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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 February 2009 (05.02.2009)

PCT

(10) International Publication Number
WO 2009/016359 A1

(51) International Patent Classification:
A61K 31/4196 (2006.01) *C07D 249/08* (2006.01)

(21) International Application Number:
PCT/GB2008/002572

(22) International Filing Date: 25 July 2008 (25.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/935,134	27 July 2007 (27.07.2007)	US
60/935,482	15 August 2007 (15.08.2007)	US
60/960,285	24 September 2007 (24.09.2007)	US

(71) Applicant *(for all designated States except US)*: **PLIVA HRVATSKA D.O.O.** [HR/HR]; Ulica grada Vukovara 49, 10000 Zagreb (HR).

(71) Applicant *(for LR only)*: **BUCKS, Teresa Anne** [GB/GB]; Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DANILOVSKI, Aleksandar** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulica grada Vukovara 49, 10000 Zagreb (HR). **DUMICIC, Aleksandra** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o, Ulica grada Vukovara 49, 10000 Zagreb (HR). **HULITA, Nada Kosutic** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulica grada Vukovara 49, 10000 Zagreb (HR). **KWOKAL, Ana** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulicia grada Vukovara 49, 10000 Zagreb (HR). **MESTROVIC, Ernest** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulicia grada Vukovara 49, 10000 Zagreb (HR). **LINARIC, Masa Rajic** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulicia grada Vukovara 49, 10000 Zagreb (HR). **ZEGARAC, Miroslav** [HR/HR]; IP Dept, PLIVA Hrvatska d.o.o., Ulicia grada Vukovara 49, 10000 Zagreb (HR).

(74) Agents: **BUCKS, Teresa, Anne** et al.; Boult Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

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

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) **Title:** NEW FORMS OF DEFERASIROX

(57) **Abstract:** The present invention is directed to pharmaceutical formulations comprising; a therapeutically effective amount of a stable anhydrous form of deferasirox; and a pharmaceutically acceptable excipient, wherein said deferasirox is substantially free of its acid addition salts. The present invention is further directed to processes to prepare the stable form, processes to prepare the pharmaceutical formulations and methods of using the formulations to treat conditions in a subject in need thereof. The present invention is also concerned with new polymorphic forms of deferasirox, and new amorphous forms of deferasirox, processes for preparing such forms, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

WO 2009/016359 A1

NEW FORMS OF DEFERASIROX

Background of Invention

Field of Invention

[0001] The present invention is concerned with new forms of deferasirox, wherein such new forms include: stable anhydrous forms, new polymorphic forms and new amorphous forms, processes for preparing such forms, pharmaceutical compositions containing the same, therapeutic uses thereof, and methods of treatment employing the same.

Background Art

[0002] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule can give rise to a variety of crystalline forms having distinct crystal structures and physical properties like melting point, x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum.

[0003] These properties can have a direct effect on the ability to process and/or manufacture a pharmaceutical substance or product, as well as on the product's stability, dissolution, and bioavailability. One crystalline form can give rise to thermal behavior different from that of another crystalline form, thus polymorphism can affect the quality, safety, and efficacy of a pharmaceutical product.

[0004] Polymorphic forms as referred to herein can include crystalline and amorphous forms as well as solvate and hydrate forms, which can be further characterized as follows: (i) crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice, (ii) amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice and (iii) solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate. When a pharmaceutical substance exists in such polymorphic forms, it is said to exhibit polymorphism.

[0005] There are a number of methods that can be used to characterize polymorphs of a pharmaceutical substance. Demonstration of a non-equivalent structure by single

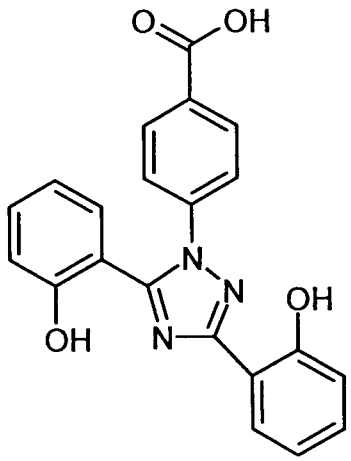
crystal X-ray diffraction is currently regarded as definitive evidence of polymorphism. X-ray powder diffraction ("XRPD") can also be used to support the existence of polymorphs. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry, and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are also helpful to further characterize polymorphic forms.

[0006] Pharmaceutical substance polymorphic forms can exhibit different chemical, physical and mechanical properties, including aqueous solubility and dissolution rate, hygroscopicity, particle shape, density, flowability, and compactibility, which in turn can affect processing of the pharmaceutical substance and/or manufacturing of the pharmaceutical product. Polymorphs can also exhibit different stabilities. The most stable polymorphic form of a pharmaceutical substance is often chosen during pharmaceutical development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability. However, a meta-stable form can alternatively be chosen for various reasons, including bioavailability enhancement.

[0007] Another important aspect of crystalline systems, besides polymorphic form, is morphology. Crystal morphology is dependent upon the manner (*i.e.*, rate and direction) in which the crystal grows. There are numerous examples in the chemical and pharmaceutical industries where crystal shape can affect essential processes such as the dissolution rate of chemicals and biological availability of pharmaceuticals, the handling, packaging and storage of crystalline products, milling, grinding, fragmentation, and dusting, density and texture optimization and wax and scale formation in petrochemicals.

[0008] Crystal morphology also causes preferred orientation of particles in polycrystalline specimens and can result in preferred orientation which can impact crystallographic analysis, such as X-ray powder diffraction (XRPD).

[0009] Deferasirox has the following structure, of Formula I:



I

[0010] Deferasirox is an iron chelating compound and is the active ingredient in the commercial product EXJADE for use in the treatment of patients suffering from chronic iron overload due to blood transfusions of greater than twenty units. EXJADE is supplied as a dispersible tablet containing 125 mg, 250 mg and 500 mg of deferasirox per tablet. The tablet is dispersed in a glass of water or other suitable drink, and the resulting suspension is then administered to the patient.

[0011] U.S. Patent No. 6,596,750 discloses the preparation of deferasirox wherein the compound is crystallized, washed with ethanol and dried. The patent describes the compound that is obtained as colorless crystals with a melting point of 264-265°C. Published PCT Appl. No. WO/03053986 also discloses the preparation of deferasirox, wherein the compound was isolated as a solid precipitate from ethanol by the addition of water, and subsequently dried, yielding the solid as a bright yellow powder which upon exposure to the air absorbed moisture and became lighter in color.

[0012] Steinhauser *et. al.*, (*Eur. J. Inorg. Chem.* 2004, 4177-4192) discloses the mode of action by which deferasirox functions as an iron chelator and methods to prepare deferasirox. The resulting crystals, on exposure to air, are described as forming the monohydrate, demonstrating the hygroscopicity of the compound.

[0013] During pharmaceutical development and manufacture, hygroscopic forms of compounds are avoided due to potential instability such as transformation to pseudo-polymorphic forms, which induce assay variability. In addition, hygroscopic forms inherently cause difficulties during manufacturing. These substances require special,

low-humidity conditions to preserve their original characteristics. There is also the potential for interaction with manufacturing equipment, such as adhesion to the walls of blenders or tablet presses, as well as potential sticking or laminating of the tablets during compression. Consequently, there is a risk that a final product containing a hygroscopic active compound would lack the desired stability and quality for pharmaceutical manufacture. Furthermore, tablets containing hygroscopic materials require special packaging material and storage conditions to prevent additional absorption of moisture and to preserve desired characteristics of the dosage forms.

[0014] As such, the present invention is directed to an anhydrous form of deferasirox that is not hygroscopic and is stable in pharmaceutical formulations including formulations that contain a significant amount of excipients that are themselves hygroscopic.

[0015] The present invention is also directed to further polymorphic forms of deferasirox which are not hygroscopic and are stable in pharmaceutical formulations including formulations that contain a significant amount of excipients that are themselves hygroscopic.

[0016] Furthermore, the present invention is also directed to an amorphous form of deferasirox. The amorphous form of deferasirox is also not hygroscopic and is stable in pharmaceutical formulations including formulations that contain a significant amount of excipients that are themselves hygroscopic. Amorphous forms are characterized as having a higher energy state than their crystalline counterparts, and as being thermodynamically metastable. In addition they offer several physical properties that have possible advantages such as a higher degree of viscoelasticity (which can aid processability) and a larger degree of molecular mobility (which can translate through to a different behavior, such as increased dissolution, solubility and bioavailability). However, amorphous forms are conversely sometimes not suitable materials for pharmaceuticals due to their thermodynamic instability which can lead to a spontaneous change to the crystalline state at any point during any process step that introduces energy into the amorphous solid, such as during formulation and storage, particularly at elevated temperatures.

Brief Summary of the Invention

Stable Anhydrous Forms of Deferasirox

[0017] A first aspect of the present invention is directed to pharmaceutical formulations comprising: a therapeutically effective amount of a stable anhydrous form of deferasirox; and a pharmaceutically acceptable excipient, wherein said deferasirox is substantially free of its acid addition salts. The present invention is further directed to processes to prepare the stable anhydrous form, processes to prepare the pharmaceutical formulations and methods of using the formulations to treat conditions in a subject in need thereof.

[0018] In some embodiments the stable anhydrous form of deferasirox is not hygroscopic and in some embodiments the stable anhydrous form of deferasirox is deferasirox Form I. In some embodiments of the present invention, the pharmaceutically acceptable excipient is selected from the group consisting of: a carrier, a diluent, a binder, a disintegrant and combinations thereof and in some further embodiments of the pharmaceutical formulation at least one pharmaceutically acceptable excipient is hygroscopic.

[0019] In some embodiments of the pharmaceutical formulation, deferasirox, according to the invention, increases in mass by less than about 0.2% when stored at about 25°C for about 24 hours and at about 80% relative humidity. In some further embodiments of the pharmaceutical formulation, the formulation is a water-dispersible tablet.

[0020] The present invention is also directed to a powder, comprising a stable anhydrous form of deferasirox, substantially free of other forms of deferasirox. In some embodiments of the powder, the stable anhydrous form of deferasirox, is substantially free of deferasirox acid addition salts. In further embodiments of the powder, the stable anhydrous form of deferasirox, is substantially free of other forms of deferasirox, and especially is substantially free of deferasirox monohydrate. In some embodiments the powder consists essentially of deferasirox Form I. In some embodiments of the powder, the deferasirox Form I has at least one peak selected

from the group consisting of: 1681±2, 1608±2, 1352±2, 1279±2 and 753±2 wavelength/cm^{-1} as measured using mid–infrared Fourier transform spectroscopy.

[0021] The present invention is further directed to a pharmaceutical formulation comprising: a therapeutically effective dose of deferasirox Form I, according to the invention, and a pharmaceutically acceptable excipient, wherein deferasirox is substantially free of its acid addition salts. In some embodiments of the pharmaceutical formulation, deferasirox Form I, according to the invention, is present in a composition having less than about 5% of any other form of deferasirox.

[0022] The present invention is also directed to deferasirox Form I, according to the invention for use in therapy.

[0023] The present invention is also directed to a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the above mentioned pharmaceutical formulation. The present invention is further directed to a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the above mentioned pharmaceutical formulation. In some embodiments of the pharmaceutical formulation, deferasirox, according to the invention has a mean particle size of about 0.5μm to about 10μm, in some embodiments of the pharmaceutical formulation deferasirox, according to the invention has a D[90] of about 10 μm or less. In some embodiments the pharmaceutical formulation of deferasirox Form I is further characterized by a melting point onset at about 260±1°C as determined by differential scanning calorimetry.

[0024] The present invention is further directed to a suspension of particles of stable anhydrous deferasirox, wherein the deferasirox is substantially free of its acid addition salts and wherein the deferasirox has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

[0025] The present invention is further directed to a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject said suspension. The present invention is also directed to a method of treating iron

overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject said suspension.

New Polymorphic Forms of Deferasirox

[0026] The present invention is also directed to new polymorphic forms of deferasirox. The polymorphic forms of deferasirox are not hygroscopic and are stable in pharmaceutical formulations including formulations that contain a significant amount of excipients that are themselves hygroscopic. The polymorphic forms of deferasirox provided by the present invention are hereinafter referred to as Form II, Form III, Form IV and form V

[0027] Therefore, we present as a feature of the invention:

[0028] Polymorphic form II of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 6.5°±0.2°, 7.4°±0.2°, 10.8°±0.2°, 13.4°±0.2°, 14.8°±0.2°, 19.2°±0.2°, 21.7°±0.2° and 26.0°±0.2°.

[0029] Polymorphic form II of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, and 24.6°±0.2°.

[0030] Polymorphic form II of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from following (2θ): 6.5°±0.2°, 7.4°±0.2°, 10.8°±0.2°, 13.4°±0.2°, 14.8°±0.2°, 19.2°±0.2°, 21.7°±0.2° and 26.0°±0.2°, and further characterized as having one or more additional X-ray powder diffraction peaks selected from following (2θ): 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, 24.6°±0.2°.

[0031] Polymorphic form II of deferasirox characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 4.

[0032] Polymorphic form II of deferasirox characterized as having a melting point observed by DSC analysis, at 228 °C ± 1 °C.

[0033] Polymorphic form II of deferasirox characterized as having an IR spectrum substantially as shown in FIG. 5.

[0034] Polymorphic form III of deferasirox characterized as having either one or both of the following characteristic X-ray powder diffraction peaks (2θ): 12.5°±0.2° or 15.7°±0.2°.

[0035] Polymorphic form III of deferasirox characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 6.

[0036] Polymorphic form III of deferasirox characterized as having a melting point observed by DSC analysis at 208 °C ± 1 °C.

[0037] Polymorphic form IV of deferasirox characterized as having one or more characteristic X-ray powder diffraction peaks selected from the following (2θ): 10.4°±0.2°, 11.9°±0.2°, 15.0°±0.2°, 16.0°±0.2°, 21.6°±0.2°, and 22.0°±0.2°.

[0038] Polymorphic form IV of deferasirox characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 7.

[0039] Polymorphic form IV of deferasirox characterized as having an IR spectrum substantially as shown in FIG. 8.

[0040] Polymorphic form IV of deferasirox characterized as having a melting point peak observed, by DSC analysis, at 202 °C ± 1 °C.

[0041] Polymorphic form V of deferasirox characterized as having one or more characteristic X-ray powder diffraction peaks selected from the following (2θ): 5.5°±0.2°, 11.0°±0.2°, 11.8°±0.2°.

[0042] The present invention also provides a process of preparing polymorphic forms II and III of deferasirox, comprising alternately melting and cooling deferasirox in one or more cycles and in an inert atmosphere. Cooling of melted deferasirox is carried out down to room temperature under controlled conditions with cooling rate from 10 to 50 °C/min, preferably 20 to 40 °C/min. The preferred inert atmosphere is nitrogen.

[0043] The present invention also provides a process of preparing polymorphic form IV of deferasirox comprising crystallization from ethanol solution of deferasirox with use of sulfuric acid.

[0044] The present invention also provides a process of preparing polymorphic form V of deferasirox comprising sublimation of deferasirox.

[0045] Deferasirox is an iron chelating compound, and is thus useful in the treatment of disorders in patients suffering from elevated levels of iron.

[0046] We present a pharmaceutical formulation comprising: (a) a therapeutically effective amount of deferasirox form II, form III, form IV, form V or a mixture thereof, according to the invention, and (b) a pharmaceutically acceptable excipient. Excipients are chosen according to the pharmaceutical form and the desired mode of administration.

[0047] We present a pharmaceutical formulation of the present invention, wherein the pharmaceutically acceptable excipient is selected from the group consisting of: a carrier, a diluent, a binder, a disintegrant and combinations thereof.

[0048] We present a pharmaceutical formulation of the present invention, wherein the formulation is a water-dispersible tablet.

[0049] We present a water dispersible tablet of the present invention, wherein the dispersible tablet disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

[0050] We further present a pharmaceutical formulation of the present invention, wherein deferasirox form II or form III or form IV or form V or a mixture thereof, has a mean particle size of about 0.5μm to about 10μm.

[0051] The present invention also provides a pharmaceutical formulation, wherein the deferasirox form II or form III or form IV or form V or a mixture thereof, has a D[90] of about 10 μm or less.

[0052] The present invention also provides a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent in a subject in need thereof, comprising administering to the subject the pharmaceutical formulation described above.

[0053] We further present a method of treating iron overload following blood transfusion in a subject in need thereof, comprising administering to the subject the pharmaceutical formulation of the present invention.

[0054] A suspension of particles of deferasirox form II or form III or form IV or form V or a mixture thereof, wherein the deferasirox form II or form III or form IV or form V or a mixture thereof, has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

[0055] A method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent in a subject in need thereof, comprising administering to the subject the suspension described above.

[0056] We further present a method of treating iron overload following blood transfusion in a subject in need thereof, comprising administering to the subject a suspension of the present invention

Amorphous Forms of Deferasirox

[0057] We have found a stable amorphous form of deferasirox. In addition we have found that the amorphous form of deferasirox may also exist as at least four different amorphous forms.

[0058] We have surprisingly found that deferasirox may form several different amorphous forms with different physical properties.

