ABSTRACT

The present invention relates to novel acid addition salts of dabigatran etexilate, process for the preparation and pharmaceutical compositions containing the same. Further, the invention relates to uses of said compositions for post operative prophylaxis of deep vein thrombosis and the prevention of strokes.

CLAIMS:

Claim 1: Novel acid addition salts of Dabigatran etexilate or its solvates or hydrates thereof; wherein the acid addition salts being selected from the group comprising ferulic acid, caffeic acid, gallic acid and nitric acid.

Claim 2: A process for preparing acid addition salts of Dabigatran Etexilate, or its solvates or hydrates thereof, comprising the steps of:

a) providing a solution comprising dabigatran etexilate and acid addition salt in one or more solvents, and
b) isolating the dabigatran etexilate acid addition salt; wherein the acid addition salt being selected from the group comprising ferulic acid, caffeic acid, gallic acid and nitric acid.

Claim 3: The process according to claim 2, wherein the step a) further comprises:

a) dissolving any form of Dabigatran Etexilate in suitable organic solvent at a suitable temperature to form a solution, and
b) mixing the acid addition salt to the solution; wherein the acid addition salt being selected from the group comprising ferulic acid, caffeic acid, gallic acid and nitric acid.

Claim 4: The process according to claim 3, wherein the suitable organic solvent is selected from the group consisting of methanol, ethanol, isopropanol, acetone, methylethylketone, methyl isobutyl ketone, methyl acetate, ethyl acetate, isopropyl acetate, tetrahydrofuran (THF), isopropyl ether (IPE), ter-butyl methyl ether, acetonitrile, propionitrile, methylene chloride, chloroform, toluene, cyclohexane, hexane, heptanes and mixtures thereof.

Claim 5: The process according to claim 3, wherein the suitable temperature is at about 30°C to about 90°C.

Claim 6: Dabigatran etexilate ferulate salt, characterized by an X-ray diffraction (XRD) pattern substantially in accordance with Figure. 1.

Claim 7: Dabigatran etexilate caffate salt, characterized by an X-ray diffraction (XRD) pattern substantially in accordance with Figure. 3.

Claim 8: Dabigatran etexilate gallate salt, characterized by an X-ray diffraction (XRD) pattern substantially in accordance with Figure. 5.

Claim 9: Dabigatran etexilate nitrate salt, characterized by an X-ray diffraction (XRD) pattern substantially in accordance with Figure. 7.

Claim 10: A pharmaceutical composition comprising a therapeutically effective amount of one or more of the Dabigatran etexilate salts according to claim 1 – 9.

DATED: Second (2nd) day of September 2014

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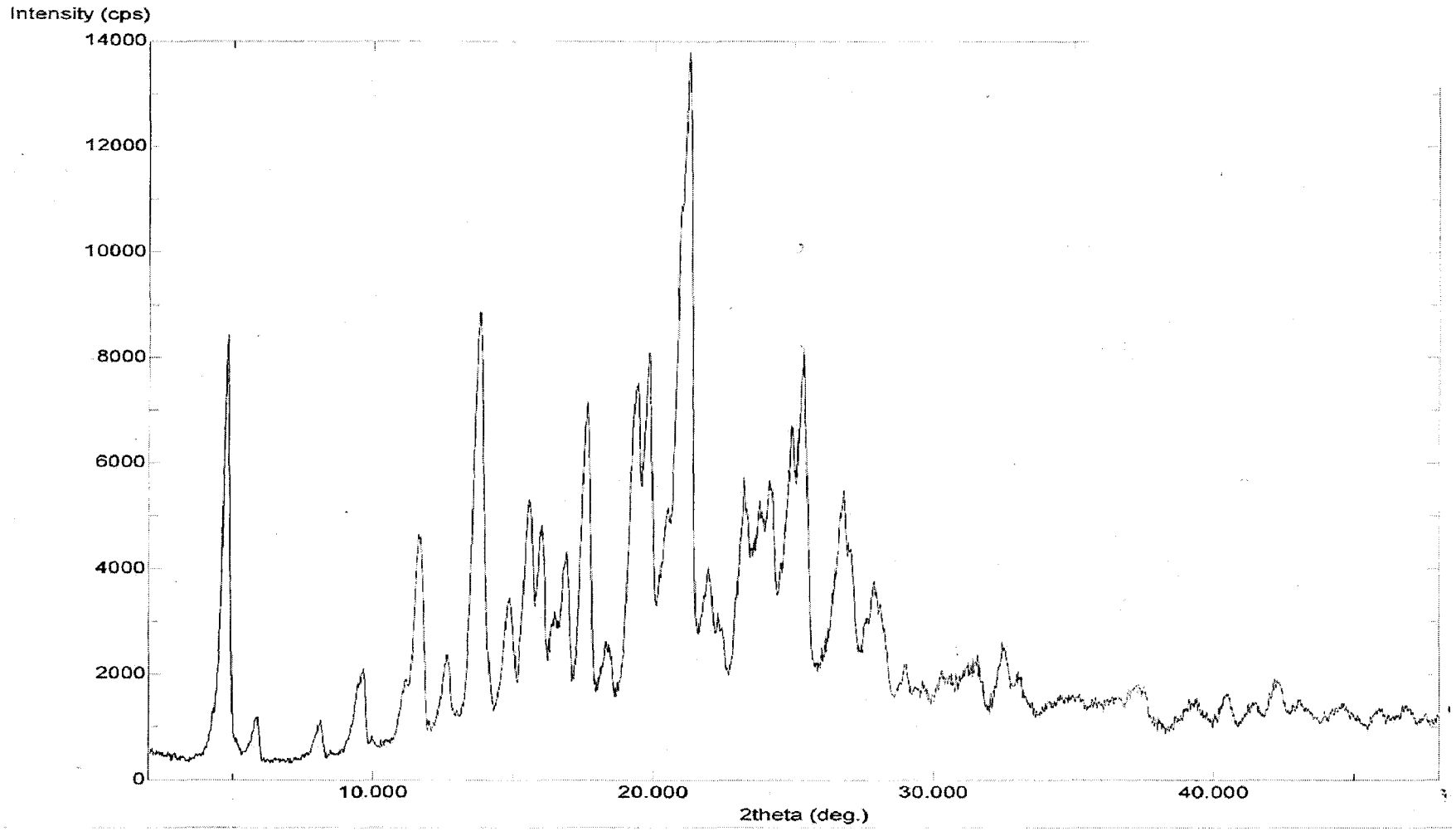

