispersion comprising amorphous eliglustat hemitartrate dispersed in a pharmaceutical carrier selected from the group consisting of hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), β -cyclodextrin and lactose monohydrate.
- 15 13. A pharmaceutical composition comprising solid dispersion of claim 12, along with one or more suitable pharmaceutical carriers, in the form of capsules, tablets, pills, powders or granules.
14. Method of treating Gaucher's disease in a subject which method comprises administering therapeutically effective amounts of a pharmaceutical composition comprising solid dispersion of claim 12, along with one or more suitable pharmaceutical carriers, in the form of capsules, tablets, pills, powders or granules.
- 20 15. A process for preparation of amorphous eliglustat hemitartrate comprising;
- a) dissolving eliglustat hemitartrate in aqueous methanol;
 - b) heating the reaction mixture to obtain an oily mass; and
 - c) drying to isolate pure amorphous eliglustat hemitartrate.
- 25 16. The process as claimed in claim 15, wherein the aqueous methanol comprises methanol and water in 9:1 ratio.

I/IV

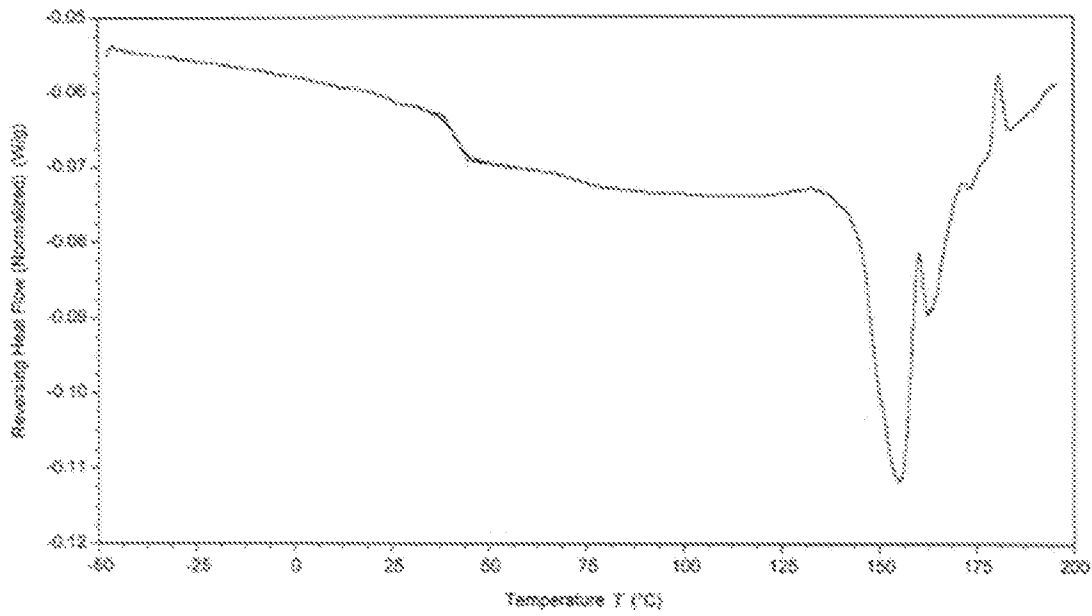


Figure. 1

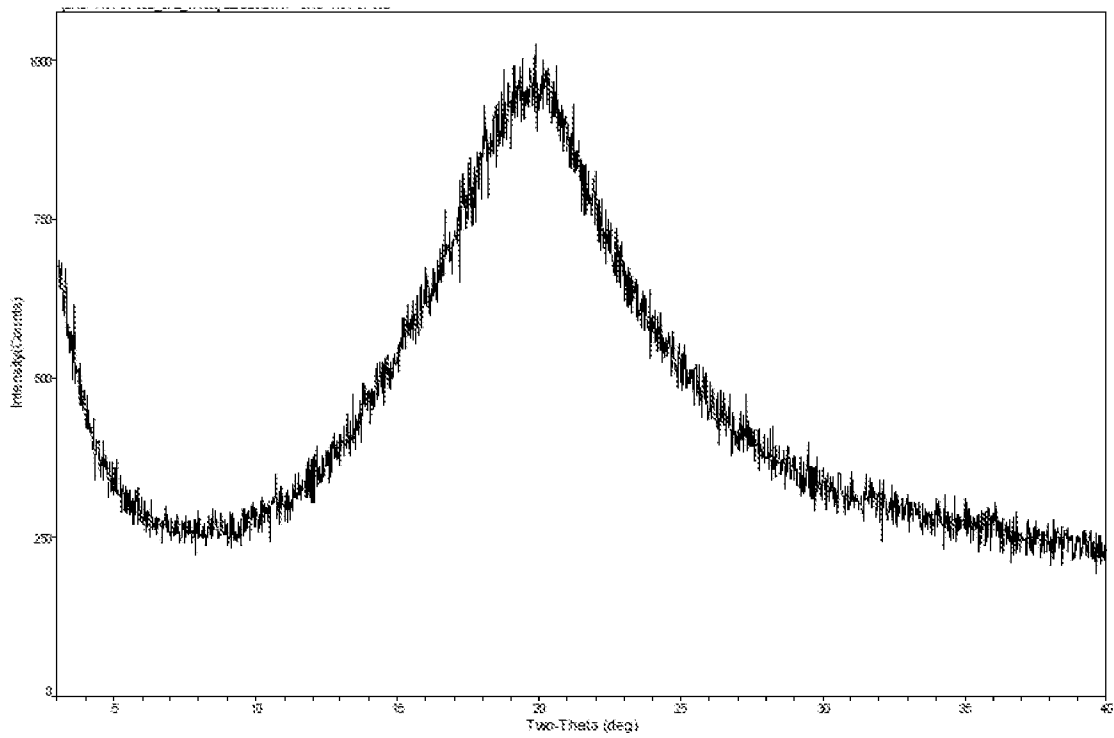


Figure. 2

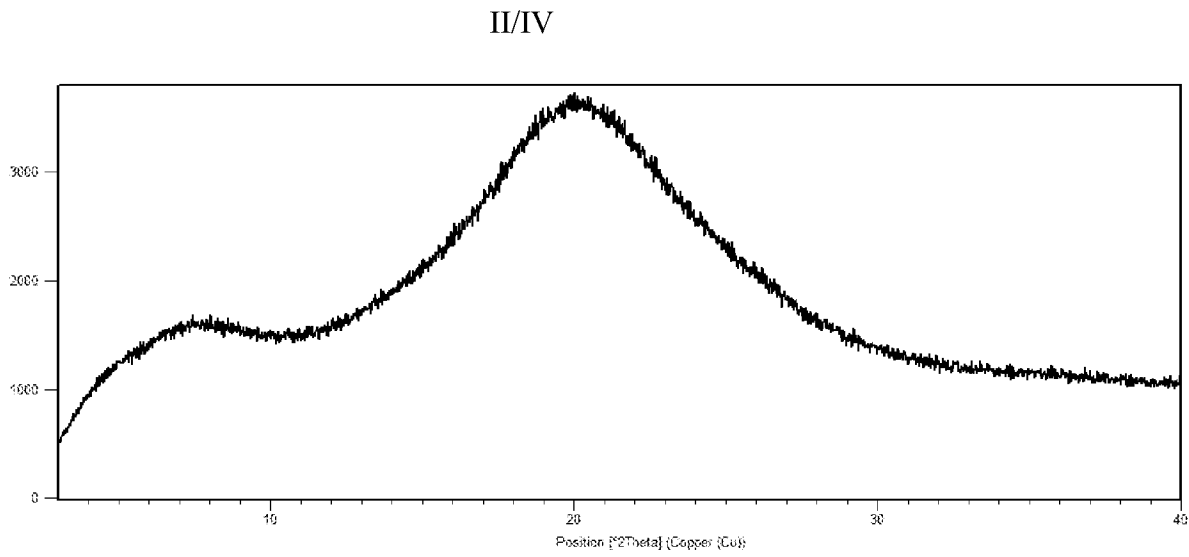


Figure. 3

5

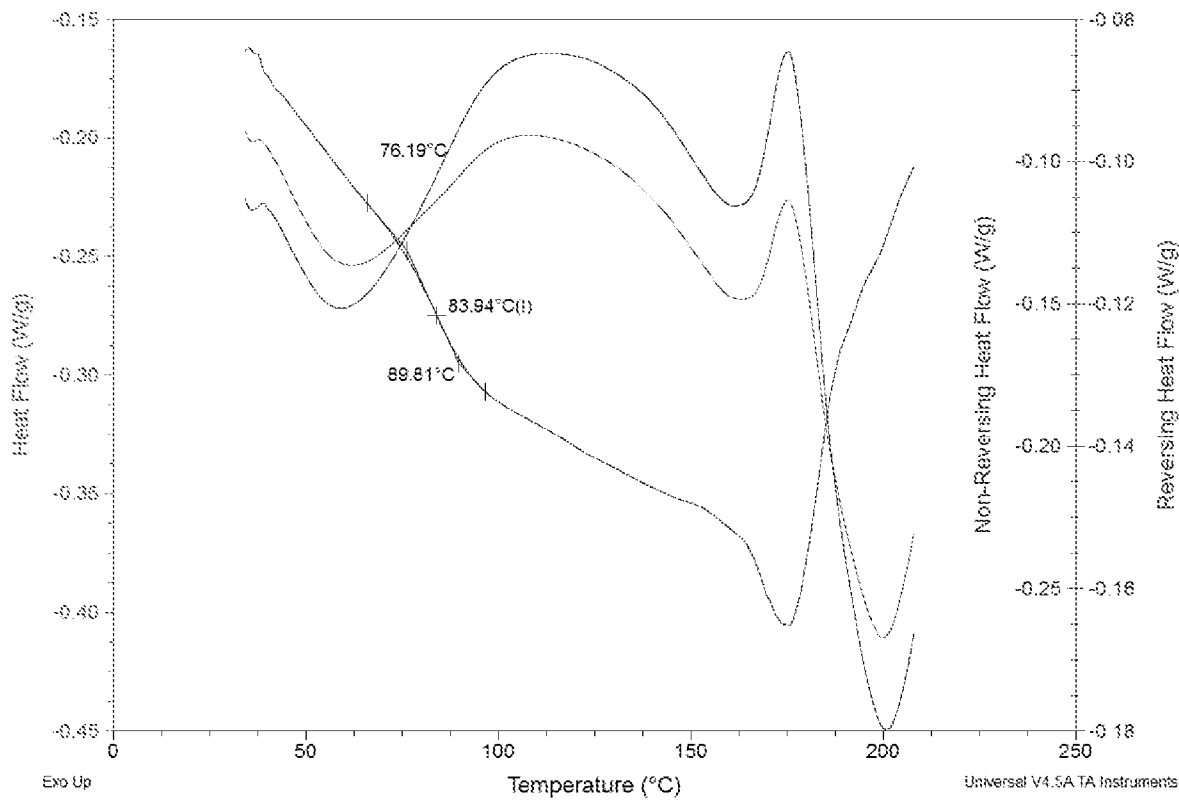


Figure. 4

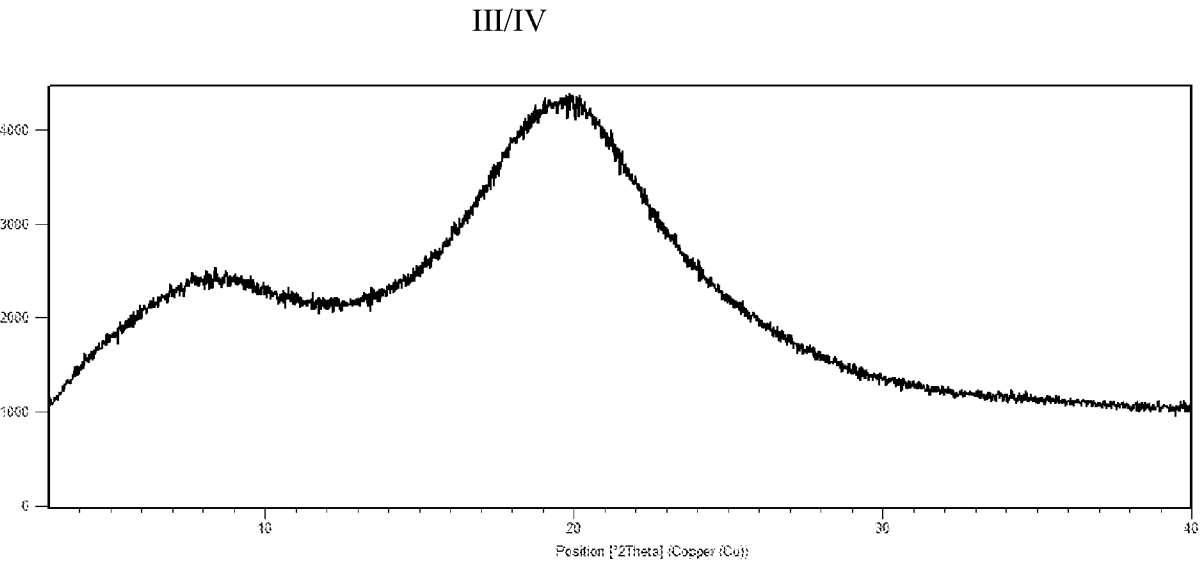


Figure. 5

5