[0059] Therefore, we present as another feature of the invention:

[0060] Amorphous deferasirox.

[0061] Amorphous form I of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of 159.0°C ±1°C, ideally ±0.5°C..

[0062] Amorphous form I of deferasirox characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of 144.6°C ±1°C, ideally ±0.5°C.

[0063] Amorphous form I of deferasirox characterized as having an X-ray diffraction pattern substantially as shown in Figure 10.

[0064] Amorphous form II of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of 153.6°C ±1°C, ideally ±0.5°C.

[0065] Amorphous form II of deferasirox characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of 143.5°C ±1°C, ideally ±0.5°C.

[0066] Amorphous form II of deferasirox characterized as having an X-ray diffraction pattern substantially as shown in Figure 12.

[0067] Amorphous form III of deferasirox characterized as having no crystallization point, as measured by differential scanning calorimetry, at any point up to 350°C.

[0068] Amorphous form III of deferasirox characterized as having an X-ray diffraction pattern substantially as shown in Figure 14.

[0069] Amorphous form IV of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of 96.5°C ±1°C, ideally ±0.5°C.

[0070] Amorphous form IV of deferasirox characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of 87.7°C ±1°C, ideally ±0.5°C.

[0071] Amorphous form IV of deferasirox characterized as having an X-ray diffraction pattern substantially as shown in Figure 16.

[0072] Amorphous form I of deferasirox characterized as having an FTIR spectra substantially as shown in Figure 18 or 19.

[0073] Amorphous form II of deferasirox characterized as having an FTIR spectra substantially as shown in Figure 18 or 19.

[0074] Amorphous form III of deferasirox characterized as having an FTIR spectra substantially as shown in Figure 18 or 19.

[0075] Amorphous form IV of deferasirox characterized as having an FTIR spectra substantially as shown in Figure 18 or 19.

[0076] Preferably the amorphous forms of deferasirox are preferably substantially free of its acid addition salts. The phrase "substantially free of its acid addition salts" refers

to amorphous deferasirox free of salts formed by addition with an acid, such acids include but are not limited to; hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, oxalic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid and benzoic acid.

[0077] The present invention also provides a process of preparing amorphous deferasirox comprising melting a sample of deferasirox and then cooling to 20 °C. Ideally the cooling step should take less than five minutes, ideally less than one minute.

[0078] We also present a pharmaceutical formulation comprising: a therapeutically effective amount of an amorphous deferasirox; according to the invention, and a pharmaceutically acceptable excipient.

[0079] We further present the pharmaceutical formulation described above, wherein the amorphous deferasirox is substantially free of its acid addition salts.

[0080] The present invention also provides a pharmaceutical formulation, wherein the therapeutically effective amount of amorphous deferasirox is selected from the group consisting of: amorphous deferasirox form I, amorphous deferasirox form II, amorphous deferasirox form III, amorphous form deferasirox IV and combinations thereof.

[0081] We present the described pharmaceutical formulation, wherein the pharmaceutically acceptable excipient is selected from the group consisting of: a carrier, a diluent, a binder, a disintegrant and combinations thereof.

[0082] We further present a pharmaceutical formulation, wherein the formulation is a water-dispersible tablet.

[0083] The present invention also provides a water dispersible tablet, wherein the dispersible tablet disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

[0084] The present invention also provides a powder, comprising an amorphous form of deferasirox selected from the group comprising of amorphous form I, amorphous form II, amorphous form III and amorphous form IV or any combination thereof.

[0085] The present invention also provides a pharmaceutical formulation, wherein the amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm.

[0086] We present a pharmaceutical formulation of the present invention, wherein the amorphous deferasirox has a D[90] of about 10 μm or less.

[0087] The present invention provides a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of the invention.

[0088] The present invention also provides a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of the invention.

[0089] We provide a suspension of particles of amorphous deferasirox, wherein the deferasirox is substantially free of its acid addition salts and wherein amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

[0090] The present invention provides a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the suspension as described above.

[0091] The present invention also provides a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the suspension as described above.

Brief Description of the Drawings

[0092] FIG. 1 depicts an FTNIR spectra of Deferasirox Form I, recorded on a Bruker spectrophotometer (MPA NIR Spectrophotometer) by the solid reflectance probe at a resolution of 8 cm^{-1}.

[0093] FIG. 2 depicts a FTMID-IR spectra of Deferasirox Form I, recorded on a Perkin Elmer spectrophotometer (Spectrum GX) in the KBr pellet at a resolution of 4 cm^{-1}.

[0094] FIG. 3 depicts a low angle laser light scattering plot used for particle size determination of Deferasirox Form I.

[0095] FIG. 4 depicts a X-ray powder diffraction pattern of Deferasirox form II.

[0096] FIG. 5 depicts an IR spectrum of Deferasirox form II.

[0097] FIG. 6 depicts an X-ray powder diffraction pattern of Deferasirox form III.

[0098] FIG. 7 depicts an X-ray powder diffraction pattern of Deferasirox form IV.

[0099] FIG. 8 depicts an IR spectrum of Deferasirox form IV.

[00100] FIG. 9 depicts a DSC thermogram of amorphous form I of Deferasirox.

[00101] FIG. 10 depicts an XRPD of amorphous form I of Deferasirox.

[00102] FIG. 11 depicts a DSC thermogram of amorphous form II of Deferasirox.

[00103] FIG. 12 depicts an XRPD of deferasirox amorphous form II of Deferasirox.

[00104] FIG. 13 depicts a DSC thermogram of Deferasirox amorphous form III of Deferasirox.

[00105] FIG. 14 depicts a XRPD of Deferasirox amorphous form III of Deferasirox.

[00106] FIG. 15 depicts a DSC thermogram of Deferasirox amorphous form IV of Deferasirox.

[00107] FIG. 16 depicts a XRPD of Deferasirox amorphous form IV of Deferasirox.

[00108] FIG. 17 depicts a comparison of the XRPD spectra of amorphous forms I, II, II and IV of Deferasirox.

[00109] FIG. 18 depicts a comparison of the FTIR spectra of amorphous forms I, II, III and IV of Deferasirox between the wavenumber 1800 and 1200 cm^{-1}.

[00110] FIG. 19 depicts a comparison of the FTIR spectra of amorphous forms I, II, III and IV of Deferasirox between the wavenumber 1220 and 400 cm^{-1}.

Detailed Description of the Invention

Stable Anhydrous Forms of Deferasirox

[00111] One aspect of the present invention is directed to a pharmaceutical formulation comprising a therapeutically effective amount of a stable anhydrous form of deferasirox; and a pharmaceutically acceptable excipient, wherein said deferasirox is substantially free of its acid addition salts. The present invention is further directed to processes to prepare the stable form, processes to prepare the pharmaceutical formulations and methods of using the formulations to treat conditions in a subject in need thereof.

[00112] Deferasirox, 4-(3,5-bis-(hydroxy-phenyl)-1,2,4)triazol-1-yl)benzoic acid, is an iron chelating agent, useful in the treatment of disorders in subjects suffering from elevated levels of iron.

[00113] In some embodiments, the stable anhydrous form of deferasirox is deferasirox Form I. As used herein, the phrase "stable anhydrous" refers to the fact that deferasirox Form I is "not hygroscopic," nor "slightly hygroscopic," or even "very hygroscopic" or even "deliquescent." The terms hygroscopic, slightly hygroscopic, very hygroscopic and deliquescent are defined by reference to the *European Pharmacopoeia Technical Guide* (1999, page 86) whereby, following storage at 25°C for 24 hours at 80% Relative Humidity (RH), slightly hygroscopic is defined as an increase in mass of less than 2% (w/w – weight per weight) and equal to or greater than 0.2% w/w. Hygroscopic is defined as an increase in mass of less than 15% (w/w) and equal to or greater than 0.2% (w/w). Very hygroscopic is defined as an increase in mass of equal to or greater than 15% (w/w), whilst deliquescent is defined as a sufficient amount of water absorbed to form a liquid. In some embodiments of the pharmaceutical formulation of the present invention, anhydrous deferasirox, according to the present invention, increases in mass less than about 0.2% when stored at about 25°C for about 24 hours at about 80% relative humidity.

[00114] The phrase "substantially free of its acid addition salts" refers to deferasirox free of salts formed by addition with an acid, such acids include but are not limited to; hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid,

methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, oxalic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid and benzoic acid.

[00115] In a further embodiment the formulation is in the form of a dispersible tablet, in some embodiments the pharmaceutical formulation is a water-dispersible tablet. It is preferable for the performance of the dispersible tablet that the at least one of the carrier, diluent or any other excipient is hygroscopic so to accelerate water intake providing rapid dispersion of the tablet. Therefore, a further advantage is that the stable anhydrous form of the present invention is particularly suitable for use in water-dispersible tablets that contain hygroscopic excipients as there will be no potential instability of the pharmaceutical substance and numerous difficulties during manufacturing stated above will be avoided.

[00116] In some embodiments of the present invention deferasirox Form I, according to the present invention, can optionally be used as a pharmaceutical formulation in the form of a powder, or in the form of granules. Controlling the particle size of the deferasirox, according the present invention, enhances bioavailability and control during the manufacturing process. Therefore for particle size within a specified narrow range, pharmaceutical formulations may be prepared which exhibit both a consistent *in vitro* dissolution profile and *in vivo* bioavailability. In addition to bringing about these desired dissolution/bioavailability characteristics, the control of particle size to a narrow range has also resulted in significant improvements in manufacturing capabilities. The particle size measurements of the deferasirox, according to the invention, are mean particle size, which means the value D[4,3], the volume moment mean of the particles, D[90], the diameter of which 90% by weight of the particles are smaller than and D[50], the diameter of which 50% by weight of the particles are smaller than. All measurements are made by low angle laser light scattering (LALLS) as determined typically by a Malvern Mastersizer machine.

[00117] The present invention is also directed to a powder, comprising a stable anhydrous form of deferasirox, substantially free of other forms of deferasirox. In some embodiments of the powder the stable anhydrous form of deferasirox, is substantially free of deferasirox hydrochloride salt and in some embodiments the

powder consisting essentially of deferasirox Form I, free of any other form of deferasirox and in some embodiments of the powder deferasirox Form I has at least one peak selected from the group consisting of: 1681±2, 1608±2, 1352±2, 1279±2 and 753±2 wavelength/cm^{-1} can be measured using mid–infrared Fourier transform spectroscopy.

[00118] In some embodiments the pharmaceutical formulation of the present invention comprises a therapeutically effective dose of deferasirox Form I, according to the present invention, and a pharmaceutically acceptable excipient, wherein deferasirox is substantially free of its acid addition salts.

[00119] In some embodiments of the pharmaceutical formulation deferasirox, Form I according to the present invention, is present in a composition having less than about 10% to about 5% of any other form of deferasirox, in some embodiments of the pharmaceutical formulation deferasirox, according to the present invention, is present in a composition having less than about 5% to about 1% of any other form of deferasirox and in some embodiments of the pharmaceutical formulation deferasirox, according to the present invention, is present in a composition having less than about 1% to about 0.1% of any other form of deferasirox.

[00120] In some embodiments of the current invention the deferasirox Form I, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 0.1μm to about 50μm, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 0.5μm to about 25μm and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 1μm to about 10μm.

[00121] In some embodiments of the current invention the deferasirox Form I, according to the present invention, of the pharmaceutical formulation has a D[90] of about 50 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[90] of about 25 μm and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[90] of about 10 μm or less.

[00122] In some embodiments of the current invention the deferasirox Form I, according to the present invention, of the pharmaceutical formulation has a D[50] of about 25 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[50] of about 10μm and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[50] of about 5 μm or less.

[00123] In some embodiments of the current invention the deferasirox Form I, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 50 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 25 μm and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 10 μm or less.

[00124] Some embodiments of the present invention include use of deferasirox Form I, according to the invention, in the manufacture of a medicament that is substantially free of any acid addition salt of deferasirox, for the treatment of a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent. Another embodiment of the present invention is use of deferasirox, according to the invention, in the manufacture of a medicament that is substantially free of any acid addition salt of deferasirox, for a treatment of iron overload following blood transfusion.

[00125] Some embodiments of the present invention include a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject a pharmaceutical formulation, according to the invention, In some further embodiments include a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject pharmaceutical formulation, according to the invention.

[00126] Further embodiments include a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject a suspension formed by the addition of the pharmaceutical formulation of the present invention in

water or other suitable drink suitable for human consumption, and in some embodiments a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the suspension of said formulation.

[00127] Deferasirox Form I has at least one characterising peak selected from; 1681±2, 1608±2, 1352±2, 1279±2 and 753±2 wavelength/cm^{-1} as measured using mid–infrared Fourier transform spectroscopy.

[00128] Deferasirox Form I has at least one characterising 2Θ peak selected from; 10.1°±0.2°, 13.2°±0.2°, 14.1°±0.2°, 16.6°±0.2° and 23.2°±0.2°, as measured using X-ray powder diffraction spectroscopy using a CuKα1 radiation source. Further additional 2Θ peaks of stable anhydrous deferasirox Form I can be selected from 6.6°±0.2°, 10.6° ±0.2°, 15.4°±0.2° and 17.4°±0.2°, as measured using X-ray powder difraction spectroscopy using a CuKα1 radiation source.

Table 1. X-ray powder diffraction (XRPD) experimental conditions

Sample holder preparation	Samples after being powdered in a mortar and pestle are applied directly on silicon PW1817/32 "zero background" holder
Instrument	Philips X'Pert PRO
Goniometer	PW3050/60
Generator	PW3040; 45 kV, 40 mA
X-Ray tube	PW3373/00; Cu anode LFF
Focus	Linear
Sample stage	PW3072/60 or PW3064
Scan angle range (2Θ)	4 – 40°
Scan mode	Continuous absolute scan
Step size (2Θ)	0.016°
Time per step	100 seconds
X-ray radiation	$\lambda(CuK\alpha_1)$ = 1.540598 Å
Primary soller slit	0.04 rad
PDS	Fixed, divergence 1/2°
Primary mask	10 mm
Secondary soller slit	0.04 rad
Monochromator	Inc. Beam α_1 Cu/Co for reflection mode
Detector	X'Celerator (2.022° 2Θ)
Control program	X'Pert Data Collector
Temperature	293±3K

[00129] The present invention is also directed to a process for preparing deferasirox Form I comprising: dissolving deferasirox, or a salt thereof, in any suitable solvent and precipitation with the use of a suitable anti-solvent. A second example provides a process of preparing deferasirox Form I comprising; dissolving deferasirox, or a salt thereof, in any suitable solvent and crystallization by cooling or seeding with crystals of deferasirox Form I.

[00130] The present invention also provides a process of preparing deferasirox Form I comprising dissolving deferasirox in solvent (or mixture of solvents)/base system and precipitation with the use of solvent (or mixture of solvents)/acid system. The present invention also provides a process of preparing deferasirox Form I comprising dissolving deferasirox in solvent (or mixture of solvents)/acid system and precipitation with the use of solvent (or mixture of solvents)/base system.

[00131] A suitable solvent can be selected from the group comprising; ethanol, acetone, acetonitrile, 1-butanol, 2-butanol, butyl-acetate, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethyl-acetate, methanol, methyl-acetate, 2-hexanone, 2-butanone, methyl-isobutyl ketone, 1-propanol, 2-propanol, propyl-acetate, tetrahydrofurane and combinations thereof and the water mixtures of any single solvent or water mixtures of any combination of solvents thereof. A suitable anti-solvent is selected from the group comprising water, pentane, hexane, heptane, octane, decane, ethyl ether, methyl-tert-butyl ether, diisopropyl ether and any combinations thereof. A suitable base is selected from following: sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide and sodium hydrogen carbonate. Suitable acid is selected from following: hydrochloric acid, hydrobromic acid, benzenesulfonic acid, camphorsulfonic acid, ethanesulfonic acid, fumaric acid, phthalic acid, maleic acid, methanesulfonic acid, oxalic acid, phosphoric acid, salicylic acid and sulfuric acid.

[00132] The process of producing deferasirox Form I in some embodiments can also include additional steps, comprising heating or cooling during either dissolution or precipitation, filtration, evaporation and washing of crystals, drying and any combination thereof.

[00133] The examples throughout this disclosure are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present

invention. It will thus be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

Examples

Preparation of Deferasirox Form I of the Invention

Example 1A

[00134] About 5 g of crude deferasirox was dissolved in about 145 ml of 96% ethanol in a 250 ml flask with heating. The temperature was set to about 65-70°C and the solution was treated with charcoal. After filtration of the charcoal, the clear solution was cooled down to room temperature, yielding crystals of deferasirox. The crystals were then filtered, washed with 96% ethanol, and dried in a vacuum oven at about 50°C to yield about 4.1 g of anhydrous stable deferasirox Form I.

Example 1B

[00135] About 90 g of crude deferasirox was dissolved in about 2.6 l of 96% ethanol in a 3 l glass reactor with heating. The solution was cooled down to about room temperature and seeded with deferasirox crystals. When crystallization started, the suspension was mixed for about 1 hour. The suspension was then cooled down to about 10°C and mixed for another 12 hours. Crystals were then filtered, washed with 50% ethanol and dried in a vacuum oven at about 50°C to yield about 70 g of anhydrous stable deferasirox Form I.