Figure 1

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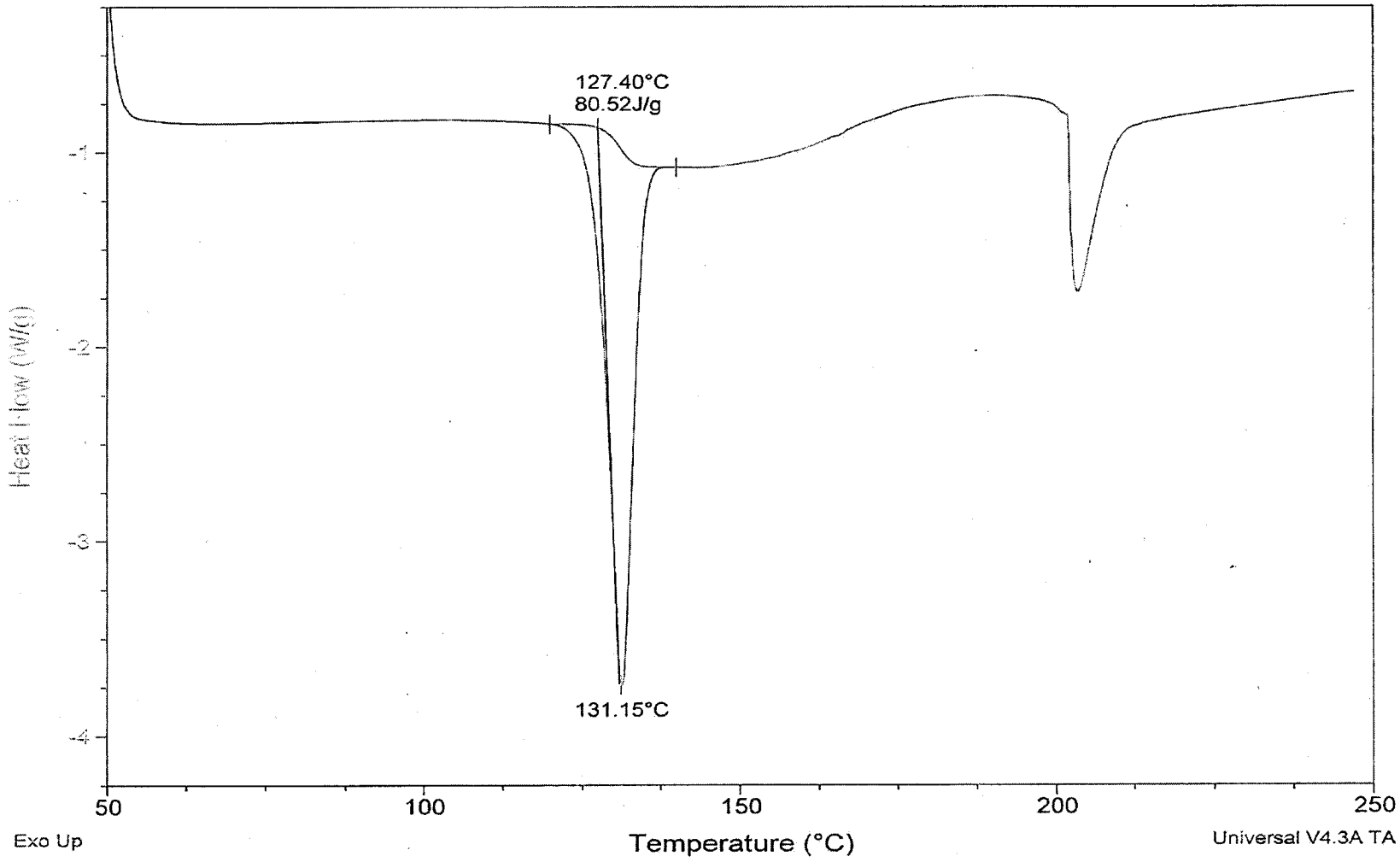

Figure 2

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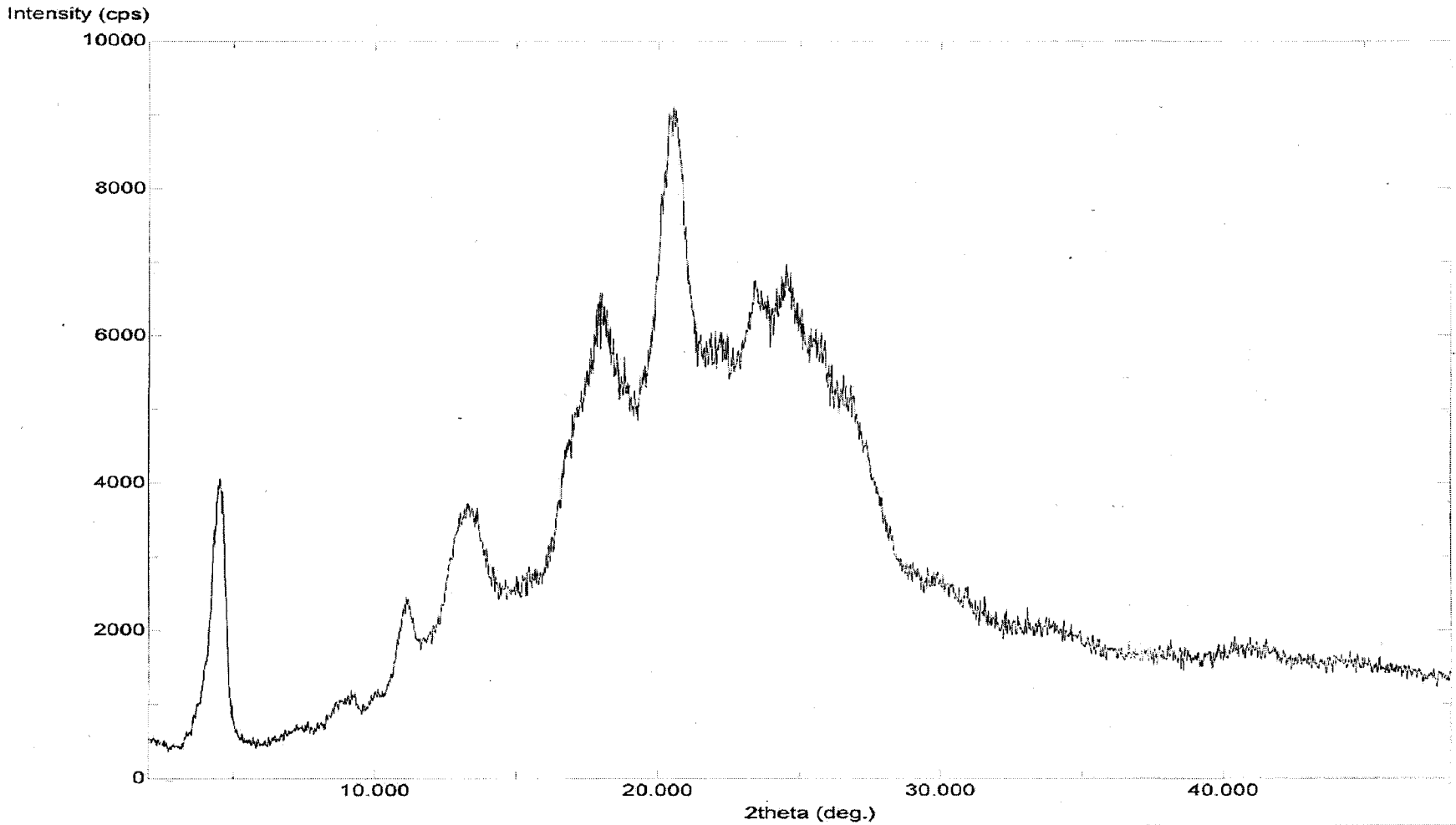