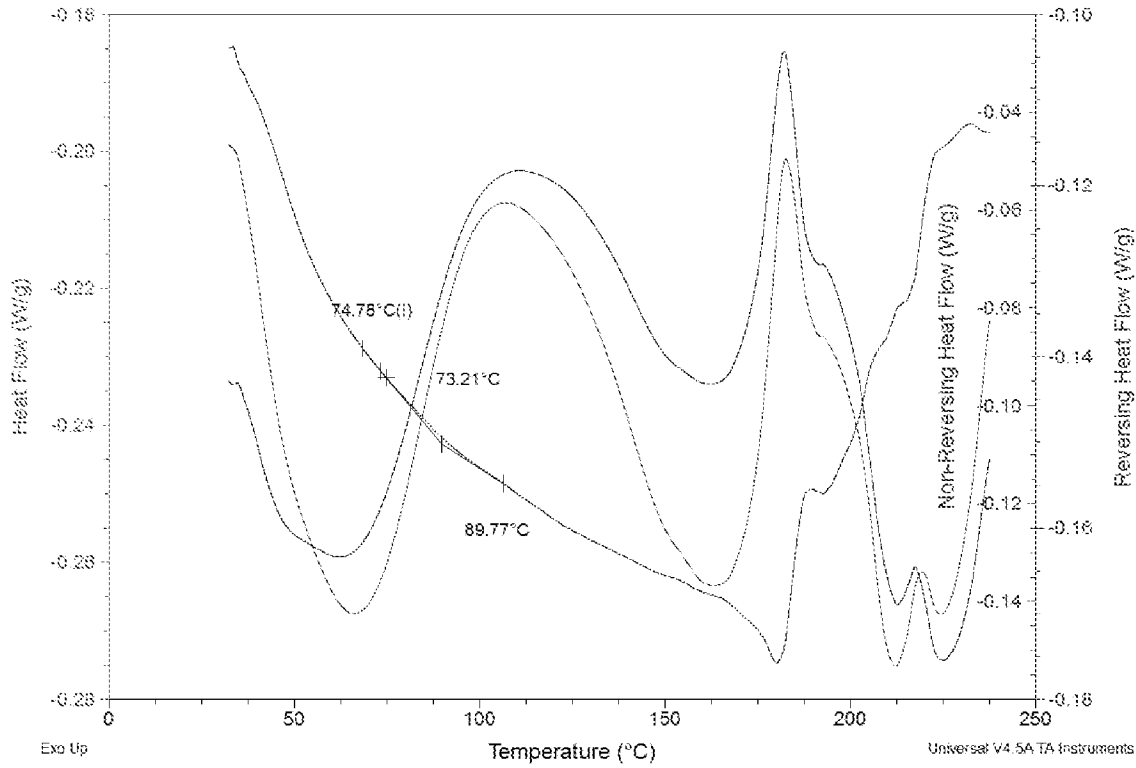


Figure. 6

IV/IV

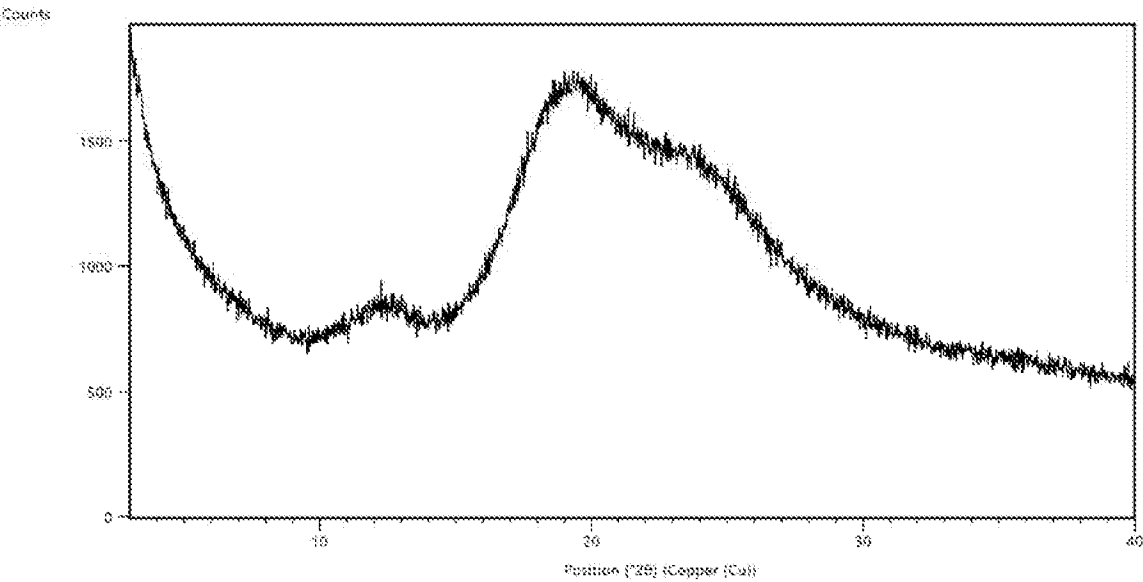


Figure. 7

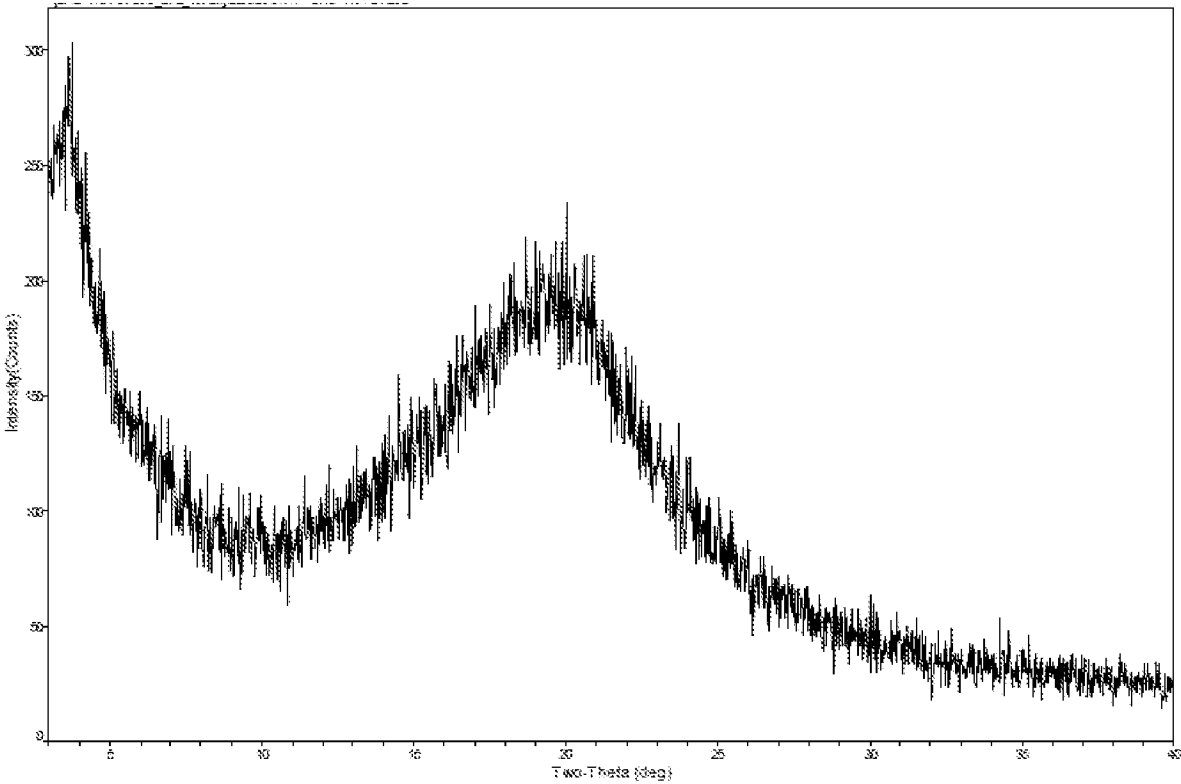


Figure. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2018/050362

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/14 A61K31/4025 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)