Example 1C

[00136] About 12 g of crude deferasirox was dissolved in about 400 ml of 96% ethanol with heating. The solution was cooled down to about 30-50°C and about 120 ml of water was added. When crystallization started, the suspension was mixed for about 1 hour. The suspension was then cooled down to about 0°C and mixed for another hour. Crystals were then filtered, washed with 10% ethanol and dried in a vacuum oven at about 70°C to yield about 11 g of anhydrous stable deferasirox Form I.

Example 1D

[00137] About 10 g of crude deferasirox was suspended in about 320 ml of water and 80 ml of 96% ethanol. Then sodium hydroxide solution was added to about pH 10. Solution was mixed for about 30 minutes and then hydrochloric acid solution was added to about pH 3. The suspension was then mixed for about 2 hours, crystals were filtered, washed with 10% ethanol and dried in a vacuum oven at about 70°C to yield about 9.4 g of anhydrous stable deferasirox Form I with particle size distribution D[10]=0.5 D[50]=1.5 D[90]= 6.5.

Example 1E

[00138] About 20 g of crude deferasirox was suspended in about 640 ml of water and 160 ml of 96% ethanol. Then hydrochloric acid solution was added to about pH 1. Solution was mixed for about 30 minutes and then sodium hydroxide solution was added to about pH 5. The suspension was then mixed for about 2 hours, crystals were filtered, washed with 10% ethanol and dried in a vacuum oven at about 70°C to yield about 19 g of anhydrous stable deferasirox Form I.

Pharmaceutical Formulations Examples

Example 1F

Formulation of the tablets	(%wt)
Deferasirox Form I	41
Microcrystalline cellulose	22
Lactose	22.95
Crospovidone	5
Mannitol	7
Sodium lauryl sulfate	0.05
Magnesium stearate	2

[00139] Intermix deferasirox with all the substances, except magnesium stearate, and homogenise for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenise for a further 5 minutes. The final blend is compressed into tablets.

Example 1G

Formulation of the tablets	(%wt)
Deferasirox Form I	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00140] Intermix deferasirox with all substances, except magnesium stearate, and homogenise for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenise for another 5 minutes. The final blend is compressed into tablets.

Example lH

Formulation of the tablets	(%wt)
Deferasirox Form I.	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00141] Granulate deferasirox with an aqueous dispersion of crospovidone and sodium lauryl sulfate. Screen the dried granules through a 30 mesh (0.6 mm) sieve, and add all of the other substances, except magnesium stearate, and homogenize for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenize for another 5 minutes. The final blend is compressed into tablets.

Example 1J

[00142] Addition methods of analysis were used to investigate deferasirox form I. An FTNIR reflectance spectra of deferasirox Form I was recorded with 32 scans on a Bruker spectrophotometer (MPA NIR Spectrophotometer) by the solid reflectance probe and at a resolution 8 cm^{-1}, an FTMID-IR spectrum was recorded on a Perkin Elmer spectrophotometer (Spectrum GX) in a KBr pellet at a resolution of 4 cm^{-1} as depicted in FIG. 2. LALLS (Low angle laser light scattering) was used to determine particle size range, the instrument used was a Malvern 2000 with Hydro 2000 μP unit. The goodness of fit were determined by a weighted residual which accounted less than 1%. Relative standard deviation between measurements were less than 15% for D(0.9) and less than 10% for D(0.1) and D(0.5).

New Polymorphic Forms of Deferasirox

[00143] The present invention is also directed to new polymorphic forms of deferasirox. The present invention is also directed to pharmaceutical formulations

thereof, processes to prepare the stable forms and the pharmaceutical formulations and methods of using the formulations.

[00144] In some embodiments of the present invention, polymorphic form II of deferasirox is characterized as having one or more characteristic X-ray powder diffraction peaks selected from following (2θ): 6.5°±0.2°, 7.4°±0.2°, 10.8°±0.2°, 13.4°±0.2°, 14.8°±0.2°, 19.2°±0.2°, 21.7°±0.2° and 26.0°±0.2°. In some embodiments of the present invention, polymorphic form II of deferasirox is characterized as having one or more characteristic X-ray powder diffraction peaks selected from following 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, 24.6°±0.2°.

[00145] In some embodiments of the present invention, polymorphic form II of deferasirox, is characterized as having one or more characteristic X-ray powder diffraction peaks selected from following (2θ): 6.5°±0.2°, 7.4°±0.2°, 10.8°±0.2°, 13.4°±0.2°, 14.8°±0.2°, 19.2°±0.2°, 21.7°±0.2° and 26.0°±0.2°, and further characterized as having one or more additional X-ray powder diffraction peaks selected from following (2θ): 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, 24.6°±0.2°.

[00146] In further embodiments of the present invention, polymorphic form II of deferasirox is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 4. In some embodiments of the present invention, polymorphic form II of deferasirox is characterized as having a melting point observed, by DSC analysis, at 228 °C ± 1 °C. In some embodiments of the present invention, polymorphic form II of deferasirox is characterized as having an IR spectrum substantially as shown in FIG 5.

[00147] In some embodiments of the present invention, polymorphic form III of deferasirox is characterized as having either one or both of the following characteristic X-ray powder diffraction peaks selected from following (2θ): 12.5°±0.2° or 15.7°±0.2°. In some embodiments of the present invention, polymorphic form III of deferasirox characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 6. In further embodiments of the present invention, polymorphic form III of deferasirox is characterized as having a melting point observed, by DSC analysis, at 208 °C ± 1 °C.

[00148] In some embodiments of the present invention, polymorphic form IV of deferasirox is characterized as having one or more characteristic X-ray powder

diffraction peaks selected from following (2θ): 10.4°±0.2°, 11.9°±0.2°, 15.0°±0.2°, 16.0°±0.2°, 21.6°±0.2°, and 22.0°±0.2°. In some embodiments of the present invention, polymorphic form IV of deferasirox is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 7. In some embodiments of the present invention, polymorphic form IV of deferasirox is characterized as having an IR spectrum substantially as shown in FIG 8. In some embodiments of the present invention, polymorphic form IV of deferasirox is characterized as having a melting point observed, by DSC analysis, at 202 °C ± 1 °C.

[00149] The present invention also provides a process of preparing polymorphic forms II and III of deferasirox comprising alternately melting and cooling of deferasirox in one or more cycles and in an inert atmosphere. Melted deferasirox is cooled to room temperature under controlled conditions with a cooling rate from about 10 °C/min to about 50 °C/min, preferably 20 °C/min to 40 °C/min. Cooling is preferably carried out in an inert atmosphere of nitrogen.

[00150] In some embodiments the present invention also provides a process of preparing polymorphic form IV of deferasirox comprising crystallization from ethanol and sulfuric acid.

[00151] In a further embodiment, the present invention is directed to a pharmaceutical formulation comprising: (a) a therapeutically effective amount of deferasirox form II or form III or form IV or form V or a mixture thereof, according to the invention, and (b) a pharmaceutically acceptable excipient.

[00152] In some embodiments, the formulation is in the form of a dispersible tablet, in some embodiments the pharmaceutical formulation is a water-dispersible tablet, in a further embodiment, the water dispersible tablet of the present invention disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

[00153] In some embodiments the present invention is directed to a powder comprising deferasirox form II, form III, form IV or a mixture thereof, according to the invention. In some embodiments of the pharmaceutical formulation of the present invention, deferasirox form II or form III or form IV or form V or a mixture thereof, according to the invention, has a mean particle size of about 0.5μm to about 10μm and in some embodiments the deferasirox form II, form III, form IV or a mixture thereof, according to the invention, has a D[90] of about 10 μm or less.

[00154] In some embodiments the present invention is directed to a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation comprising deferasirox form II, form III, form IV or a mixture thereof, of the present invention. In further embodiments the present invention is directed to a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of the present invention.

[00155] The present invention is also directed to a suspension of particles of deferasirox form II or form III or form IV or form V or a mixture thereof, according to the invention, according to the invention, in water or other drink suitable for human consumption wherein the deferasirox form II, form III, form IV or a mixture thereof, according to the invention, has a mean particle size of about 0.5μm to about 10μm. The present invention is further directed to a suspension of particles of deferasirox form II, form III, form IV or a mixture thereof, according to the invention, wherein the deferasirox has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

[00156] In some embodiments of the present invention also provides a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, such method comprises administering to the subject the suspension, according to the invention. In further embodiments the present invention provides a method of treating iron overload following blood transfusion in a subject in need of such treatment, the method comprising administering to the subject the suspension of the present invention.

[00157] Additionally the X-ray powder diffraction analysis was performed by the experimental methods as previously detailed in Table 1, where X-ray powder diffraction analysis was carried out on Philips X'Pert PRO diffractometer using CuKα1 radiation.

[00158] DSC analysis performed in Experiments 2A and 2B were carried out on a Q 1000 MDSC (TA instruments). The instrument was calibrated with indium.

[00159] IR spectrums of form II and IV shown in FIGS. 5 and 8 are obtained by using a KBr pellet and Spectrum GX manufactured by Perkin-Elmer.

[00160] All particle size measurements are made by low angle laser light scattering (LALLS) as determined typically by a Malvern Mastersizer machine.

[00161] This aspect of the present invention can be further illustrated by the following non-limiting examples.

EXAMPLES

Example 2A

Preparation of deferasirox form II

[00162] 10 mg of deferasirox is placed in open platinum sample pan (volume 50 µl) under nitrogen stream with a flow rate of 35 ml/min. The sample is equilibrated at 20 °C, heated with heating rate of 10 °C up to 270 °C (melting), isothermal point was held at 270 °C for 1 minute, then cooled with a rate of 30 °C/min down to 20 °C, and then heated with 5 °C/min up to 215 °C to obtain polymorphic form II of deferasirox.

Example 2B

Preparation of deferasirox form III

[00163] Around 11 mg of deferasirox is placed in open platinum sample pan (volume 50 µl) under nitrogen stream with a flow rate of 35 ml/min. The sample is equilibrated at 20 °C, heated with heating rate of 10 °C up to 270 °C (melting), isothermal point was held at 270 °C for 1 minute, then cooled with a rate of 30 °C/min up to 20 °C, and then heated with 10 °C/min up to 180 °C and then the isothermal point held at 180 °C for 5 min to obtain polymorphic form III of deferasirox.

Example 2C

Preparation of deferasirox form IV

[00164] 50 mg of deferasirox (DEF-05-K) was dissolved in 10 ml of ethanol (96%). The solution having an initial pH=4.70 was filtered, 3M sulfuric acid was added until

pH=0.59 was reached. 10 ml of acid was used and the total solution volume was 20 ml. 5 ml of solution was then cooled on ice. After a few hours, small white crystals appeared. The crystals were isolated (after storage overnight at room temperature) by filtration and the crystals were dried in the open, at room temperature for four hours to obtain polymorphic form IV of deferasirox.

Example 2D:

[00165] 50 mg of crystalline deferasirox was sublimate in sublimation apparatus. Crude material was heated under vacuum by external heater in the temperature range from about 250 °C to 260 °C and the cool surface of apparatus (cold finger) was set at temperature between 75 °C -80 °C. Material harvested from cold finger was mixture of deferasirox form I and form V.

Example 2E:

Pharmaceutical Formulation

Formulation of the tablets	(%wt)
Deferasirox form II or form III or form IV or form V	41
Microcrystalline cellulose	22
Lactose	22.95
Crospovidone	5
Mannitol	7
Sodium lauryl sulfate	0.05
Magnesium stearate	2

[00166] Deferasirox form II or form III or form IV or form V is mixed with all the inert substances, except magnesium stearate, and homogenize for 15 minutes. Magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve is added to the final blend and homogenize for a further 5 minutes. The final blend is compressed into tablets.

Example 2F

Pharmaceutical Formulation

Formulation of the tablets	(%wt)
deferasirox form II or form III or form IV or form V	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00167] Deferasirox form II or form III or form IV or form V is mixed with all the inert ingredients, except magnesium stearate, and homogenize for 15 minutes. Magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, is added to the final blend and homogenize for another 5 minutes. The final blend is compressed into tablets.

Example 2G

Pharmaceutical Formulation

Formulation of the tablets	(%wt)
Deferasirox form II or form III or form IV or form V	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00168] Granulate deferasirox form II or form III or form IV or form V is formed with an aqueous dispersion of crospovidone and sodium lauryl sulfate. The dried granules are screened through a 30 mesh (0.6 mm) sieve, and all of the other inert ingredients, except magnesium stearate, are added and homogenize for 15 minutes. Magnesium

stearate, previously screened through a 30 mesh (0.6 mm) sieve, is added to the final blend and homogenize for another 5 minutes. The final blend is compressed into tablets.

Amorphous Forms of Deferasirox:

[00169] Another aspect of the present invention relates to amorphous deferasirox. The present invention is also directed to pharmaceutical formulations thereof; processes to prepare the stable form and the pharmaceutical formulations and methods of using the formulations.

[00170] In some embodiments of the present invention, amorphous forms of deferasirox can be characterized by their crystalization point by diferential scanning calorimetry. As defined herein the crystalization point is the temperature, as measured by DSC, at which conversion of the amorphous form into a non amorphous form occurs. The higher the crystallisation point then the greater is the thermal stability of the amorphous form. The greater the thermal stability of the amorphous form then it can be predicted that the amorphous form is less likely to undergo a rearrangement into a crystalline form during a formulation process and during the storage conditions of the formulation.

[00171] In some embodiments amorphous form I of deferasirox is characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of about 159.0 °C ±1°C, ideally ±0.5 °C. In some embodiments amorphous form I of deferasirox is characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of about 144.6 °C ±1 °C, ideally ±0.5 °C. In further embodiments amorphous form I of deferasirox is characterized as having an X-ray diffraction pattern substantially as shown in FIG. 10. In some embodiments amorphous form I of deferasirox is further characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

[00172] In some embodiments, amorphous form II of deferasirox is characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of 153.6 °C ±1°C, ideally ±0.5 °C. In some embodiments amorphous form II of deferasirox characterized as having an onset of the crystallization point, as measured

by differential scanning calorimetry, of 143.5 °C ±1 °C, ideally ±0.5 °C. In further embodiment's amorphous form II of deferasirox characterized as having an X-ray diffraction pattern substantially as shown in FIG. 12. In some embodiments, amorphous form II of deferasirox is characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

[00173] In some embodiments of the present invention, amorphous form III of deferasirox can be characterized as having no crystallization point, as measured by differential scanning calorimetry, at any point up to 350 °C, also in some embodiments amorphous form III of deferasirox is characterized as having an X-ray diffraction pattern substantially as shown in FIG. 14. In some embodiments of the present invention, amorphous form III of deferasirox is characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

[00174] In some embodiments of the present invention amorphous form IV of deferasirox is characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of about 96.5 °C ±1°C, ideally ±0.5 °C, in some embodiments amorphous form IV of deferasirox characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of about 87.7 °C ±1 °C, ideally ±0.5 °C and in further embodiments amorphous form IV of deferasirox can be characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 16, in some embodiments, amorphous form IV of deferasirox is characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

[00175] In some embodiments the present invention also provides a process for preparing an amorphous form of deferasirox, comprising melting a sample of deferasirox and then cooling to 20 °C. Ideally the cooling step should take less than five minutes, ideally less than one minute

[00176] In a further embodiment, the present invention is directed to a pharmaceutical formulation comprising: a therapeutically effective amount of an amorphous deferasirox; according to the invention, and a pharmaceutically acceptable excipient.

[00177] A further embodiment of the present invention is directed to a pharmaceutical formulation comprising amorphous deferasirox, wherein the amorphous deferasirox is substantially free of its acid addition salts and in some embodiments wherein the

therapeutically effective amount of amorphous deferasirox is selected from the group consisting of: amorphous deferasirox form I, amorphous deferasirox form II, amorphous deferasirox form III, amorphous form deferasirox IV and combinations thereof.

[00178] In some embodiments, the formulation is in the form of a dispersible tablet, in some embodiments the pharmaceutical formulation is a water-dispersible tablet, in a further embodiment, the water dispersible tablet of the present invention disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

[00179] In some embodiments the present invention is directed to a powder, comprising an amorphous form of deferasirox selected from the group comprising of amorphous form I, amorphous form II, amorphous form III and amorphous form IV or any combination thereof. In some embodiments of the pharmaceutical formulation of the present invention, amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm and in some embodiments the amorphous deferasirox has a D[90] of about 10 μm or less.

[00180] In some embodiments the present invention is directed to a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation comprising an amorphous form of deferasirox selected from the group comprising of amorphous form I, amorphous form II, amorphous form III and amorphous form IV or any combination thereof; of the present invention. In further embodiments the present invention is directed to a method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of the present invention

[00181] The present invention is also directed to a suspension of particles of amorphous deferasirox according to the invention, in water or other drink suitable for human consumption wherein the amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm. The present invention is further directed to a suspension of particles of amorphous deferasirox, wherein the deferasirox is substantially free of its acid addition salts and wherein the deferasirox has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

[00182] In some embodiments of the present invention also provides a method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, such method comprises administering to the subject the suspension, according to the invention. In further embodiments the present invention provides a method of treating iron overload following blood transfusion in a subject in need of such treatment, the method comprising administering to the subject the suspension of the present invention.