Figure 3

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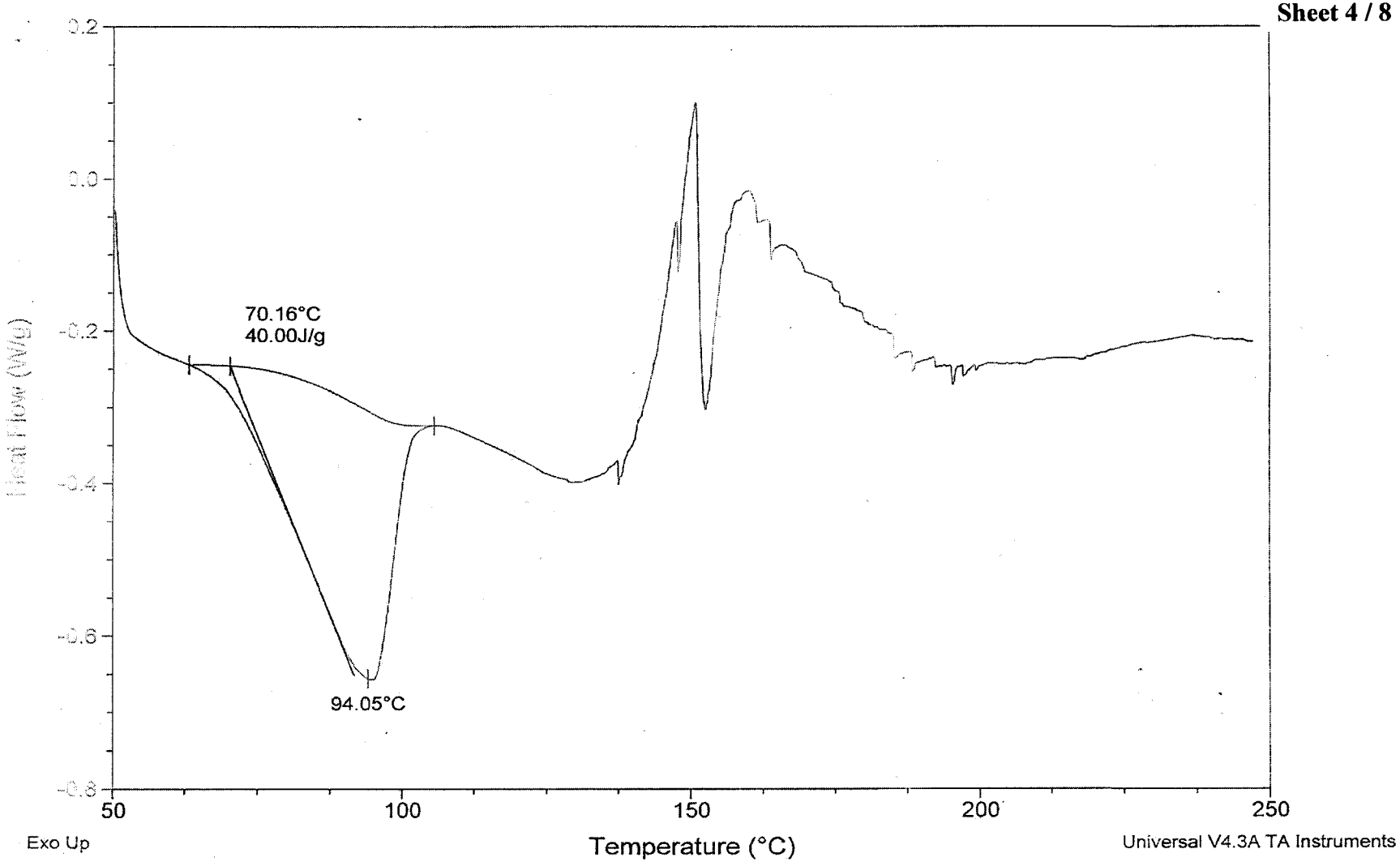

Figure 4

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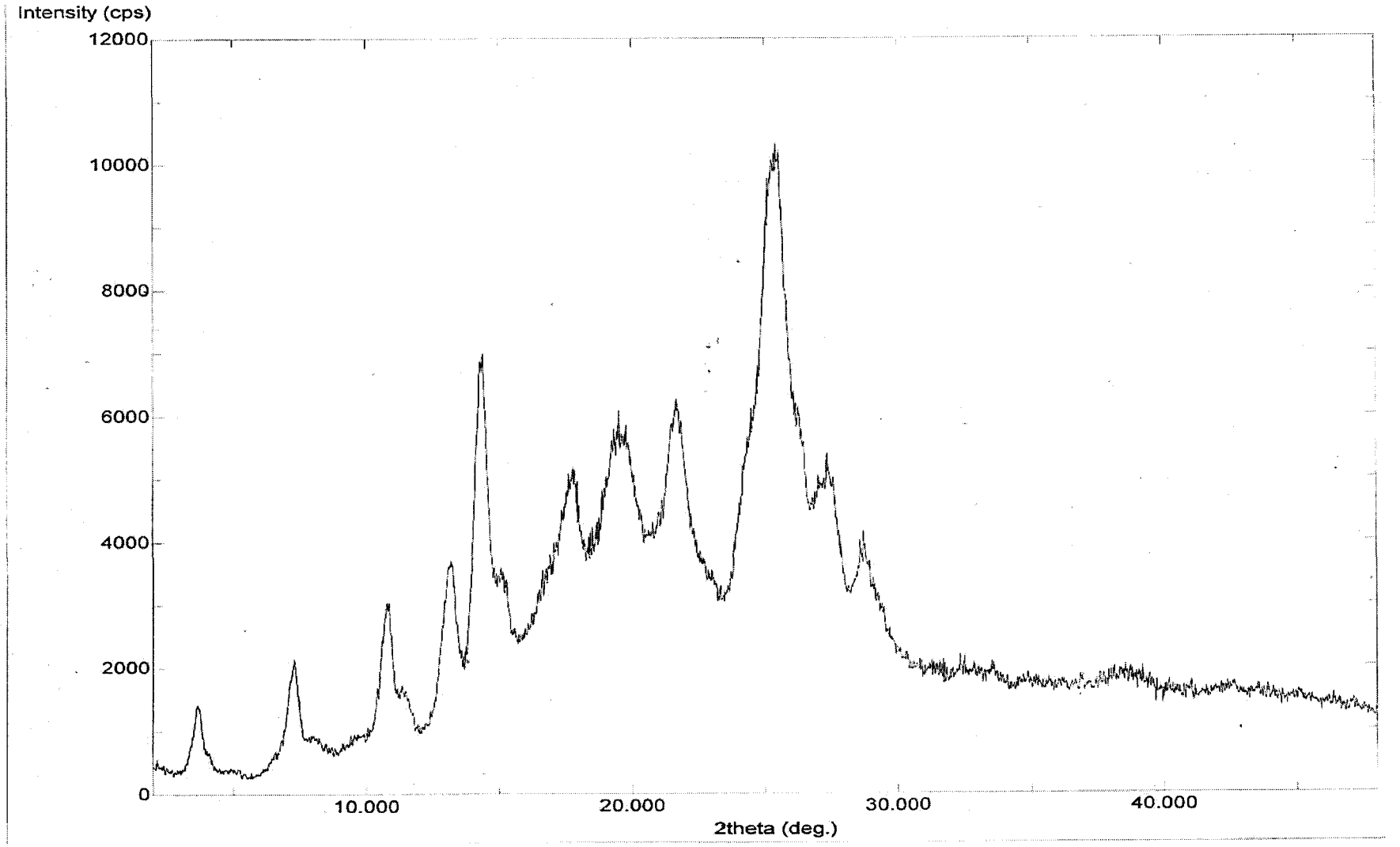