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 practicable, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/001885 A2 (REDDY'S LAB LTD DR [IN]) 7 January 2016 (2016-01-07) cited in the application page 1, paragraph 2 page 2, paragraph 4 - page 3, paragraph 4 page 4, last paragraph - page 6, paragraph 2 page 8, paragraph 3 - page 11, paragraph 3 examples 3,5-7,9,10 claims 1-11	1-16
X	US 2013/137743 A1 (LIU HANLAN [US] ET AL) 30 May 2013 (2013-05-30) cited in the application page 1, paragraph 9 page 4, paragraphs 53,57 page 5, paragraph 66 page 18; example 10 claim 1	15,16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 August 2018

Date of mailing of the international search report

30/08/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Gómez Gallardo, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2018/050362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016001885	A2	07-01-2016	CA 2954030 A1 07-01-2016
		EP 3164128 A2 10-05-2017	
		US 2017129869 A1 11-05-2017	
		WO 2016001885 A2 07-01-2016	

US 2013137743	A1	30-05-2013	AR 079152 A1 28-12-2011
		AU 2010324810 A1 07-06-2012	
		AU 2016202591 A1 19-05-2016	
		AU 2017265180 A1 14-12-2017	
		BR 112012012947 A2 01-03-2017	
		CA 2781676 A1 03-06-2011	
		CN 102712629 A 03-10-2012	
		CN 105753846 A 13-07-2016	
		CN 105777707 A 20-07-2016	
		CR 20120277 A 05-09-2012	
		CY 1115880 T1 25-01-2017	
		CY 1117996 T1 17-05-2017	
		DK 2504332 T3 25-08-2014	
		DK 2796457 T3 29-08-2016	
		DO P2012000141 A 30-09-2012	
		DO P2016000250 A 15-02-2017	
		EA 201270646 A1 30-01-2013	
		EA 201592195 A1 29-04-2016	
		EC SP12011926 A 31-07-2012	
		EP 2504332 A1 03-10-2012	
		EP 2796457 A1 29-10-2014	
		EP 3133070 A1 22-02-2017	
		ES 2493940 T3 12-09-2014	
		ES 2586947 T3 19-10-2016	
		GT 201200161 A 27-01-2014	
		HK 1172031 A1 15-05-2015	
		HK 1203485 A1 30-10-2015	
		HR P20140780 T1 07-11-2014	
		HR P20161038 T1 21-10-2016	
		HU E029371 T2 28-02-2017	
		JP 2013512252 A 11-04-2013	
		JP 2015212291 A 26-11-2015	
		JP 2016138124 A 04-08-2016	
		KR 20120115972 A 19-10-2012	
		KR 20150125734 A 09-11-2015	
		KR 20180049255 A 10-05-2018	
		LT 2796457 T 12-09-2016	
		MA 33838 B1 03-12-2012	
		ME 02477 B 20-02-2017	
		MY 160542 A 15-03-2017	
		NZ 600155 A 31-10-2014	
		NZ 625712 A 26-02-2016	
		NZ 715108 A 30-06-2017	
		PE 12552017 A1 28-08-2017	
		PE 13372012 A1 12-10-2012	
		PH 12015502514 A1 15-08-2016	
		PL 2796457 T3 28-04-2017	
		PT 2504332 E 02-09-2014	
		PT 2796457 T 14-07-2016	
		SG 10201407881W A 29-01-2015	
		SG 10201800136Q A 27-02-2018	
		SI 2504332 T1 30-09-2014	
		SM T201600273 B 31-08-2016	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2018/050362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		TN 2012000237 A1	12-12-2013
		TW 201130822 A	16-09-2011
		TW 201639562 A	16-11-2016
		TW 201737910 A	01-11-2017
		UA 113491 C2	10-02-2017
		US 2013137743 A1	30-05-2013
		US 2016120842 A1	05-05-2016
		US 2016166542 A1	16-06-2016
		WO 2011066352 A1	03-06-2011