[00183] The amorphous forms of deferasirox can be characterized by the experimental method of FTIR, wherein a Perkin Elmer Spectrum, GX at a resolution of 4 cm^{-1} and 32 scan spectra was produced of each sample of amorphous deferasirox compressed with KBr into pellet (FIG.18 and FIG.19).

[00184] Additionally the X-ray powder difraction analysis was performed by the experimental methods previously detailed in Table 1, where XRPD analysis was carried out on Philips X'Pert PRO diffractometer using CuKα1 radiation and the amorphous forms of deferasirox were subjected to thermal analysis by the experimental procedure and condition listed in Table 2.

Experimental DSC:

Table 2. Experimental conditions for DSC analysis.

1	Equipment Q 1000 MDSC TA instruments
2	Dynamic flow of nitrogen 50 ml/min
3	Heating rate of 10 °C/min
4	Standard closed aluminum pan and platinum pan
5	Sample mass about 1 to 2 mg
6	Temperature range from 20 up to 300 °C

[00242] This aspect of the present invention is further illustrated by the following non-limiting examples.

EXAMPLES

Example 3a

[00243] Deferasirox amorphous form I was prepared by melting a sample of deferasirox to around 260 °C and cooling quickly with an air stream to room temperature, within less than one minute.

Example 3b

[00244] Deferasirox amorphous form II is prepared by controlled cooling of a melted sample of deferasirox in a DSC instrument (Q1000 TA Instruments). 11 mg of deferasirox was placed in an open platinum sample pan under nitrogen pouring at a flow rate of 35 ml/min. The sample is equilibrated at 20 °C, heated with heating rate of 10 °C per min up to 270 °C (where the sample was in a melted state) isothermal heating was continued at 270 °C for 1 minute. The sample was then cooled at a rate of 30 °C/min to 20 °C, (the DSC was calibrated with indium).

Example 3c

[00245] Deferasirox amorphous form III was prepared by controlled cooling of a melted sample of deferasirox in a DSC instrument (Q1000 TA Instruments). 10 mg of deferasirox is placed in an open platinum sample pan under nitrogen pouring at a flow rate of 35 ml/min. The sample is equilibrated at 20 °C, heated with heating rate of 10 °C per min up to 270 °C (where the sample was in a melted state) isothermal heating was continued at 270 °C for 1 minute. The sample was then cooled with a rate of 0.5 °C/min to 20 °C, (the DSC was calibrated with indium).

Example 3d

[00246] Deferasirox form IV is prepared by grinding of a (10 mg) sample of deferasirox in a ball mill FRITSCH Pulversette 7 at 800 rpm for 6 hours.

Pharmaceutical Formulations Examples

Example 3e

Formulation of the tablets	(%wt)
Amorphous deferasirox	41
Microcrystalline cellulose	22
Lactose	22.95
Crospovidone	5
Mannitol	7
Sodium lauryl sulfate	0.05
Magnesium stearate	2

[00247] Intermix amorphous deferasirox with all the substances, except magnesium stearate, and homogenize for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenize for a further 5 minutes. The final blend is compressed into tablets.

Example 3f

Formulation of the tablets	(%wt)
Amorphous deferasirox	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00248] Intermix amorphous deferasirox with all substances, except magnesium stearate, and homogenize for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenize for another 5 minutes. The final blend is compressed into tablets.

Example 3g

Formulation of the tablets	(%wt)
Amorphous deferasirox	41
Microcrystalline cellulose	24
Lactose	24.95
Crospovidone	7
Sodium lauryl sulfate	0.05
Sodium stearyl fumarate	3
Magnesium Stearate	2

[00249] Granulate deferasirox with an aqueous dispersion of crospovidone and sodium lauryl sulfate. Screen the dried granules through a 30 mesh (0.6 mm) sieve, and add all of the other substances, except magnesium stearate, and homogenize for 15 minutes. Add magnesium stearate, previously screened through a 30 mesh (0.6 mm) sieve, to the final blend and homogenize for another 5 minutes. The final blend is compressed into tablets.

Formulations and Uses of Novel Deferasirox Forms

[00250] Throughout the present invention disclosure the term "therapeutically effective amount" means an amount of deferasirox, according to the present invention, which is capable of preventing, ameliorating or eliminating a disease for which administration of deferasirox is indicated.

[00251] As used herein, a "pharmaceutical formulation" refers to a medium useful for administering deferasirox, according to the present invention, to a subject in need thereof. In addition to anhydrous deferasirox such formulations of the present invention can contain one or more pharmaceutically acceptable excipients. "Pharmaceutically acceptable" refers to those compounds, materials, and/or compositions which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other possible complications commensurate with a

reasonable benefit/risk ratio. By pharmaceutically acceptable it is further meant that the carrier, diluent or excipient is compatible with deferasirox, according to the invention, and not deleterious to a recipient thereof.

[00252] One of skill in the art will recognize that a wide variety of pharmaceutically acceptable excipients can be used with the present invention including those listed in the *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press 4th Ed. (2003), and *Remington: The Science and Practice of Pharmacy*, Lippincott Williams & Wilkins, 21st ed. (2005), which are incorporated herein by reference in their entirety. In particular, pharmaceutically acceptable excipients for use with the present invention include, but are not limited to, a carrier, a diluent, a binder, a disintegrant and combinations thereof, preferably wherein at least one pharmaceutically acceptable excipient is hygroscopic.

[00253] A "carrier" refers to a pharmaceutically acceptable excipient that is suitable for formulating with a pharmaceutical compound. Non-limiting examples of suitable carriers are, in particular, fillers such as sugars (preferably selected from lactose, sucrose, mannitol or sorbitol), cellulose preparations and/or calcium phosphates (preferably selected from tricalcium phosphate or calcium hydrogen phosphate).

[00254] A "diluent" refers to an inert substance that can be added to a composition to increase its bulk. Non-limiting examples of diluents suitable for use with the present invention include low substituted hydroxypropyl cellulose, pregelatinized starch, starch cellulose, lactose, dextrose, sucrose, dextrates, mannitol, maltodextrin, methylcellulose, microcrystalline cellulose, polyethylene glycol, calcium phosphate dibasic, calcium phosphate tribasic, calcium carbonate, calcium sulfate, and combinations thereof.

[00255] A "disintegrant" refers to refers to any exipient which decreases the disintegration time (accelerates the rate of disintegration) of a formulation. Non-limiting examples of disintegrants can be selected from the group consisting of sodium starch glycolate, crosscarmellose sodium, crosslinked polyvinylpyrrolidone (crospovidone), agar or alginic acid or a salt thereof (such as sodium alginate) and low substituted hydroxypropylcellulose.

[00256] A "binder" refers to an excipient that can improve the cohesive qualities of a composition. In some embodiments, a binder can improve the compressibility of a

composition (i.e., compactable binders can increase the cohesive properties of a composition upon compression). In some embodiments, binders for use with the present invention are polymers. In some embodiments, polymers for use as binders with the present invention are hydrophilic polymers. A "hydrophilic polymer" refers to a polymeric material with an affinity for water, that is to say that a hydrophilic polymer can be hygroscopic in nature, wherein hygroscopic is defined as readily absorbing moisture. Such hydrophilic polymers include polymers with polar or polarizable side groups, charged side groups, or combinations thereof. Non-limiting examples of binders include hydroxyethyl cellulose (e.g., available as NATROSOL® *250 HX Pharm*, Hercules Inc. Corp., Wilmington, DE), hydroxypropyl cellulose, hydroxypropylmethyl cellulose (e.g., Hypromellose 2208, available as METHOCEL® *K3 Premium LV*, The Dow Chemical Company, Midland, MI), hydroxypropylethyl cellulose, sodium carboxymethylcellulose, carboxyethyl cellulose, powdered cellulose, methylcellulose, microcrystalline cellulose, polyethylene glycol, polymers of alginic acid and salts thereof (e.g., "alginates," such as sodium alginate, potassium alginate, and propane-1,2-diol alginate), polyvinyl pyrrolidone (e.g., povidone), hydrophilic gums (e.g., guar gum, karaya gum, xanthan gum, and the like), homopolymers of acrylic acid cross-linked with an allyl ether, pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene (e.g., a carbomer), and combinations thereof. Further adjuncts may be added to the formulation and are primarily flow-regulating and lubricating agents, such as, salicylic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable, if desired enteric, coatings, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, and colorants or pigments.

[00257] The pharmaceutical formulations or pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration of deferasirox, are administered to animals and humans in unit forms of administration, mixed with

conventional pharmaceutical excipients, for the prophylaxis or treatment of disorders or diseases related to the accumulation of iron in the body. In some embodiments the form of administration includes tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration.

[00258] When a solid composition in the form of tablets is prepared deferasirox, according to the present invention, is mixed with a pharmaceutical vehicle such as lactose, crospovidone, microcrystalline cellulose, povidone, sodium lauryl sulphate, silica and magnesium stearate or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances, or treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

[00259] In further embodiments the formulation is in the form of a dispersible tablet, in some embodiments the pharmaceutical formulation is a water-dispersible tablet. Such water-dispersible tablets are formed by mixing deferasirox, according to the invention, with said carrier, diluent(s), and disintegrating agent(s), with additional dispersing agent(s), wetting agent(s), and/or suspending agent(s) such as polyvinylpyrrolidone, as well as with other optional or desirable excipients such as sweeteners, taste correctors or other flavoring agents. It will be appreciated that certain excipients may have more than one function, for example certain disintegrating agents may also act as a dispersing agent.

[00260] Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

[00261] The dispersible tablets are immersed in water or other suitable liquids or drink suitable for human consumption before administration to provide a suspension. Therefore, these tablets preferably satisfy the disintegration test, whereby the dispersible tablet should disintegrate within 3 minutes in 1 liter of water at 15 °C to 25 °C. In addition the dispersible tablet preferably create a fineness of a dispersion which passes through a sieve screen with a nominal mesh aperture of 710 μm.

Dispersing agents are selected from the group comprising of crospovidone, sodium starch glycolate, croscarmellose sodium, starch and starch derivatives, alginates, cellulose and its derivatives, pharmaceutically acceptable gums, agar, chitin and chitosan or any combination thereof. In some embodiments the dispersant is present in an amount of about 0.5% wt, in some embodiments the dispersant is present in an amount of about greater than 2.5% wt and in some embodiments the dispersant is present in an amount of about 5% wt. In some embodiments the maximum amount of dispersant is about 20% wt, in some embodiments the maximum amount of dispersant is about 18% wt and in some embodiments the maximum amount of dispersant is about 15% wt.

[00262] A feature of the invention is a suspension of particles of deferasirox, according to the invention in water or other drink suitable for human consumption wherein the deferasirox, has a mean particle size of about 0.5μm to about 10μm.

[00263] Wetting agents are selected from the group comprising alkyl sulfate salts and sodium lauryl sulfate or any combination thereof. In some embodiments a wetting agent is present in an amount of about 0.05% wt, in some embodiments a wetting agent is present in an amount of about 0.5% wt, in some embodiments a wetting agent is present in an amount of about 1% wt, in some embodiments a wetting agent is present in an amount of about 3% wt, in some embodiments a wetting agent is present in an amount of about 4% wt and in some embodiments a wetting agent is present in an amount of about 5% wt.

[00264] Suspending agents are selected from one or more of the following alginates, cellulose and its derivatives, pharmaceutically acceptable gums, agar, or chitosan. In some embodiments a suspending agent is present in an amount of about 0.01% wt, in some embodiments a suspending agent is present in an amount of about greater than 0.05% wt and in some embodiments a suspending agent is present in an amount of about 0.1% wt. In some embodiments the maximum amount of suspending agent is less than about 10% wt, less than about 7.5% wt and less than about 5% wt.

[00265] It will be appreciated by those of skill in the art that certain ingredients may have more than one function, for example a dispersing agent may also act as a suspending agent. It is preferable for the performance of the dispersible tablet that at

least one carrier, diluent or any other excipient is hygroscopic so to accelerate water intake providing rapid dispersion of the tablet.

[00266] In some embodiments of the present invention deferasirox, can optionally be used as a pharmaceutical formulation in the form of a powder, or in the form of granules. Controlling the particle size of the deferasirox enhances bioavailability and control during the manufacturing process. It has now been found that by bringing the particle size of the deferasirox forms of the present invention within a specified range, pharmaceutical formulations may be prepared which exhibit a consistent *in vitro* dissolution profile and *in vivo* bioavailability. In addition to bringing about these desired dissolution/bioavailability characteristics, the control of particle size to a preferred range has also resulted in significant improvements in manufacturing capabilities.

[00267] Therefore, in some embodiments of the current invention the deferasirox, of the pharmaceutical formulation has a mean particle size of about 0.1μm to about 50μm, in some embodiments of the current invention the deferasirox, of the pharmaceutical formulation has a mean particle size of about 0.5μm to about 25μm and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 1μm to about 10μm.

[00268] In some embodiments of the current invention the deferasirox, of the pharmaceutical formulation has a D[90] of about 50 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[90] of about 25 μm or less and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[90] of about 10 μm or less.

[00269] In some embodiments of the current invention the deferasirox, of the pharmaceutical formulation has a D[50] of about 25 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[50] of about 10μm or less and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a D[50] of about 5 μm or less.

[00270] In some embodiments of the current invention the deferasirox, of the pharmaceutical formulation has a mean particle size of about 50 μm or less, in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 25 μm or less and in some embodiments of the current invention the deferasirox, according to the present invention, of the pharmaceutical formulation has a mean particle size of about 10 μm or less.

[00271] The particle size measurements of the deferasirox, according to the invention, are mean particle size, which means the value D[4,3], the volume moment mean of the particles, D[90], the diameter of which 90% by weight of the particles are smaller than and D[50], the diameter of which 50% by weight of the particles are smaller than. All measurements are made by low angle laser light scattering (LALLS) as determined typically by a Malvern Mastersizer machine.

[00272] There is also provided by the present invention deferasirox according to the invention, for use in therapy. Deferasirox, according to the invention, for use in a disease state prevented, ameliorated or eliminated by the administration of an iron chelating agent. Deferasirox, according to the invention, for use in treating iron overload following a blood transfusion.

[00273] The present invention further provides deferasirox, according to the invention, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of an iron chelating agent. More specifically, the present invention provides deferasirox, according to the invention, for use in the manufacture of a medicament for the treatment of iron overload following blood transfusion.

[00274] The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of deferasirox, according to the invention. More specifically, the present invention provides a method of treating iron overload following blood transfusion in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of deferasirox, according to the invention.

[00275] To achieve the desired prophylactic or therapeutic effect, the dose of deferasirox, according to the invention, can vary between about 10 mg per kg and about 30 mg per kg of body weight per day. Each unit dose can contain from about 100 to about 600 mg, preferably about 125 to about 500 mg of deferasirox in combination with a pharmaceutical carrier. These unit doses are preferably administered once a day.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising; (a) a therapeutically effective amount of a stable anhydrous form of deferasirox; and (b) a pharmaceutically acceptable excipient, wherein said deferasirox is substantially free of its acid addition salts.

2. The pharmaceutical formulation of claim 1, wherein the stable anhydrous form of deferasirox is not hygroscopic.

3. The pharmaceutical formulation of claim 2, wherein the stable anhydrous form of deferasirox is deferasirox Form I.

4. The pharmaceutical formulation of claim 3, wherein deferasirox Form I increases in mass less than about 0.2% when stored at about 25°C for about 24 hours at about 80% relative humidity.

5. The pharmaceutical formulation of claim 1, wherein the pharmaceutically acceptable excipient is selected from the group consisting of a carrier, a diluent, a binder, a disintegrant, and combinations thereof.

6. A pharmaceutical formulation of claim 1, wherein the formulation is a water-dispersible tablet.

7. A powder, comprising a stable anhydrous form of deferasirox, substantially free of other forms of deferasirox.

8. The powder of claim 7, wherein the stable anhydrous form of deferasirox, is substantially free of deferasirox acid addition salts.

9. The powder of claim 7, wherein the stable anhydrous form of deferasirox, is substantially free of deferasirox monohydrate.

10. The powder of claim 7, consisting essentially of deferasirox Form I.

11. The powder of claim 7, wherein deferasirox Form I has at least one peak selected from the group consisting of: 1681±2, 1608±2, 1352±2, 1279±2 and 753±2 wavelength/cm^{-1} as measured using mid–infrared Fourier transform spectroscopy.

12. A pharmaceutical formulation comprising (a) a therapeutically effective dose of deferasirox Form I, and (b) a pharmaceutically acceptable excipient, wherein deferasirox Form I is substantially free of its acid addition salts.

13. The pharmaceutical formulation of claim 12, wherein deferasirox Form I is present in a composition having less than about 5% of any other form of deferasirox.

14. The pharmaceutical formulation of claim 12, wherein deferasirox Form I has a mean particle size of about 0.5μm to about 10μm

15. The pharmaceutical formulation of claim 12, wherein deferasirox Form I has a D[90] of about 10 μm or less.

16. The pharmaceutical formulation of claim 12, wherein deferasirox Form I is characterized by an FTIR spectrum as depicted in FIG. 2.