Figure 5

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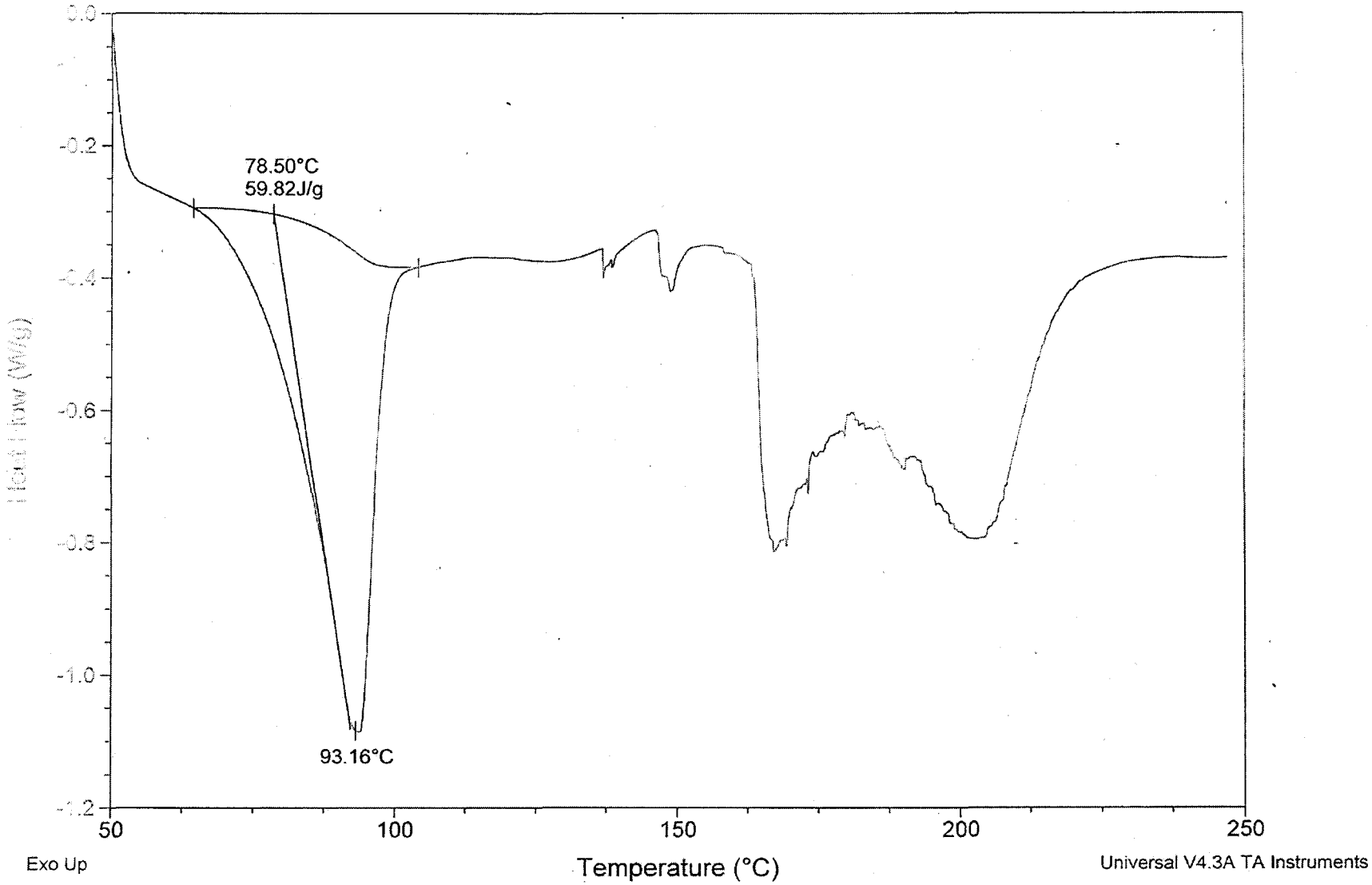

Figure 6

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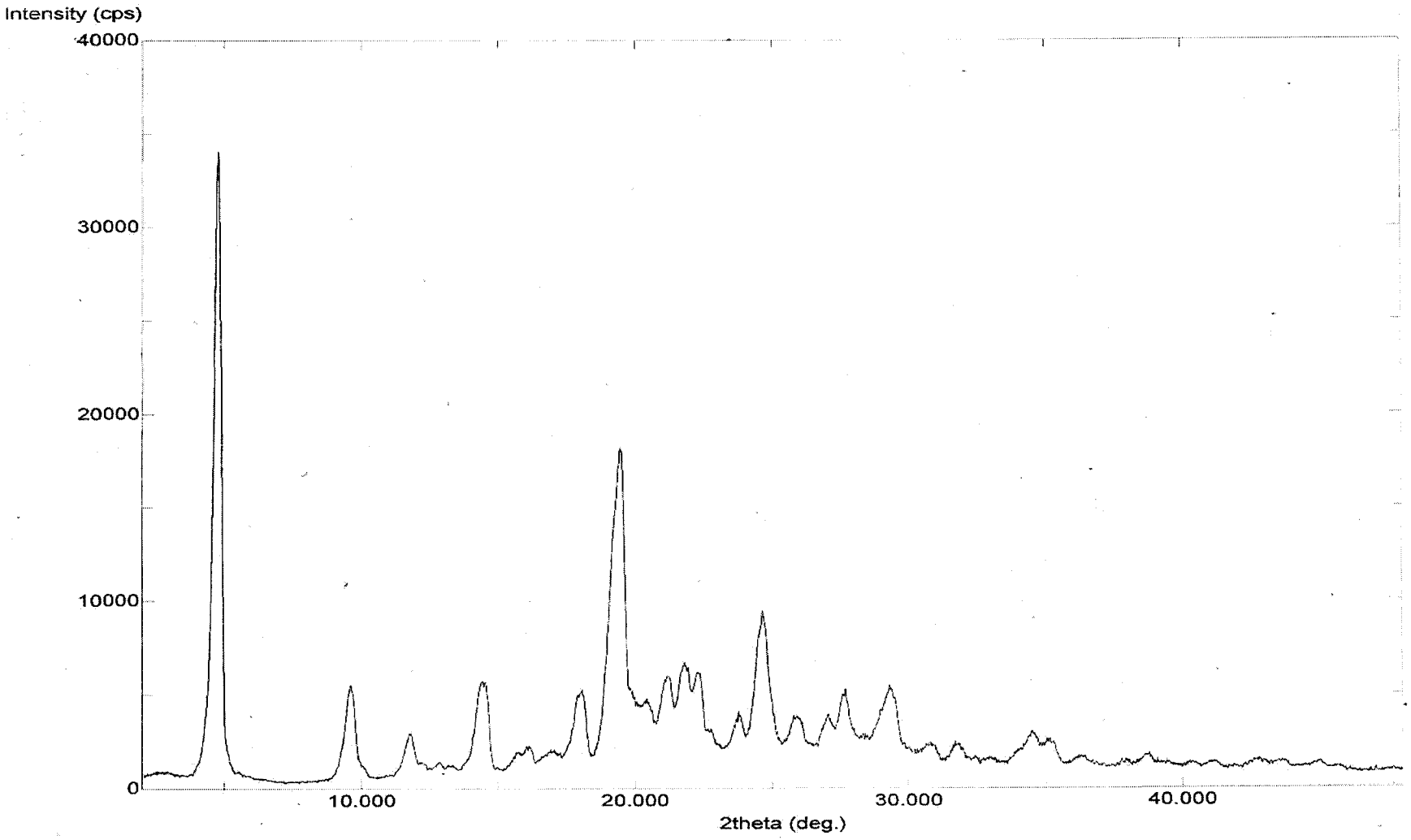

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Figure 7

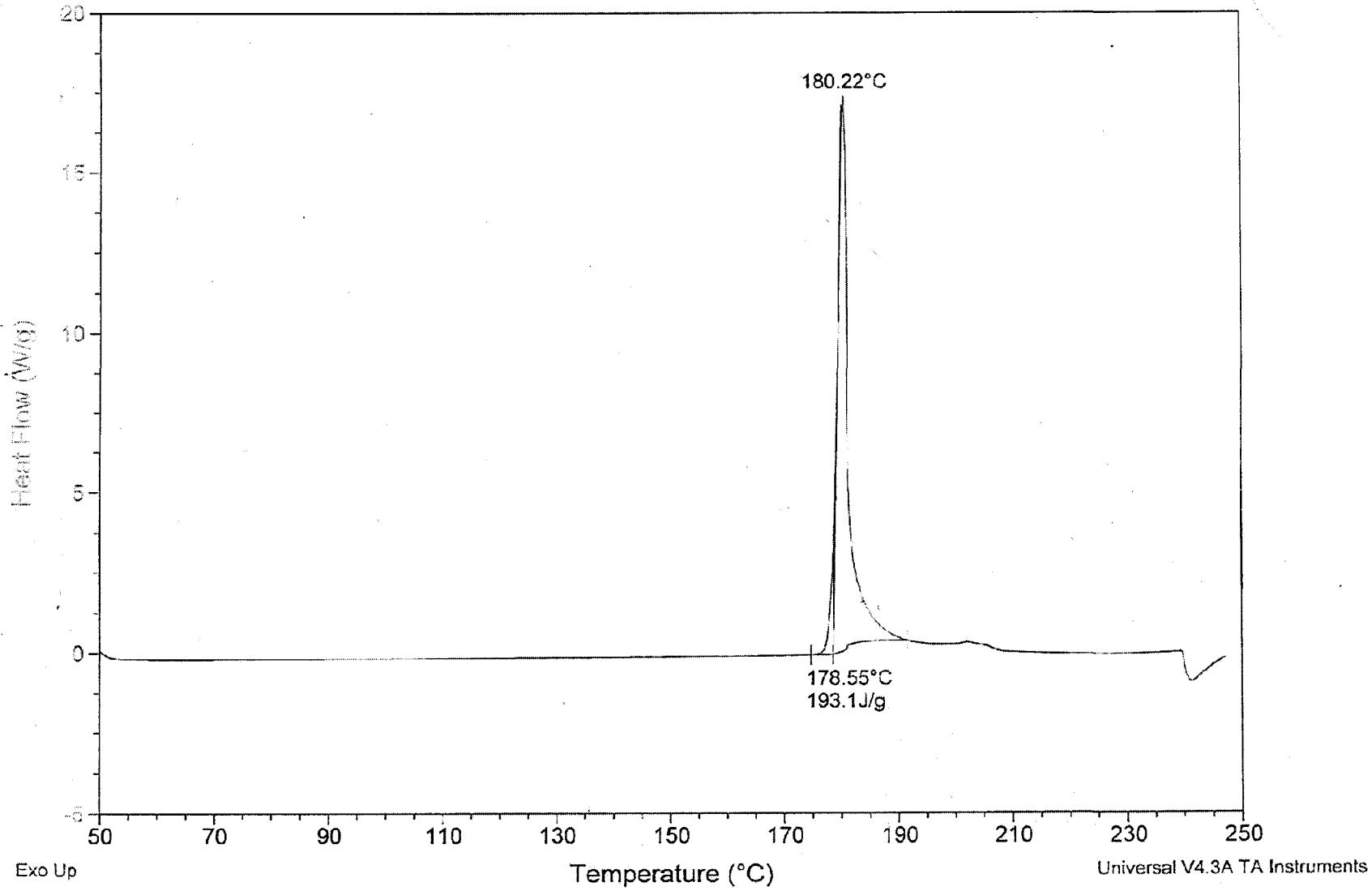

Figure 8

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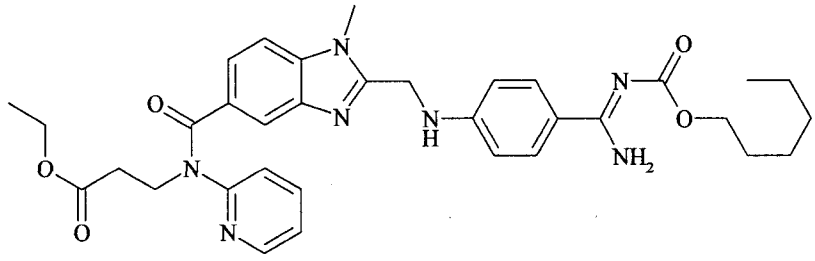
FILED OF THE INVENTION

The present invention relates to novel acid addition salts of Dabigatran etexilate, processes for its preparation and a pharmaceutical composition containing the same.

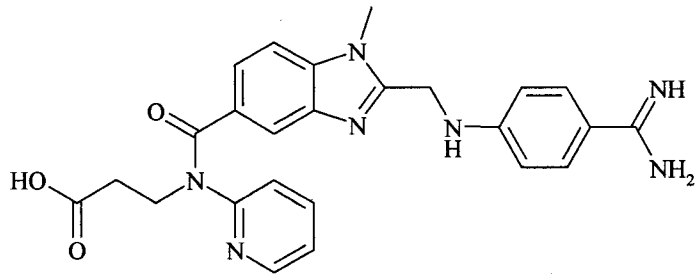
BACK GROUND OF THE INVENTION

The compound Ethyl N-{[2-({[4-((E)- amino{[(hexyloxy)carbonyl]imino}methyl)phenyl] -amino}methyl)-1-methyl-1H-benzimidazol-5-yl]carbonyl}-N-pyridin-2-yl-β-alaninate (Formula 1) generally named as Dabigatran etexilate, has the following chemical structure:



FORMULA I

Dabigatran etexilate is the oral pro-drug of the active moiety dabigatran (Formula 2) which is a *univalent direct thrombin inhibitor* that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin.



FORMULA 2

Dabigatran etexilate pro-drug was developed due to the limited oral availability of dabigatran. Dabigatran etexilate of Formula 1 is converted to actual effective compound namely dabigatran of Formula 2, in the body. The main category of indication for dabigatran etexilate of Formula 1 is the post operative prophylaxis of deep vein thrombosis and the prevention of strokes.

Dabigatran and dabigatran etexilate were first disclosed in US Patent No. 6,087,380 ("the '380 patent"). According to the '380 patent dabigatran etexilate of the Formula 1 is prepared by reacting l-methyl-2-[N-(4-amidino-pheny])-aminomethyl]-5-benzirnidazol-carbonate-N-(2-pyridyl)-[2-(ethoxy-carbonyl)-ethyl]-amide hydrochloride and hexyl-

chloroformate. The thus-formed dabigatran etexilate is characterized by thin layer chromatography and mass spectrometry, however the '380 patent remain silent about the description relating to the crystallographic properties of the dabigatran etexilate base.

The process of dabigatran etexilate described in the above patent is also disclosed in Hauel et al. (J Med. Chem. 2002, 45, 1757-1766) with melting point of about 128- 129 °C and 1H-NMR.

Physical properties of solid pharmaceutical ingredients are essential for preparation of pharmaceutical compositions and its bioavailability. Salts often improve biological characteristics of mother compounds without modifying of primary pharmacological activity, based on mechanism of action. Dabigatran etexilate is marketed in many countries as its methane sulfonate salt (Dabigatran etexilate mesylate) under the trade name PRADAXA® by Boehringer Ingelheim. The marketed dabigatran etexilate mesylate salt was disclosed in US Patent Application No. 2003/181488A1.

PCT publication WO2005/028468 discloses three polymorphic forms of dabigatran etexilate mesylate. The polymorphic forms (Form I, II and hemihydrate) obtained from the base by crystallization are characterized by X-ray powder diffraction pattern and differential scanning calorimetry curves.

US Patent Application No 2006/0247278 discloses various pharmaceutically acceptable salts of dabigatran etexilate namely hydrochloride, maleate, tartrate, salicylate, citrate, malonate salts and their hydrates thereof. These salts are characterized by differential scanning calorimetry curves. The melting points ranked in order are as follows: 135 °C, 170 °C, 160 °C, 100 °C, 120 °C and 155°C.

US Patent Application No 2010/0087488 discloses various salts of dabigatran etexilate and polymorphic forms thereof, wherein the salts are a) 2,5-dihydroxybenzoate, b) besylate, c) forms II, V and VI of the hydrochloride, d) cyclamate, e) edisylate, f) esylate, g) fumarate, h) D-glucuronate, i) glycolate, j) isethionate, k) L-malate, l) D-malate, m) mandelate, n) naphthalene-1,5-disulfonate, o) naphthalene-2-sulfonate, p) oxalate, q) phosphate, r) propionate, s) saccharinate, t) forms II and III of the salicylate, u) succinate, v) Forms I and II of D-tartrate, w) tosylate, or a polymorph or hydrate thereof.

PCT publication WO2011/110876 discloses salt forms of dabigatran etexilate such as phosphoric acid, fumaric acid, sulfuric acid (includes its monohydrate and dihydrate also), maleic acid, oxalic acid, hydrochloride salt (four forms), pTSA salt, mesylate salt form IV.

PCT publication WO2012/044595 discloses crystalline dabigatran etexilate bismesylate, which intern prepared from dabigatran etexilate mesylate Form I in ethyl acetate.