17. The pharmaceutical formulation of claim 12, wherein deferasirox Form I is characterized by a melting point onset at about 260 ± 2 °C as determined by differential scanning calorimetry.

18. A suspension of particles of stable anhydrous deferasirox, wherein the deferasirox is substantially free of its acid addition salts and wherein deferasirox Form I has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

19. Polymorphic form II of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 6.5°±0.2°, 7.4°±0.2°, 10.8°±0.2°, 13.4°±0.2°, 14.8°±0.2°, 19.2°±0.2°, 21.7°±0.2° and 26.0°±0.2°.

20. Polymorphic form II of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, 24.6°±0.2°.

21. Polymorphic form II of deferasirox, according to claim 19, further characterized as having one or more additional X-ray powder diffraction peaks selected from following (2θ): 18.1°±0.2°, 19.7°±0.2°, 23.4°±0.2°, 24.6°±0.2°.

22. The polymorphic form II of deferasirox, according to claim 19 or 20, characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 4.

23. The polymorphic form II of deferasirox, according to claim 19 or 20, characterized as having a melting point observed by DSC analysis at 228 °C ± 1 °C.

24. The polymorphic form II of deferasirox, according to claim 19 or 20, characterized as having an IR spectrum substantially as shown in FIG 5.

25. Polymorphic form III of deferasirox characterized as having either one or both of the following X-ray powder diffraction peaks selected from following (2θ): 12.5°±0.2° or 15.7°±0.2°.

26. The polymorphic form III of deferasirox, according to claim 25, characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 6.

27. The polymorphic form III of deferasirox, according to claim 25, characterized as having a melting point observed by DSC analysis at 208 °C ± 1 °C.

28. Polymorphic form IV of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 10.4°±0.2°, 11.9°±0.2°, 15.0°±0.2°, 16.0°±0.2°, 21.6°±0.2°, 22.0°±0.2°.

29. The polymorphic form IV of deferasirox, according to claim 28, characterized as having an X-ray powder diffraction pattern substantially as shown in FIG 7.

30. The polymorphic form IV of deferasirox, according to claim 28, characterized as having an IR spectrum substantially as shown in FIG 8.

31. The polymorphic form IV of deferasirox, according to claim 28, characterized as having a melting point observed by DSC analysis at 202 °C ± 1 °C.

32. Polymorphic form V of deferasirox characterized as having one or more X-ray powder diffraction peaks selected from the following (2θ): 5.5°±0.2°, 11.0°±0.2°, 11.8±0.2.

33. A process of preparing polymorphic forms II or III of deferasirox comprising alternately melting and cooling deferasirox in one or more cycles and in an inert atmosphere.

34. The process of claim 33, wherein the melted deferasirox is allowed to cool to room temperature under controlled conditions with cooling rate from about 10 °C/min to about 50 °C/min.

35. The process of claim 34, wherein the melted deferasirox is allowed to cool to room temperature under controlled conditions with cooling rate from about 20 °C/min to about 40 °C/min.

36. The process of claim 33, wherein said inert atmosphere is an atmosphere of nitrogen.

37. A process of preparing polymorphic form IV of deferasirox comprising crystallizing deferasirox from ethanol and sulfuric acid.

38. A pharmaceutical formulation comprising; (a) a therapeutically effective amount of a deferasirox form II or form III or form IV or form V or a mixture thereof, and (b) a pharmaceutically acceptable excipient.

39. The pharmaceutical formulation of claim 38, wherein the pharmaceutically acceptable excipient is selected from the group consisting of: a carrier, a diluent, a binder, a disintegrant and combinations thereof.

40. The pharmaceutical formulation of claim 38, wherein the formulation is a water-dispersible tablet.

41. The water dispersible tablet of claim 40, wherein the dispersible tablet disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

42. The pharmaceutical formulation of claim 38, wherein deferasirox form II or form III or form IV or form V or a mixture thereof, has a mean particle size of about 0.5μm to about 10μm.

43. The pharmaceutical formulation of claim 38, wherein the deferasirox form II or form III or form IV or form V or a mixture thereof, has a D[90] of about 10 μm or less.

44. A suspension of particles of deferasirox form II or form III or form IV or form V or a mixture thereof, wherein the deferasirox form II or form III or form IV or form V or a mixture thereof, has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

45. Amorphous deferasirox.

46. Amorphous form I of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of about 159 °C + 1°C.

47. The amorphous form I of deferasirox, of claim 46, characterized as having an onset of crystallization point, as measured by differential scanning calorimetry, of about 145 °C + 1°C.

48. The amorphous form I of deferasirox, of claim 46, characterized as having an X-ray diffraction pattern substantially as shown in FIG. 10.

49. The amorphous form I of deferasirox of claim 46, characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

50. Amorphous form II of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of about 154 °C + 1°C.

51. The amorphous form II of deferasirox of claim 50, characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of about 143.5 °C ± 1°C.

52. The amorphous form II of deferasirox of claim 50, characterized as having an X-ray diffraction pattern substantially as shown in FIG. 12.

53. The amorphous form II of deferasirox of claim 50, characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

54. Amorphous form III of deferasirox, characterized as having no crystallization point, as measured by differential scanning calorimetry, at any point up to about 350 °C.

55. The amorphous form III of deferasirox of claim 54, characterized as having an X-ray diffraction pattern substantially as shown in FIG. 14.

56. The amorphous form III of deferasirox of claim 54, characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

57. Amorphous form IV of deferasirox characterized as having a peak crystallization point, as measured by differential scanning calorimetry, of about 97 °C +1°C.

58. The amorphous form IV of deferasirox, of claim 57, characterized as having an onset of the crystallization point, as measured by differential scanning calorimetry, of about 87.7 °C ± 1°C.

59. The amorphous form IV of deferasirox of claim 57, characterized as having an X-ray diffraction pattern substantially as shown in FIG 16.

60. The amorphous form IV of deferasirox of claim 57, characterized as having an FTIR spectra substantially as shown in FIG. 18 or 19.

61. A method of making amorphous form I of deferasirox comprising: (a) melting deferasirox to about 260 °C (b) cooling the melted deferasirox with an air stream to room temperature, wherein the cooling step (b) comprises about 6 minutes to about 0.5 minutes.

62. A pharmaceutical formulation comprising; (a) a therapeutically effective amount of an amorphous deferasirox; and (b) a pharmaceutically acceptable excipient.

63. The pharmaceutical formulation of claim 62, wherein the amorphous deferasirox is substantially free of its acid addition salts.

64. The pharmaceutical formulation of claim 62, wherein the therapeutically effective amount of amorphous deferasirox is selected from the group consisting of: amorphous deferasirox form I, amorphous deferasirox form II, amorphous deferasirox form III, amorphous form deferasirox IV and combinations thereof.

65. The pharmaceutical formulation of claim 62, wherein the pharmaceutically acceptable excipient is selected from the group consisting of: a carrier, a diluent, a binder, a disintegrant and combinations thereof.

66. A pharmaceutical formulation of claim 62, wherein the formulation is a water-dispersible tablet.

67. The pharmaceutical formulation of claim 66, wherein the dispersible tablet disintegrates in about 3 minutes in about 1 l of water at about 15 °C to about 25 °C.

68. A powder, comprising an amorphous form of deferasirox selected from the group comprising of amorphous form I, amorphous form II, amorphous form III and amorphous form IV or any combination thereof.

69. The pharmaceutical formulation of claim 62, wherein the amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm.

70. The pharmaceutical formulation of claim 62, wherein the amorphous deferasirox has a D[90] of about 10 μm or less.

71. A method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of any one of the claims 12, 38, 44, or 62.

72. A method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the pharmaceutical formulation of any one of the claims 12, 38, 44, or 62.

73. A suspension of particles of amorphous deferasirox, wherein the deferasirox is substantially free of its acid addition salts and wherein amorphous deferasirox has a mean particle size of about 0.5μm to about 10μm, in water or other drink suitable for human consumption.

74. A method of treating a disease prevented, ameliorated or eliminated by the administration of an iron chelating agent, in a subject in need thereof, the method comprising administering to the subject the suspension of claim 73.

75. A method of treating iron overload following blood transfusion in a subject in need thereof, the method comprising administering to the subject the suspension of claim 73.

76. A process of preparing deferasirox Form I comprising crystallizing deferasirox from an ethanol solution by alternately heating and cooling said solution.

77. The process of claim 76, wherein the deferasirox Form I is further filtered, washed and vacuum dried.

78. The process of claim 76, wherein said heating is from about 10 °C to about 100 °C.

79. The process of claim 76, wherein said cooling is from about 100 °C to about 0 °C.

80. A process of preparing deferasirox Form I comprising:

(a) suspending deferasirox in aqueous ethanol;

(b) adding sodium hydroxide to form an alkaline solution;

(c) stirring said solution;

(d) acidifying said solution to form crystals;

(e) filtering said crystals; and

(d) vacuum drying said crystals.

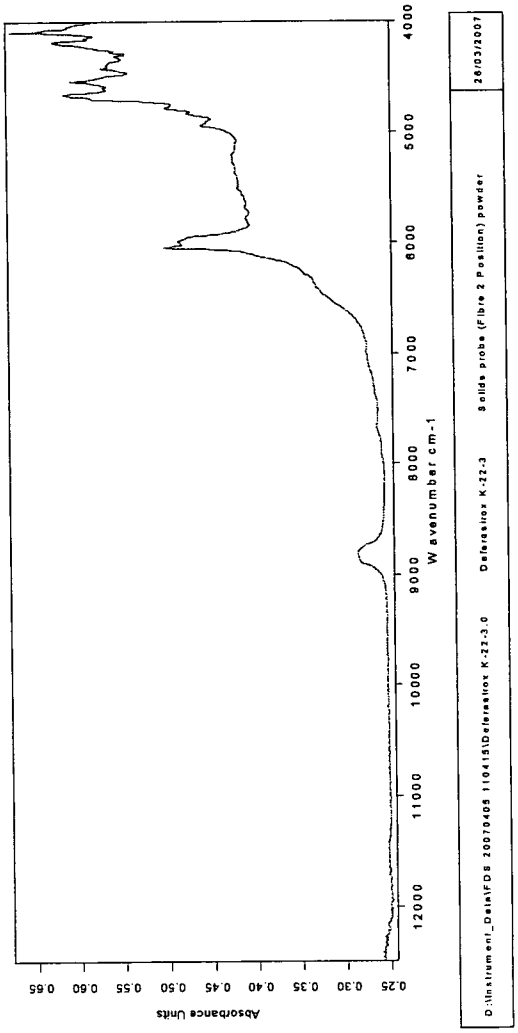

Absorbance Units
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
12000
11000
10000
9000
8000
7000
6000
5000
4000
Wavenumber cm-1
D:\Instrument_Data\FDS 20070405 110415\Deferasirox K-22-3.0
Deferasirox K-22-3
Solids probe (Fibre 2 Position) powder
28/03/2007

FIG. 1

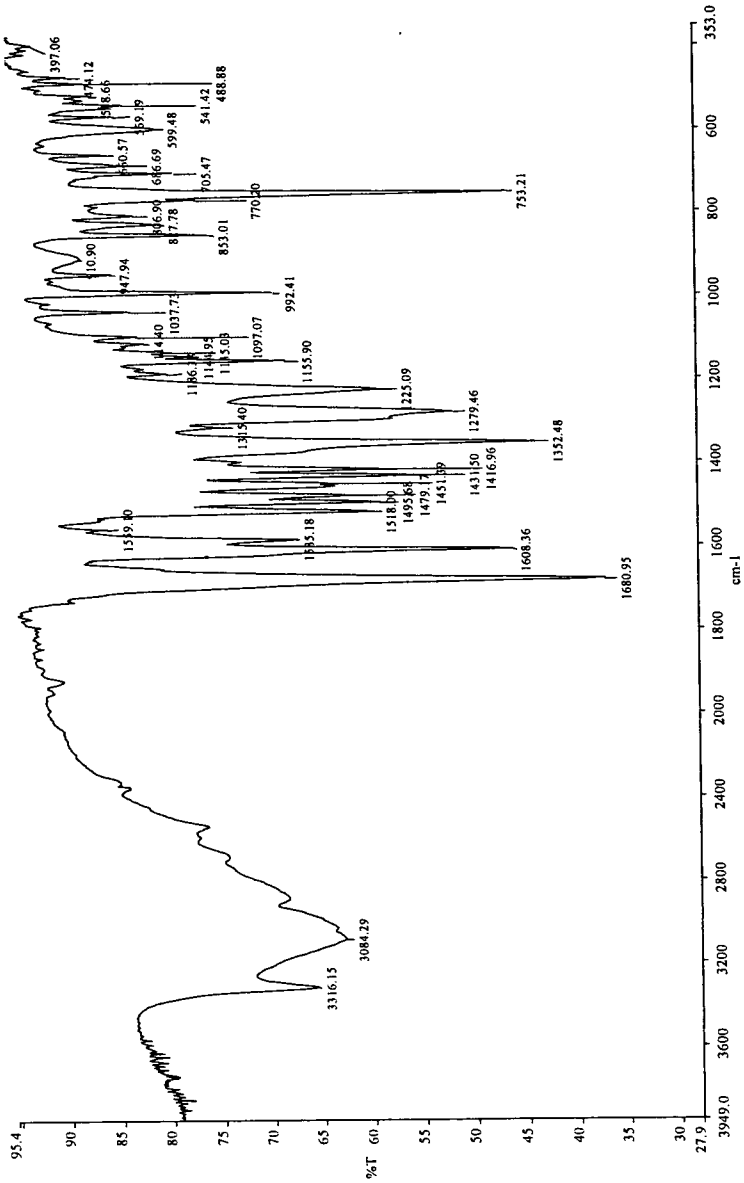

%T
cm-1
95.4
90
85
80
75
70
65
60
55
50
45
40
35
30
27.9
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
353.0
3316.15
3084.29
1680.95
1608.36
1559.80
1518.00
1495.68
1479.12
1451.09
1431.50
1416.96
1352.48
1315.40
1279.46
1225.09
1155.90
1135.08
1097.07
1037.73
992.41
947.94
910.90
853.01
817.78
770.20
753.21
705.47
686.69
660.57
599.48
541.42
488.88
474.12
397.06

FIG. 2

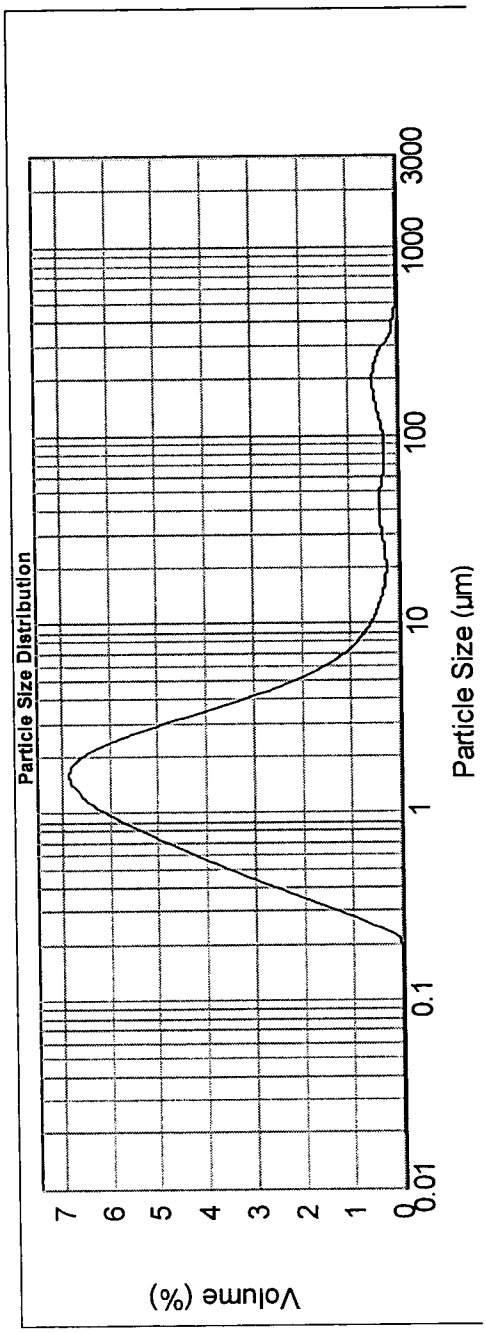

Particle Size Distribution
Volume (%)
0
1
2
3
4
5
6
7
0.01
0.1
1
10
100
1000
3000
Particle Size (µm)