It is well-known that various salts and polymorphs differ from each other in important properties such as solubility, chemical stability, polymorph stability, bioavailability, filtration, drying and tabletting properties etc without modifying of primary pharmacological activity.

Although dabigatran etexilate mesylate provides good pharmaceutical activity, it would be beneficial to discover new salts of dabigatran etexilate and new polymorphic forms of dabigatran etexilate or its salts. Such discoveries can also enlarge the repertoire of materials that a formulation scientist has available for designing for example a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

The pharmaceutically acceptable acid addition salts of dabigatran etexilate showing the same pharmacological activity as dabigatran etexilate mesylate may be used as active ingredients of anticoagulants. They may also serve as intermediates in manufacturing process of high pharmaceutical purity dabigatran etexilate.

Therefore, there is a strong need for developing various polymorphic forms of salts of dabigatran etexilate, having improved physical and/or chemical properties. The present invention satisfies this need by providing pharmaceutically acceptable acid addition salts of dabigatran etexilate with enhanced solubility in water or aqueous media as an essential property of active pharmaceutical ingredients determining the performance of pharmaceutical formulation.

OBJECT OF THE INVENTION

It is an object of the present invention to provide novel acid addition salts of dabigatran etexilate.

Another object of the present invention is to provide processes for preparing novel acid addition salts of dabigatran etexilate.

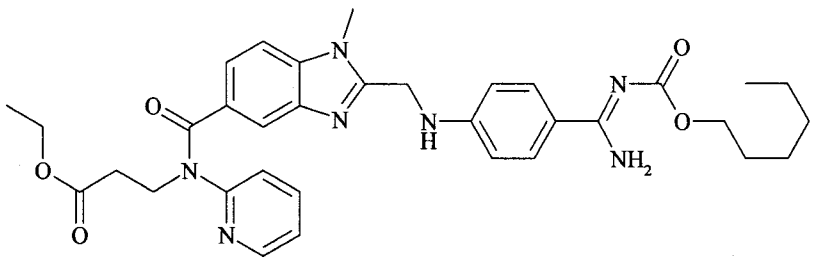
Yet another object of the present invention is to provide a pharmaceutical composition comprising acid addition salts of dabigatran etexilate.

SUMMARY OF THE INVENTION

It has now been found that novel acid addition salts of dabigatran etexilate of Formula 1 or hydrates or solvates thereof of the present invention can be obtained which have improved properties as compared to presently-known form of such compound.

In an aspect, the improved pharmaceutical property is selected from the group consisting of: increased solubility, increased dissolution, increased bioavailability, increased dose response, decreased hygroscopicity, decreased form diversity, more desired morphology, or other property described herein.

Accordingly, the present invention provides novel acid addition salts of dabigatran etexilate of Formula 1 or hydrates or solvates thereof;



FORMULA I

wherein the acid addition salts are selected from the group comprising an anti-oxidative acids such as cinnamic acid and its derivatives selected from the group consisting of p-coumaric acid, Ferulic acid, Sinapic acid, Caffeic acid, Chlorogenic acid, Caftaric acid, Coutaric acid and the like; benzoic acid and its derivatives selected from the group consisting of p-hydroxy benzoic acid, Vanillic acid, Syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid and the like; and other acids such as Quinic acid, Nitric acid, Lipoic acid and Aspartic acid.

In another embodiment, the present invention provides novel acid addition salts of dabigatran etexilate, which exist in the form of polymorphs of salts, co-crystals, or polymorphs of co-crystals.

In another embodiment, the present invention provides a process for preparation of acid addition salts of dabigatran etexilate of Formula 1 or hydrates or solvates thereof, comprising:

a) providing a solution comprising dabigatran etexilate and acid addition salt in one or more solvents, and
b) isolating the dabigatran etexilate acid addition salt;

wherein the acid addition salts are selected from the group comprising an anti-oxidative acids such as cinnamic acid and its derivatives selected from the group consisting of p-coumaric acid, Ferulic acid, Sinapic acid, Caffeic acid, Chlorogenic acid, Caftaric acid, Coutaric acid and the like; benzoic acid and its derivatives selected from the group consisting of p-hydroxy benzoic acid, Vanillic acid, Syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid and the like; and other acids such as Quinic acid, Nitric acid, Lipoic acid and Aspartic acid.

In another embodiment the present invention provides a pharmaceutical composition comprising acid addition salts of dabigatran etexilate prepared by the processes of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following, the present invention will be described in more detail by preferred embodiments and examples while referring to the attached drawings, noting, however, that these embodiments, examples and drawings are presented for illustrative purposes only and shall not limit the invention in any way.

Fig. 1 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline dabigatran etexilate ferulate salt.

Fig. 2 is the characteristic differential scanning calorimetric (DSC) thermogram of crystalline dabigatran etexilate ferulate salt.

Fig. 3 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline dabigatran etexilate caffate salt.

Fig. 4 is the characteristic differential scanning calorimetric (DSC) thermogram of crystalline dabigatran caffate salt.

Fig. 5 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline dabigatran etexilate gallate salt.

Fig. 6 is the characteristic differential scanning calorimetric (DSC) thermogram of crystalline dabigatran etexilate gallate salt.

Fig. 7 is the characteristic powder X-ray diffraction (XRD) pattern of crystalline dabigatran etexilate nitrate salt.

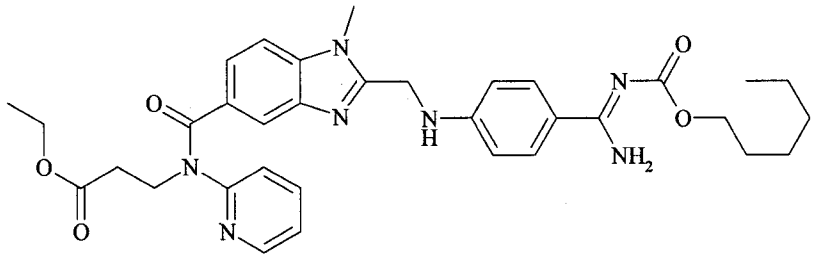
Fig. 8 is the characteristic differential scanning calorimetric (DSC) thermogram of crystalline dabigatran etexilate nitrate salt.

DETAILED DESCRIPTION OF THE INVENTION

The present invention addresses a need in the art by providing new acid addition salts of dabigatran etexilate, or hydrates or solvates thereof.

The present inventors have identified new acid addition salts of dabigatran etexilate, or hydrates or solvates thereof. These salt forms may be in the form of solvates, hydrates, polymorphs of salts, co-crystals, or polymorphs of co-crystals.

In one embodiment, the present invention provides novel acid addition salts of dabigatran etexilate of Formula 1 or hydrates or solvates thereof;



FORMULA I

wherein the acid addition salts are selected from the group comprising an anti-oxidative acids such as cinnamic acid and its derivatives selected from the group consisting of p-coumaric acid, Ferulic acid, Sinapic acid, Caffeic acid, Chlorogenic acid, Caftaric acid, Coutaric acid and the like; benzoic acid and its derivatives selected from the group consisting of p-hydroxy benzoic acid, Vanillic acid, Syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid and the like; and other acids such as Quinic acid, Nitric acid, Lipoic acid and Aspartic acid.

In another embodiment, the present invention provides novel acid addition salts of dabigatran etexilate, in particular anti-oxidant acid addition salts of dabigatran etexilate or hydrates or solvates thereof; wherein the anti-oxidative acids are selected from the group comprising cinnamic acid and its derivatives selected from the group consisting of p-coumaric acid, Ferulic acid, Sinapic acid, Caffeic acid, Chlorogenic acid, Caftaric acid, Coutaric acid and the like; benzoic acid and its derivatives selected from the group consisting of p-hydroxy benzoic acid, Vanillic acid, Syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid and the like.