FIG. 3

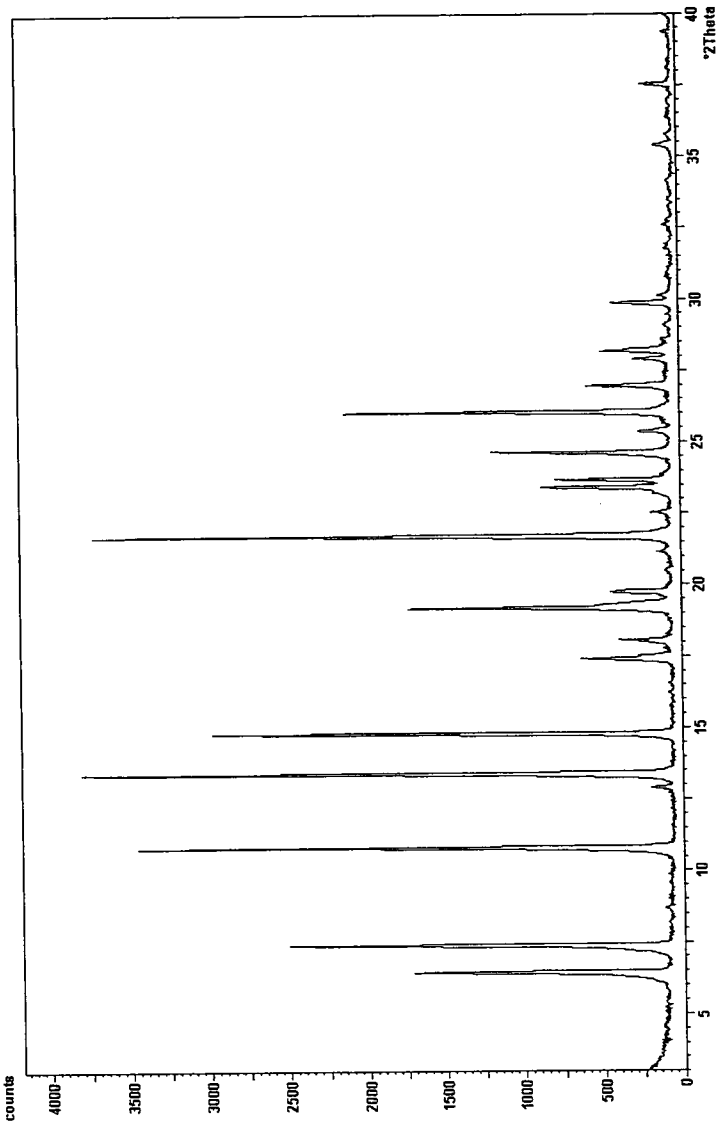

counts
4000
3500
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
°2Theta

FIG. 4

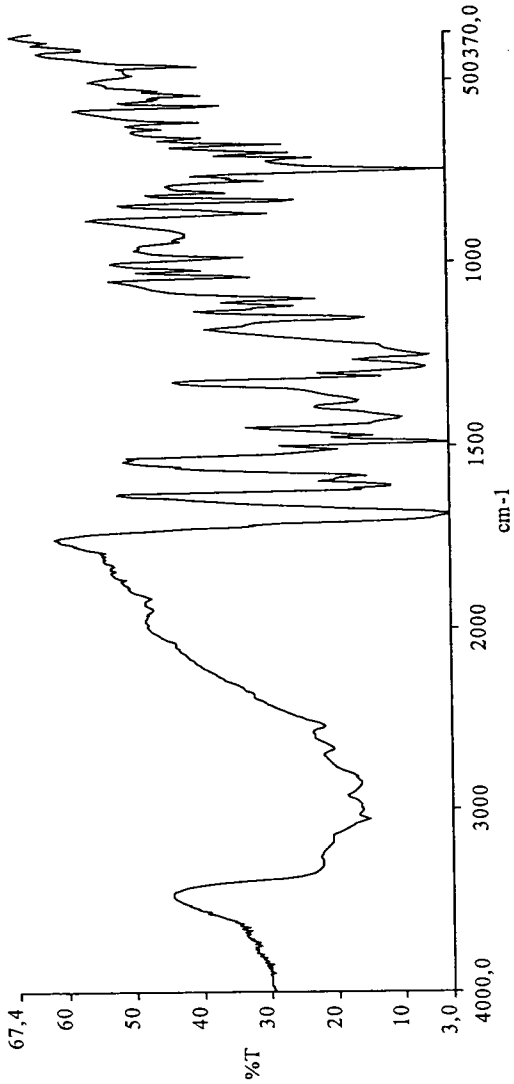


FIG. 5

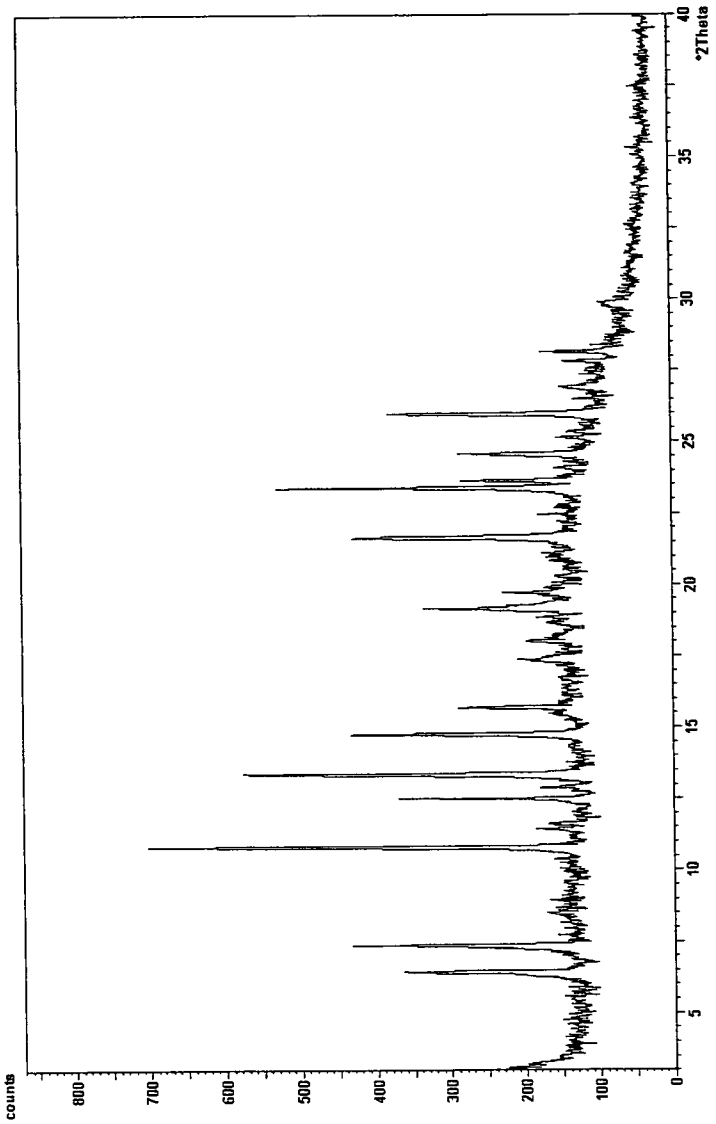

counts
800
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
40
°2Theta

FIG. 6

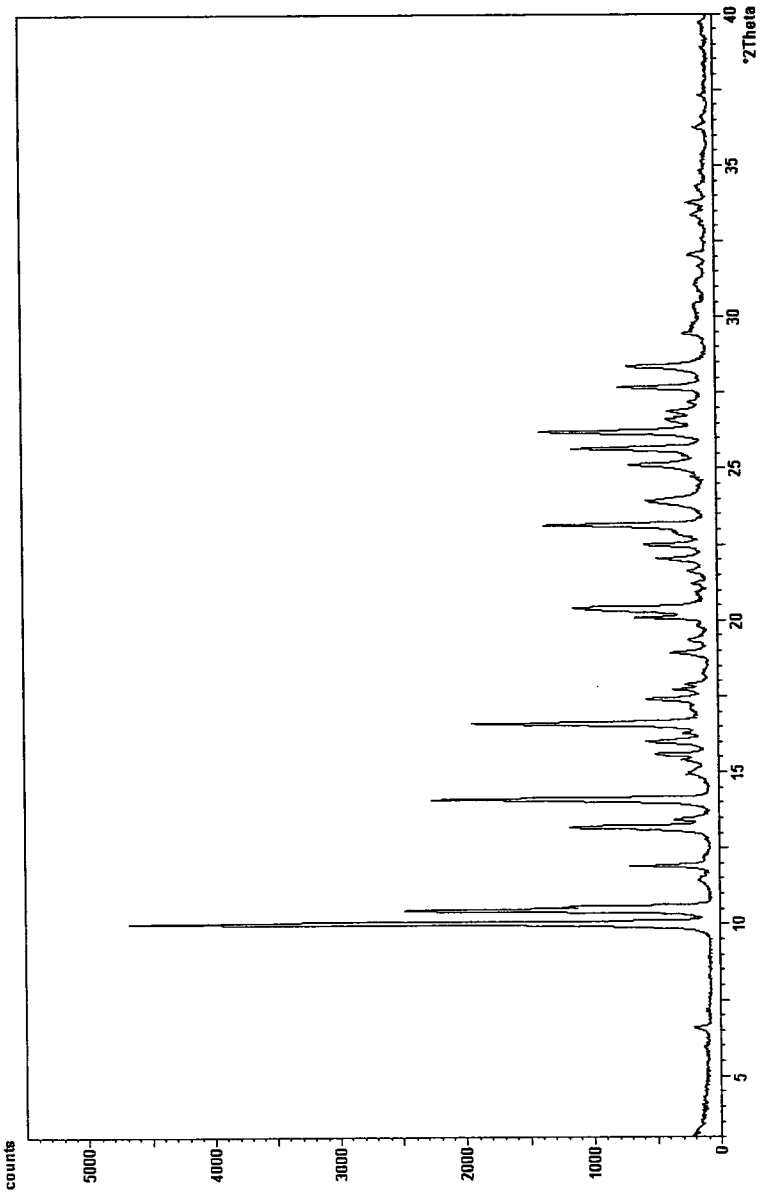


FIG. 7

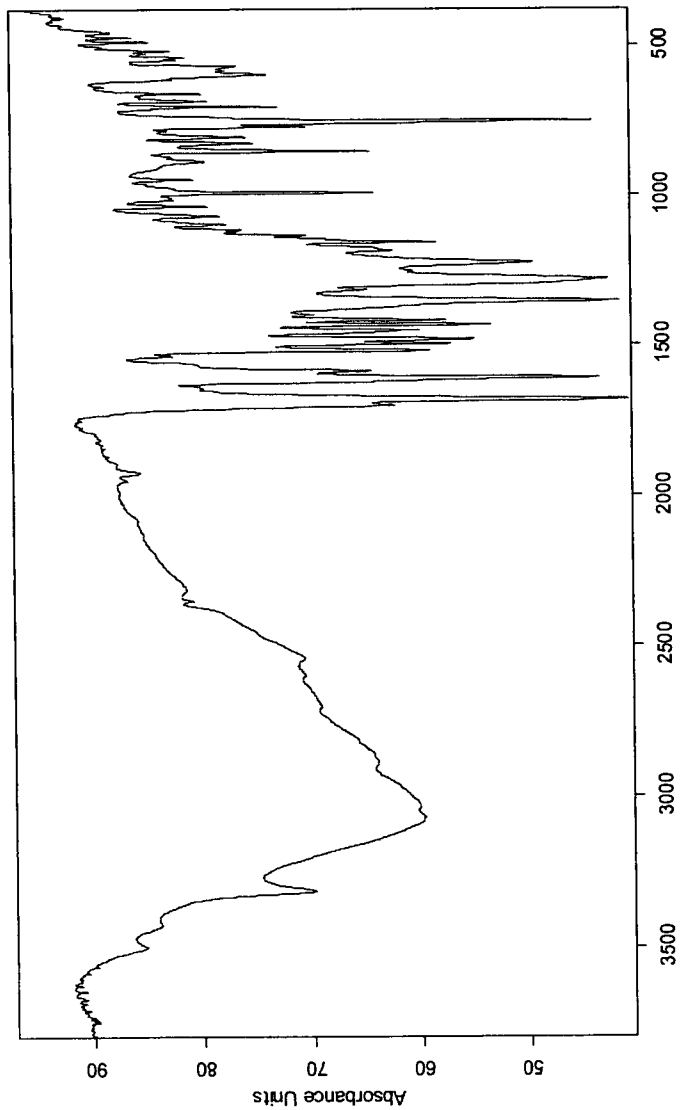

Absorbance Units
50
60
70
80
90
500
1000
1500
2000
2500
3000
3500

FIG. 8

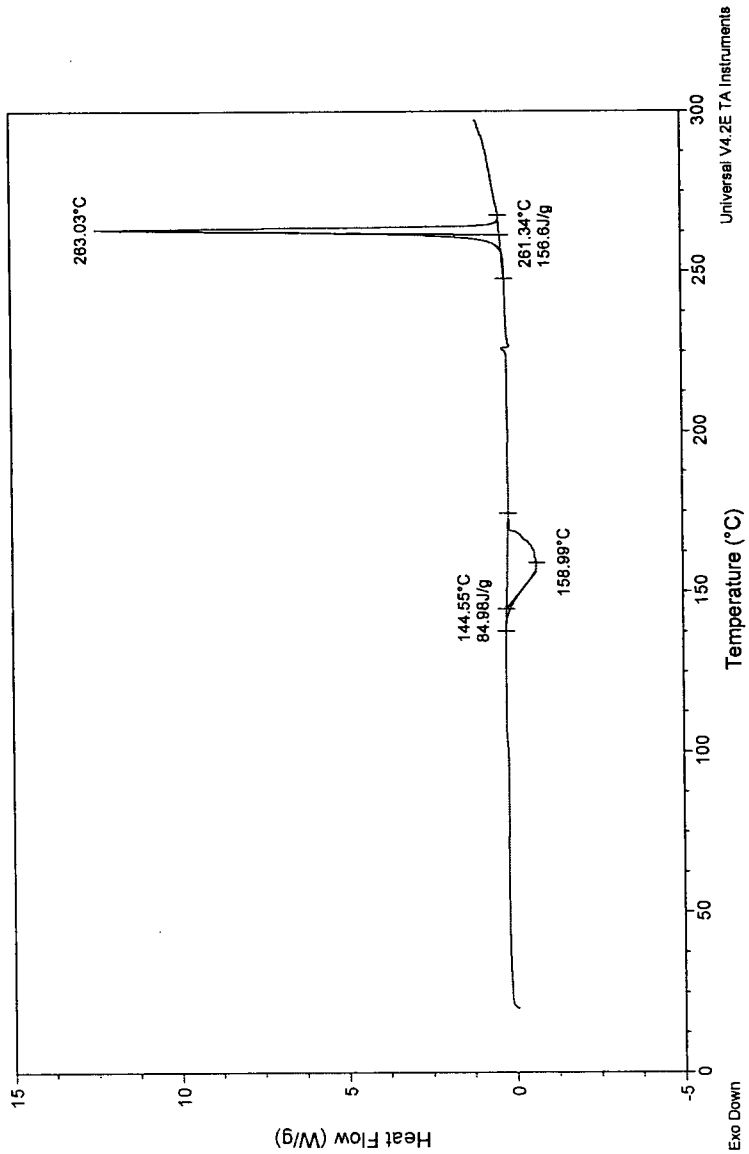

283.03°C
261.34°C
156.6J/g
144.55°C
84.98J/g
158.99°C
Heat Flow (W/g)
Exo Down
Temperature (°C)
Universal V4.2E TA Instruments
15
10
5
0
-5
0
50
100
150
200
250
300

FIG. 9

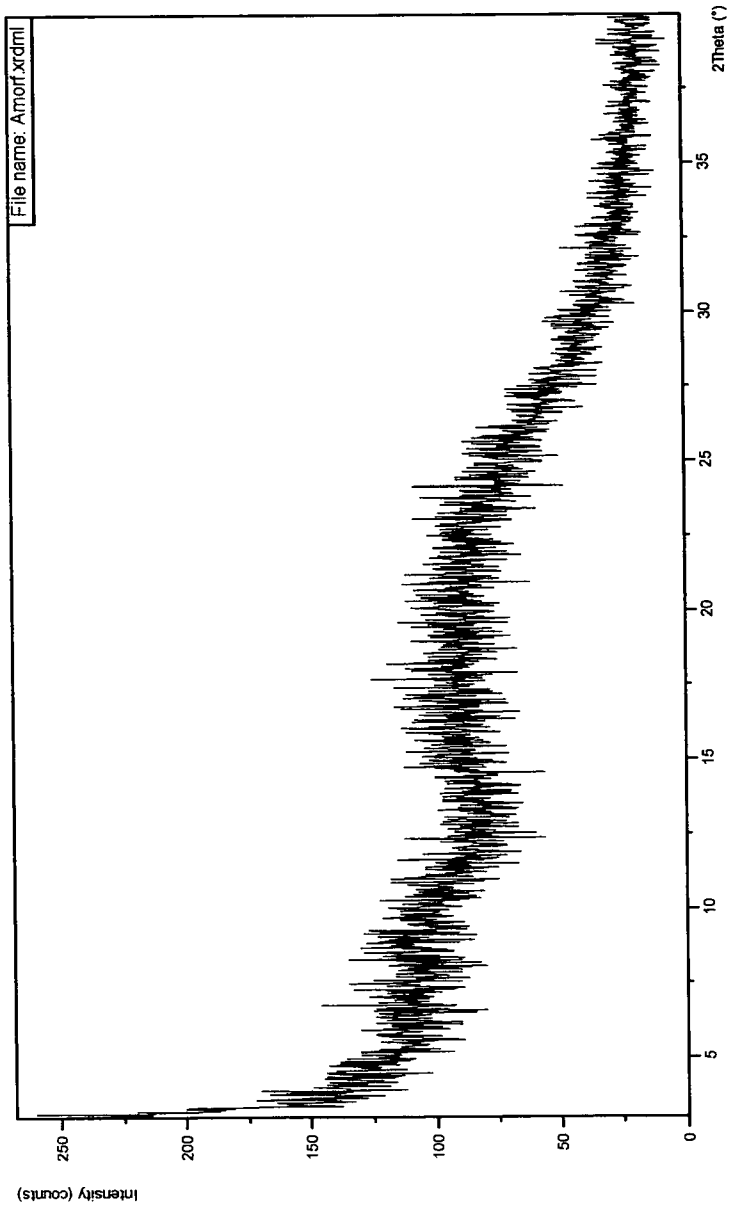

File name: Amorf.xrdml
Intensity (counts)
2Theta (°)
0
50
100
150
200
250
5
10
15
20
25
30
35