The anti-oxidant acids used in the present invention are not only intended for formation of pharmaceutically acceptable salt forms of dabigatran etexilate, the obtained salts of dabigatran etexilate itself can advantageously be useful for therapeutical use, for example,

anti-oxidant acids can stabilize the body's metabolism by defending against damage caused by free radicals. The anti-oxidant acid salts of dabigatran etexilate are more effective with respect to therapeutic activity of the dabigatran etexilate as compared to the dabigatran etexilate salt form with non anti-oxidant acids described in the afore mentioned literature.

In another embodiment, the present invention provides dabigatran etexilate ferulate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate ferulate salt in crystalline form.

In another embodiment, the present invention provides crystalline dabigatran etexilate ferulate salt characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Fig. 1.

In another embodiment, the present invention provides crystalline dabigatran etexilate ferulate salt characterized by differential scanning calorimetric (DSC) thermogram substantially in accordance with Fig. 2.

In another embodiment, the present invention provides dabigatran etexilate caffate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate caffate salt in crystalline form.

In another embodiment, the present invention provides crystalline dabigatran etexilate caffate salt characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Fig. 3.

In another embodiment, the present invention provides crystalline dabigatran etexilate caffate salt characterized by differential scanning calorimetric (DSC) thermogram substantially in accordance with Fig. 4.

In another embodiment, the present invention provides dabigatran etexilate gallate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate gallate salt in crystalline form.

In another embodiment, the present invention provides crystalline dabigatran etexilate gallate salt characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Fig. 5.

In another embodiment, the present invention provides crystalline dabigatran etexilate gallate salt characterized by differential scanning calorimetric (DSC) thermogram substantially in accordance with Fig. 6.

In another embodiment, the present invention provides novel acid addition salts of dabigatran etexilate, wherein the acid addition salts of dabigatran etexilate are selected from dabigatran etexilate cinnamic acid salt, dabigatran etexilate sinapic acid salt, dabigatran etexilate p-coumaric acid salt, dabigatran etexilate chlorogenic acid salt, dabigatran etexilate caftaric acid salt, dabigatran etexilate coutaric acid salt, dabigatran etexilate benzoic acid salt, dabigatran etexilate p-hydroxy benzoic acid salt, dabigatran etexilate vanillic acid salt, dabigatran etexilate syringic acid salt, dabigatran etexilate 4-(4-phenoxybenzoyl) benzoic acid salt, dabigatran etexilate gentisic acid salt and dabigatran etexilate protocatechuic acid salt.

In another embodiment, the present invention provides novel acid addition salts of dabigatran etexilate, in particular acid addition salt selected from the group comprising Quinic acid, Nitric acid, Lipoic acid and Aspartic acid.

In another embodiment, the present invention provides dabigatran etexilate quinate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate nitrate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate nitrate salt in crystalline form.

In another embodiment, the present invention provides crystalline dabigatran etexilate nitrate salt characterized by an X-Ray diffraction (XRD) pattern substantially in accordance with Fig. 7.

In another embodiment, the present invention provides crystalline dabigatran etexilate nitrate salt characterized by differential scanning calorimetric (DSC) thermogram substantially in accordance with Fig. 8.

In another embodiment, the present invention provides dabigatran etexilate lipoate salt or hydrate or solvate thereof.

In another embodiment, the present invention provides dabigatran etexilate aspartate salt or hydrate or solvate thereof.

The present invention provides characterization of acid addition salts of dabigatran etexilate of the present invention characterized by X-ray powder diffraction (XRD) pattern and/or melting point. The X-Ray powder diffraction can be measured by an X-ray powder diffractometer equipped with a Cu-anode ([λ] =1.54 Angstrom), X-ray source operated at 30kV, 15 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=3-45°2θ; step width=0.020°; and scan speed=5°/minute.

All DSC data reported herein were analyzed in hermitically sealed aluminium pan, with a blank hermitically sealed aluminium pan as the reference and were obtained using DSC (DSC Q200, TA instrumentation, Waters) at a scan rate of 2°C per minute with an Indium standard.

In another embodiment, the present invention provides a process for preparation of acid addition salts of dabigatran etexilate of Formula 1 or hydrates or solvates thereof, comprising:

a) providing a solution comprising dabigatran etexilate and acid addition salt in one or more solvents, and
b) isolating the dabigatran etexilate acid addition salt;

wherein the acid addition salts are selected from the group comprising an anti-oxidative acids such as cinnamic acid and its derivatives selected from the group consisting of p-coumaric acid, Ferulic acid, Sinapic acid, Caffeic acid, Chlorogenic acid, Caftaric acid, Coutaric acid and the like; benzoic acid and its derivatives selected from the group consisting of p-hydroxy benzoic acid, Vanillic acid, Syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid and the like; and other acids such as Quinic acid, Nitric acid, Lipoic acid and Aspartic acid.

The starting dabigatran etexilate, used in the present invention, can be prepared by any known method for example dabigatran etexilate may be synthesized as disclosed in U.S. Patent No. 6,087,380.

The dabigatran etexilate in the step a) may be any crystalline or other form of dabigatran etexilate, including various solvates, hydrates or dabigatran etexilate obtaining as existing solution from a previous processing step.
The one or more solvent include, but are not limited to water, lower alcohols, ketones, esters, ethers, C5-C7 linear, branched or cyclic, saturated or unsaturated hydrocarbons, nitriles, halogenated hydrocarbons, or mixtures thereof.

Preferably the suitable organic solvent includes, but are not limited to methanol, ethanol, isopropanol, acetone, methylethylketone, methyl iso butyl ketone, methyl acetate, ethyl acetate, isopropyl acetate, tetrahydrofuran (THF), isopropyl ether (IPE), ter-butyl methyl ether, acetonitrile, propionitrile, methylene chloride, chloroform, toluene, cyclohexane, hexane, heptanes and the like and the mixtures thereof.

The solution comprising dabigatran etexilate free base and acid addition salt of step a) can be provided by mixing the solution of dabigatran etexilate free base with acid addition salt. Wherein, solution of dabigatran etexilate free base intern can be provided by dissolving dabigatran etexilate free base in suitable organic solvent.

Further acid addition salts may be added to the solution of dabigatran etexilate either in natural state or in solution. And solution of acid addition salt can be prepared by dissolving the acid addition salt in a suitable solvent.

The temperature suitable for providing a solution comprising dabigatran etexilate and acid addition salt in one or more solvents is from ambient temperature to about boiling point of the solvent; preferably at a temperature of about 30°C to about 90°C.

The isolation of the dabigatran etexilate acid addition salt can be induced by reducing the temperature of reaction mixture, especially if initial temperature of reaction mixture is elevated. The isolation can also be induced by reduction of solution volume, preferably under reduced pressure, spray drying, freeze drying, agitated thin film evaporator (ATFE), by complete evaporation of solvent or crystallization. Furthermore, the isolation may be caused by adding an antisolvent to the reaction solution to precipitation.

In an alternative embodiment, the isolated acid addition salt of dabigatran etexilate can optionally be washed with one or more organic solvents, and finally resulted pure dabigatran etexilate may be recovered by any conventional methods such as filtering.

The suitable organic solvent used include any suitable solvent as described herein; preferably the suitable organic solvent is selected from the group consisting of methanol, ethanol, acetone, THF, acetonitrile, ethyl acetate, IPE and mixtures thereof.

Finally the resulted pure dabigatran etexilate may be recovered by any conventional methods such as filtration, solvent precipitation, spray drying, freeze drying, agitated thin film evaporator (ATFE) and the like.

In another embodiment, the present invention provides a process for preparing acid addition salts of dabigatran etexilate, wherein the acid addition salt is ferulic acid,

comprising a) providing a solution of dabigatran etexilate and ferulic acid in one or more solvents and b) isolating the dabigatran etexilate ferulate salt.