FIG. 10

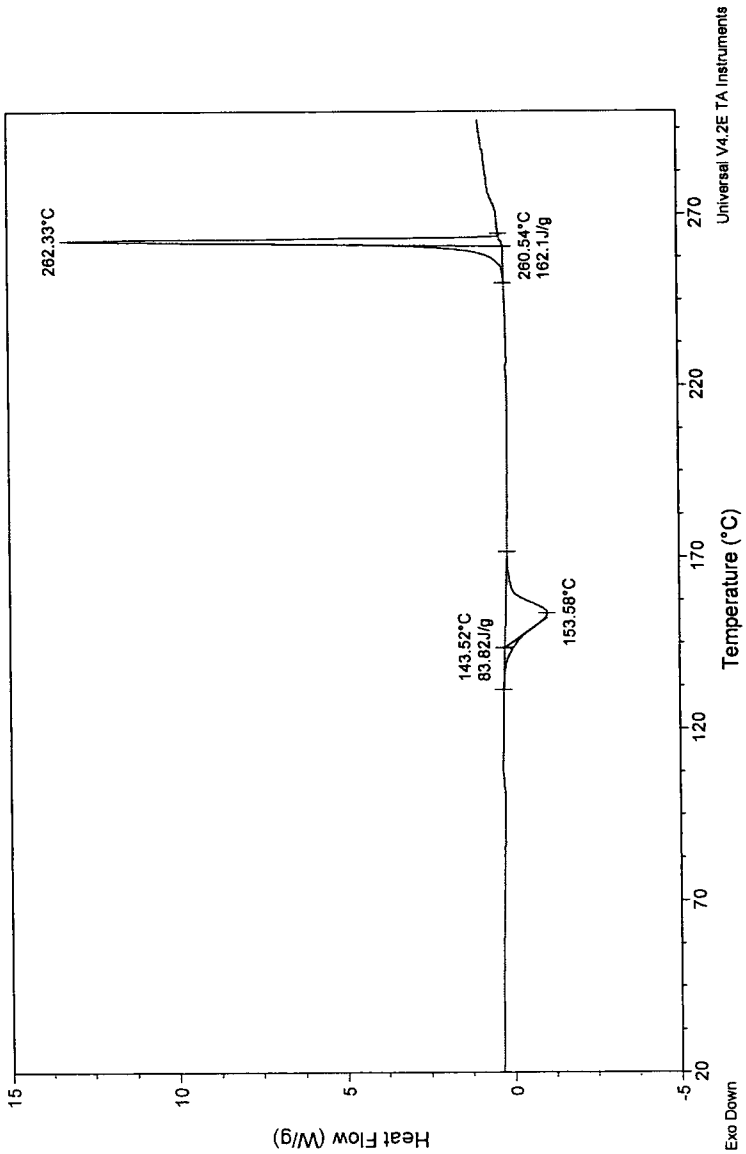

282.33°C
280.54°C
162.1J/g
143.52°C
83.82J/g
153.58°C
Heat Flow (W/g)
Exo Down
Temperature (°C)
Universal V4.2E TA Instruments

FIG. 11

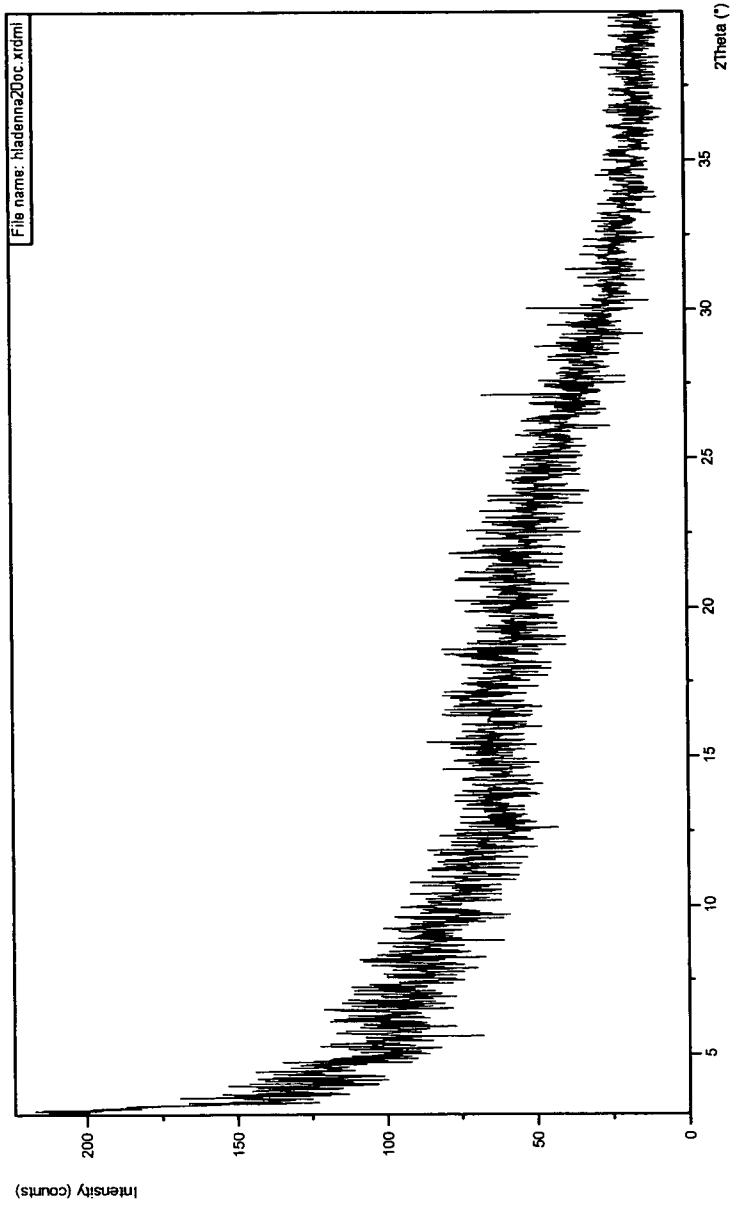

File name: hladenna20oc.xrdml
Intensity (counts)
2Theta (°)
0
50
100
150
200
5
10
15
20
25
30
35

FIG. 12

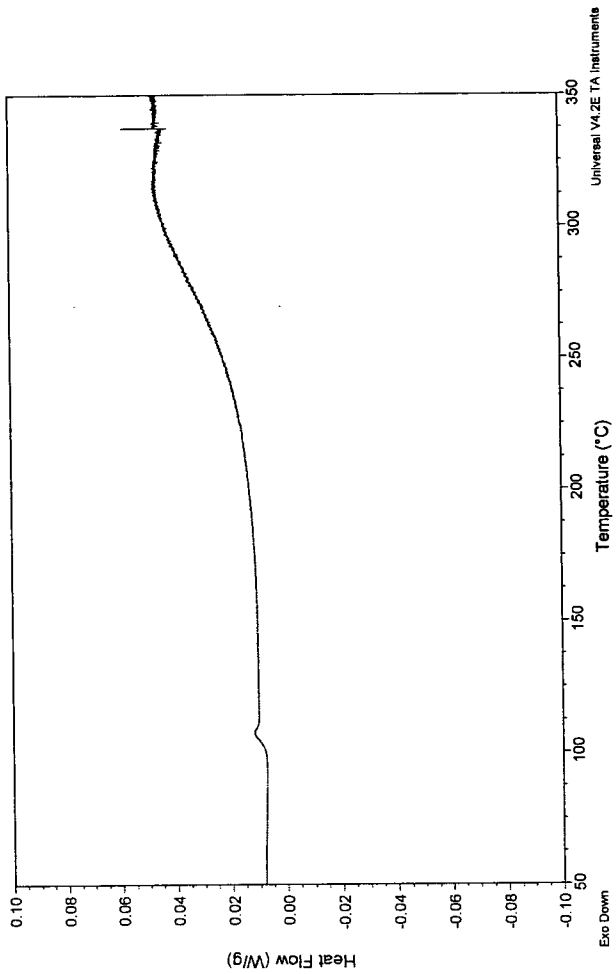

Universal V4.2E TA Instruments
Temperature (°C)
Heat Flow (W/g)
Exo Down
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
50
100
150
200
250
300
350

FIG. 13

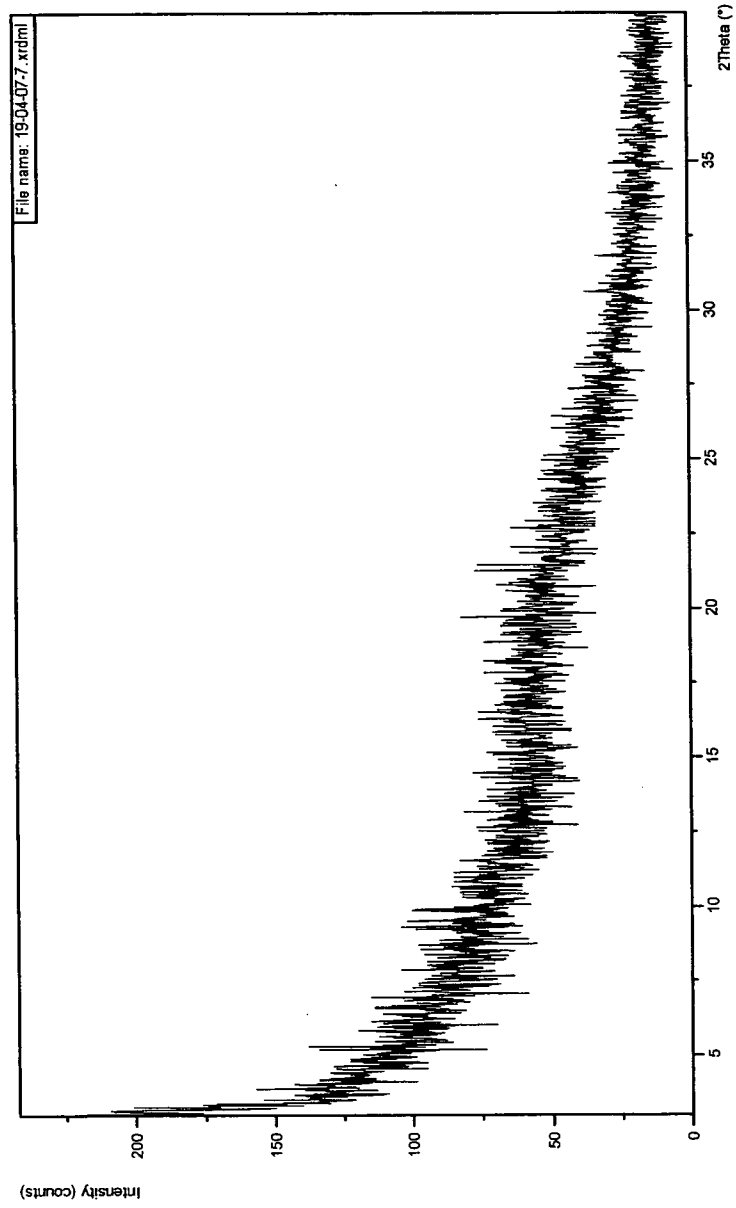

File name: 19-04-07-7.xrdml
Intensity (counts)
2Theta (°)
0
50
100
150
200
5
10
15
20
25
30
35

FIG. 14

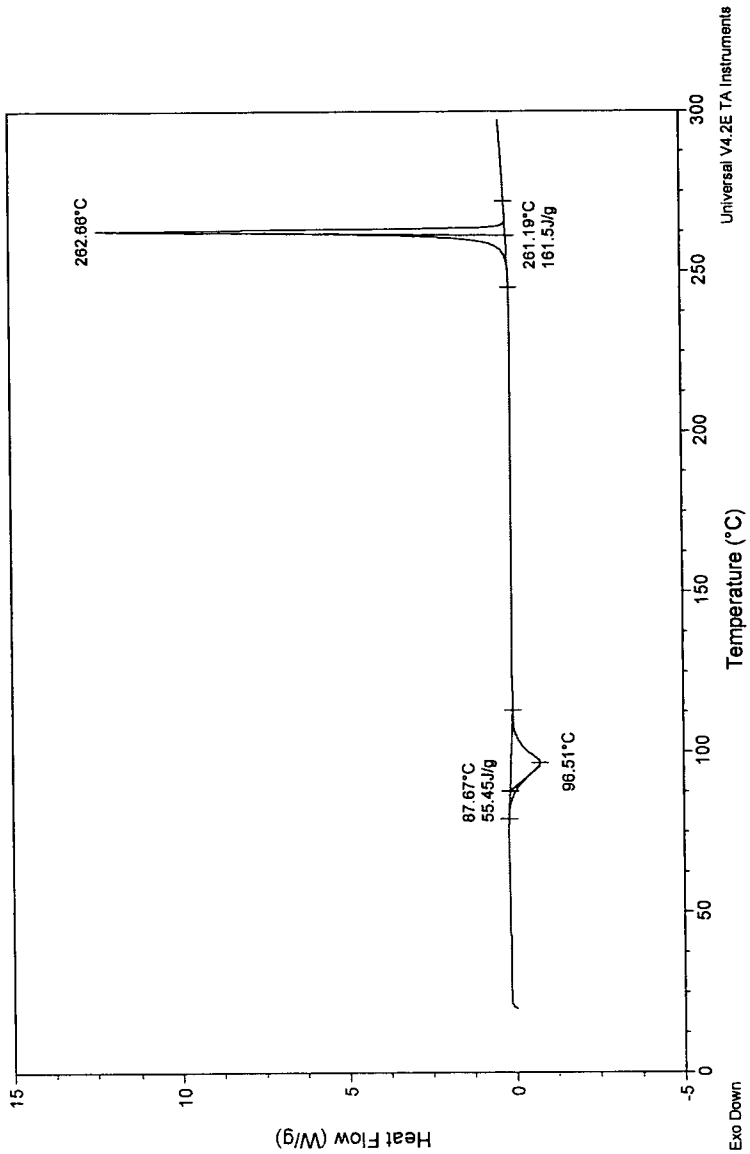

262.68°C
261.19°C
161.5J/g
87.67°C
55.45J/g
96.51°C
Heat Flow (W/g)
Temperature (°C)
Exo Down
Universal V4.2E TA Instruments

FIG. 15

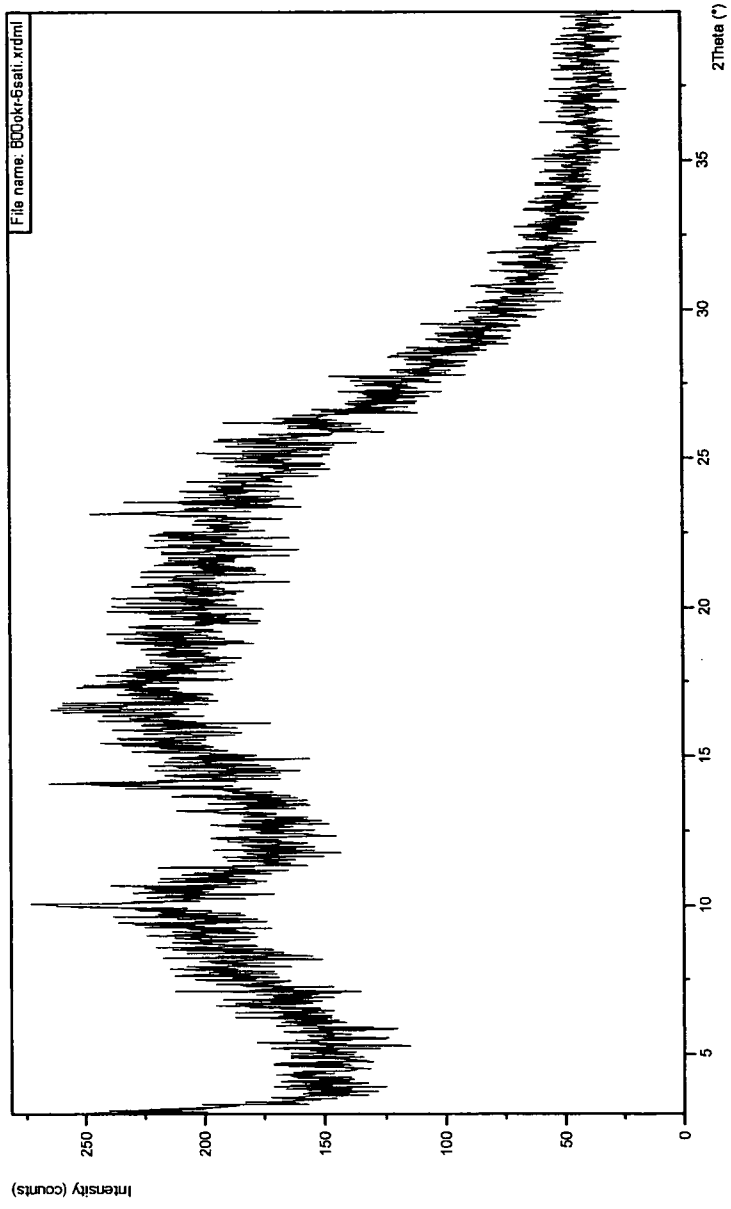

File name: 800okr-6sati.xrdml
Intensity (counts)
2Theta (°)
0
50
100
150
200
250
5
10
15
20
25
30
35

FIG.16

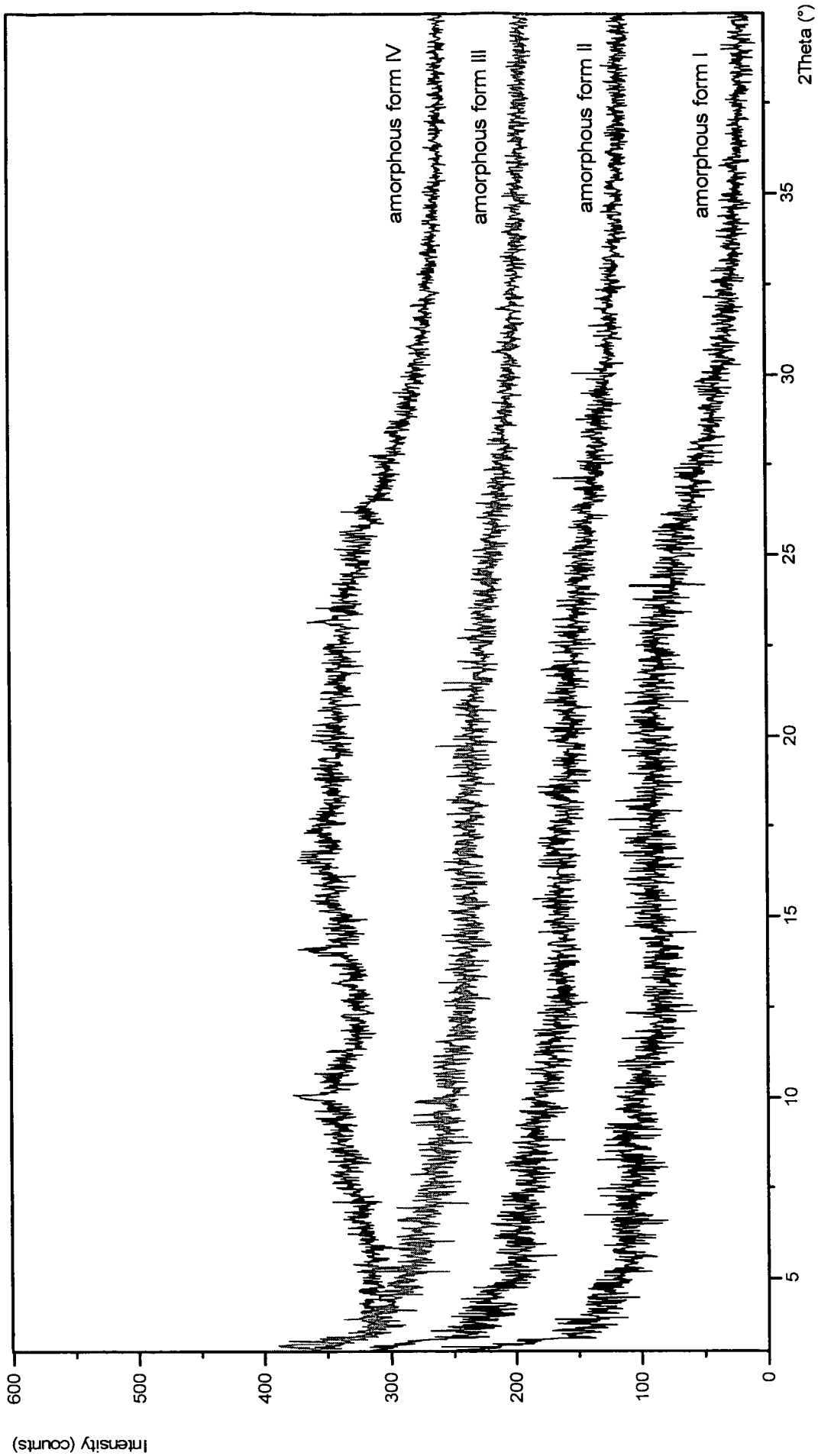

amorphous form IV
amorphous form III
amorphous form II
amorphous form I
Intensity (counts)
2Theta (°)
0
100
200
300
400
500
600
5
10
15
20
25
30
35

FIG. 17

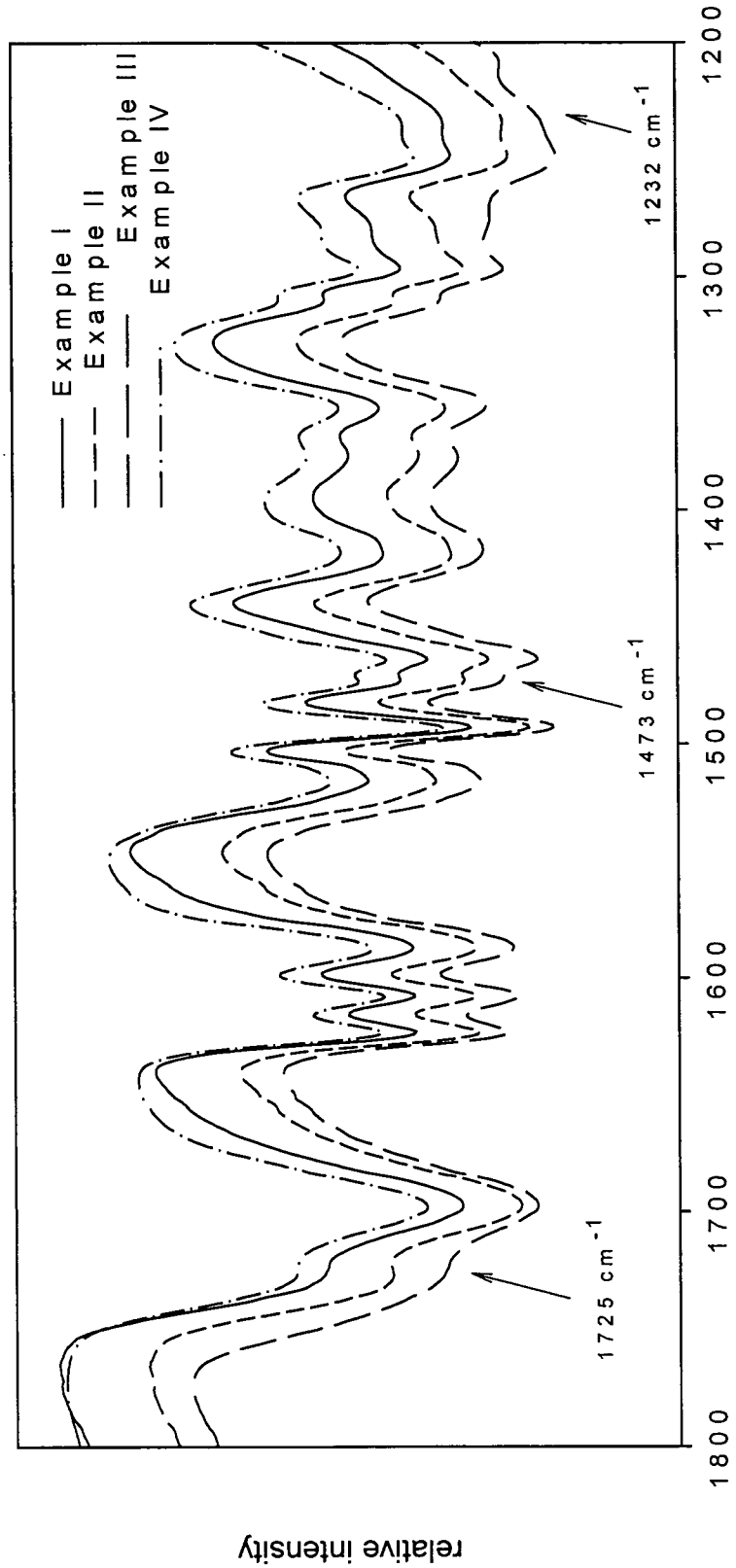

Example I
Example II
Example III
Example IV
1725 cm-1
1473 cm-1
1232 cm-1
1800
1700
1600
1500
1400
1300
1200
wavenumber / cm-1
relative intensity

FIG. 18

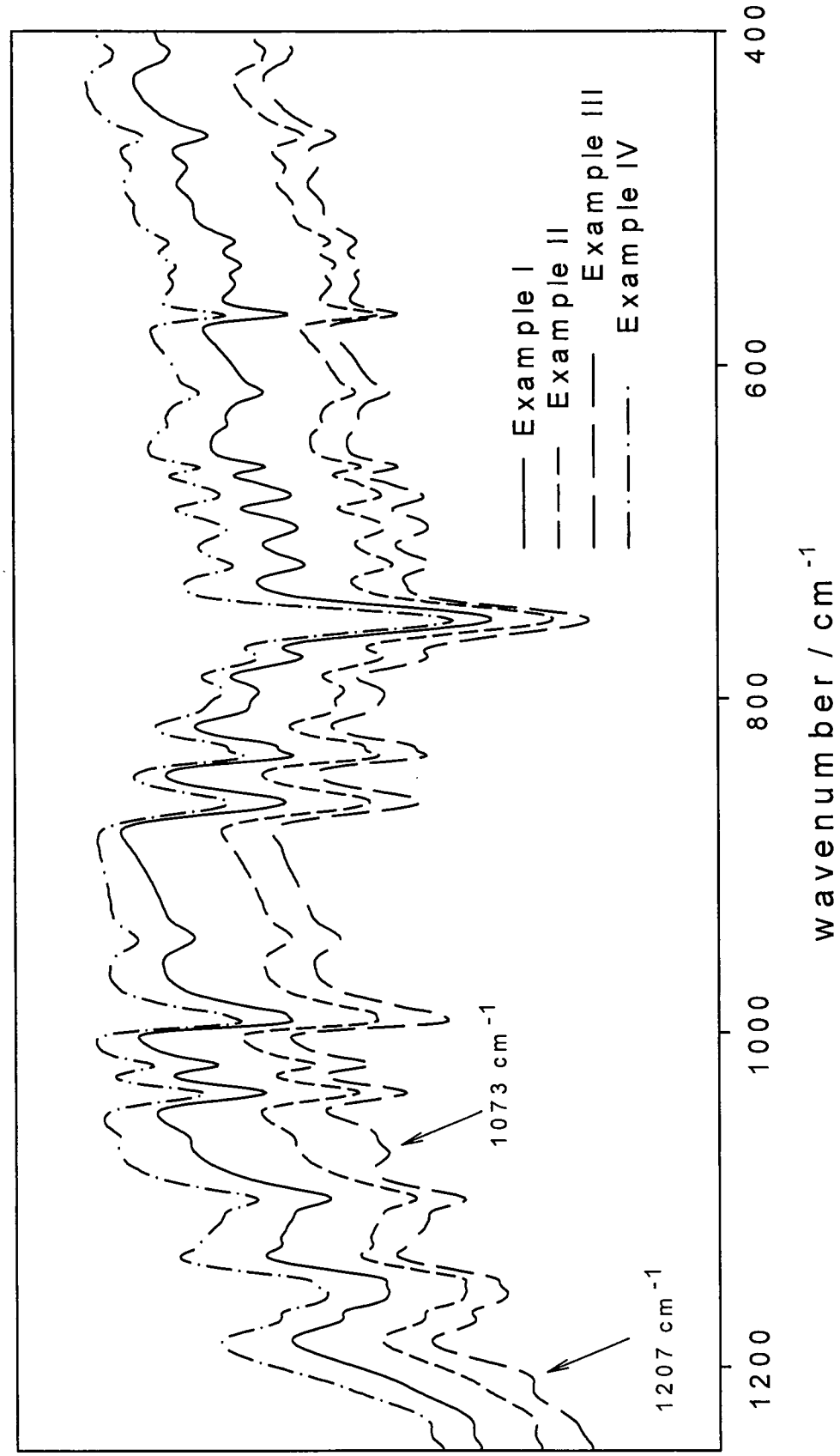

relative intensity
wavenumber / cm-1
400
600
800
1000
1200
1073 cm-1
1207 cm-1
Example I
Example II
Example III
Example IV

FIG. 19

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/002572

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4196 C07D249/08

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 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANONYMOUS: "Crystalline (4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid and process for preparation thereof" IP.COM PRIOR ART DATABASE, [Online] no. ipcom000146862D, 26 February 2007 (2007-02-26), XP002506935 Retrieved from the Internet: URL:www.ip.com> [retrieved on 2008-12-04] the whole document	1-19
X	US 2003/069273 A1 (LATTMANN RENE [CH] ET AL) 10 April 2003 (2003-04-10) cited in the application page 8; example 5	1-44

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2008	19/12/2008

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/002572

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/49395 A (CIBA GEIGY AG [CH]; LATTMANN RENE [CH]; ACKLIN PIERRE [CH]) 31 December 1997 (1997-12-31) page 19; example 5	1-44
X	WO 2004/035026 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DEFFEZ KARINE [FR]; CASSI) 29 April 2004 (2004-04-29) page 1, paragraph 1 page 3, paragraphs 3,4 claims 1-5	45-80
A	VAN ORDEN HEIDI E ET AL: "Deferasirox - An oral agent for chronic iron overload" ANNALS OF PHARMACOTHERAPY,, vol. 40, no. 6, 1 June 2006 (2006-06-01), pages 1110-1117, XP009109627 ISSN: 1060-0280 the whole document	1-80
E	WO 2008/094617 A (TEVA GYOGYSZERGYAR ZARTKOERUEE [HU]; TEVA PHARMA [US]; TOTH ZOLTAN G []) 7 August 2008 (2008-08-07) page 1, paragraph 1 - page 2, paragraph 6 figures 1-6 page 10 - page 12; examples 1-9	1-44
P,X	WO 2008/065123 A (NOVARTIS AG [CH]; MUTZ MICHAEL [DE]) 5 June 2008 (2008-06-05) page 1, paragraph 3 - page 3, paragraph 3	1-80

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/002572

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003069273 A1	10-04-2003	NONE	
WO 9749395 A	31-12-1997	AP 1127 A	06-12-2002
		AT 226435 T	15-11-2002
		AU 718037 B2	06-04-2000
		AU 3262997 A	14-01-1998
		BG 64248 B1	30-07-2004
		BG 103003 A	30-09-1999
		BR 9709973 A	10-08-1999
		CA 2255951 A1	31-12-1997
		CN 1223579 A	21-07-1999
		CY 2429 A	12-11-2004
		CZ 9804272 A3	17-03-1999
		DE 69716602 D1	28-11-2002
		DE 122007000020 I1	24-05-2007
		DE 69716602 T2	26-06-2003
		DK 914118 T3	24-02-2003
		EP 0914118 A1	12-05-1999
		ES 2187785 T3	16-06-2003
		HK 1020530 A1	13-06-2003
		HU 9903111 A2	28-01-2000
		JP 2000507601 T	20-06-2000
		JP 3541042 B2	07-07-2004
		KR 20000022222 A	25-04-2000
		KR 20050098029 A	10-10-2005
		LU 91291 A9	29-01-2007
		NL 300248 I1	01-02-2007
		NO 986024 A	21-12-1998
		NO 2006017 I1	18-12-2006
		NZ 333308 A	26-05-2000
		OA 10946 A	27-02-2003
		PL 330119 A1	26-04-1999
		PT 914118 T	28-02-2003
		RU 2208010 C2	10-07-2003
		SK 178598 A3	11-06-1999
		TR 9802693 T2	21-05-1999
		TW 533205 B	21-05-2003
		US 6465504 B1	15-10-2002
WO 2004035026 A	29-04-2004	AU 2003278078 A1	04-05-2004
		BR 0315264 A	23-08-2005
		CA 2501659 A1	29-04-2004
		CN 1705471 A	07-12-2005
		EP 1556013 A1	27-07-2005
		JP 2006504748 T	09-02-2006
		KR 20050071578 A	07-07-2005
		MX PA05003999 A	22-06-2005
		NZ 539354 A	27-04-2007
		US 2006110446 A1	25-05-2006
		ZA 200502488 A	04-10-2005
WO 2008094617 A	07-08-2008	US 2008262060 A1	23-10-2008
WO 2008065123 A	05-06-2008	NONE	