The suitable solvent used is selected from the group consisting of methanol, ethanol, acetone, THF, acetonitrile, ethyl acetate, IPE and mixtures thereof.

The solution may be formed by heating the mixture at a temperature of about 30°C to about reflux temperature, preferably about 40°C to about 75°C. The dabigatran ferulate salt can be isolated by any known techniques such as cooling the solution to precipitation, crystallization, solvent precipitation, spray drying, freeze drying, agitated thin film evaporator (ATFE) and the like.

Dabigatran etexilate ferulate salt prepared according to such procedure exhibits a powder X-ray diffraction pattern substantially in accordance with Figure. 01.

In another embodiment, the present invention provides a process for preparing acid addition salt of dabigatran etexilate, wherein acid addition salt is caffeic acid comprising a) providing a solution of dabigatran etexilate and caffeic acid in one or more solvents and b) isolating the dabigatran etexilate caffate salt.

The suitable solvent used is selected from the group consisting of methanol, ethanol, acetone, THF, acetonitrile, ethyl acetate, IPE and mixtures thereof.

The solution may be formed by heating the mixture at a temperature of about 30°C to about reflux temperature, preferably about 40°C to about 75°C. The dabigatran caffate salt can be isolated by any known techniques such as cooling the solution to precipitation, crystallization, solvent precipitation, spray drying, freeze drying, agitated thin film evaporator (ATFE) and the like.

Dabigatran etexilate caffate salt prepared according to such procedure exhibits a powder X-ray diffraction pattern substantially in accordance with Figure. 03.

In another embodiment, the present invention provides a process for preparing acid addition salt of dabigatran etexilate, wherein acid addition salt is gallic acid comprising a) providing a solution of dabigatran etexilate and gallic acid in one or more solvents and b) isolating the dabigatran etexilate gallate salt.

The suitable solvent used is selected from the group consisting of methanol, ethanol, acetone, THF, acetonitrile, ethyl acetate, IPE and mixtures thereof.

The solution may be formed by heating the mixture at a temperature of about 30°C to about reflux temperature, preferably about 40°C to about 75°C. The dabigatran gallate salt can be isolated by any known techniques such as cooling the solution to precipitation, crystallization, solvent precipitation, spray drying, freeze drying, agitated thin film evaporator (ATFE) and the like.

Dabigatran etexilate gallate salt prepared according to such procedure exhibits a powder X-ray diffraction pattern substantially in accordance with Figure. 05.

In another embodiment, the present invention provides a process for preparing acid addition salt of dabigatran etexilate, wherein acid addition salt is nitric acid comprising a) providing a solution of dabigatran etexilate and nitric acid in one or more solvents and b) isolating the dabigatran etexilate nitrate salt.

The suitable solvent used is selected from the group consisting of methanol, ethanol, acetone, THF, acetonitrile, ethyl acetate, IPE and mixtures thereof.

The solution may be formed by heating the mixture at a temperature of about 30°C to about reflux temperature, preferably about 40°C to about 75°C. The dabigatran nitrate salt can be isolated by any known techniques such as cooling the solution to precipitation, crystallization, solvent precipitation, spray drying, freeze drying, agitated thin film evaporator (ATFE) and the like.

Dabigatran etexilate nitrate salt prepared according to such procedure exhibits a powder X-ray diffraction pattern substantially in accordance with Figure. 07.

In another embodiment, the present invention provides novel acid addition salts of dabigatran etexilate, having a chemical purity of 96% or more as measured by HPLC, preferably 99% or more, more preferably 99.5% or more.

In another embodiment, the novel acid addition salts of dabigatran etexilate of the present invention can be used as intermediate or as starting material for the preparation of other pharmaceutically acceptable acid salts of dabigatran etexilate, for example dabigatran etexilate mesylate.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of acid addition salts of dabigatran etexilate of the invention, preferably dabigatran etexilate ferulate salt, dabigatran etexilate caffate salt, dabigatran etexilate gallate salt or dabigatran etexilate nitrate salt with at least one pharmaceutically acceptable carrier or other excipients. The pharmaceutical composition

can be useful for post operative prophylaxis of deep vein thrombosis and the prevention of strokes.

Pharmaceutical acceptable salts in accordance with present invention can be embodied for example in form of tablet, capsules, pellets, granules and suppositories or their combined forms. Pharmaceutical composition in accordance with present invention can be suitable for immediate release or modified release of dabigatran etexilate salts of the present invention. Solid pharmaceutical compositions can be for example coated with aim of increasing peletibility or regulating the disintegration or absorption.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

Reference Example 1: Preparation of Dabigatran etexilate free base

1.1g of l-methyl-2-[N-(4-amidino-pheny)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonylethyl)-amide-hydrochloride was dissolved in a mixture of 40 ml of tetrahydrofuran and 10 ml of water, then 570 mg (4.12 mMol) of potassium carbonate and 362 mg (2.2 mMol) of n-hexyl chloroformate were added and stirred for two hours at room temperature. The solvent was then distilled off, the residue was mixed with about 50 ml of saturated saline solution and the resulting solution was extracted three times with 20 ml of dichloromethane. The extracts were dried over sodium sulphate and evaporated down. The crude product thus obtained was purified by column chromatography (100 g silica gel; dichloromethane+5% ethanol).

Reference Example-2: Preparation of Dabigatran etexilate free base

To a stirred suspension of p-TSA salt of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide(20g) in acetonitrile (80 mL), at 27°C, was charged a solution of potassium carbonate (24.7 g) in DM water (50 mL).The reaction mass was stirred for 30 min, and then cooled to 12-15°C. n-Hexyl chloroformate (4.9g) was added and stirred for 30 min. The temperature of the reaction mass was raised 17°C and stirred for 30 min. Second lot of n-hexylchloroformate (1.49 g) was charged and the reaction mass stirred for another hour at 16-20°C, when

analytical HPLC revealed completion of the reaction. DM water (50mL) was added and the reaction mass slurred for 15 min at 30°C. The precipitate was filtered, washed with water, dried under vacuum, at 50°C, to afford Dabigatran Etexilate as off-white solid material (16.4g, >96% hplc pure).

A solution of crude Dabigatran Etexilate (15g) in IPA (45 mL) and ethanol (45 mL), heated up to 50-55°C till a clear solution is obtained. Then cooled to 20-25°C and stirred for 12hr, at 20-25°C. The precipitated product was filtered, washed with IPA and dried under vacuum, at 50°C, to afford pure Dabigatran Etexilate as off-white solid material (12.5 g, >99.5% hplc pure).

Example 1: Preparation of Dabigatran etexilate nitrate salt

5.0 g of Dabigatran Etexilate free base in 45 mL of acetone was heated up to 40-45^{0}C till clear solution was observed. Filter the reaction mass to remove undissolved particles if any. Cooled the reaction mass to 30-32^{0}C followed by gradual addition of pre cooled solution of 0.4 g of 70% nitric acid in 4 mL of acetone. Stirred the reaction mass at 30-32^{0}C for 30 min. Cooled down to 10-12^{0}C and stirred further for 30 min. Filtered the resulted solid, washed with pre cooled acetone (5 mLx2) and dried under vacuum at 45-55°C to obtain off-white solid material of Dabigatran Etexilate nitrate salt (5.0 g, >99.5% hplc pure).

Example 2: Preparation of Dabigatran etexilate bisferulate salt

5.0 g of Dabigatran Etexilate free base in 30 mL of acetone was heated up to 38-42^{0}C till clear solution was observed. 4.5 g of ferulic acid was added to the reaction mass and stirred the reaction mass at the same temperature for 1hr. Cooled down to 23-27^{0}C and stirred for 1hr. Further cooled down to 1-5^{0}C and stirred the reaction mass for 1hr. The solid material was filtered and washed with pre cooled acetone. Wet product was slurred in 20 mL of acetone at 20-30^{0}C for 15 min. Cooled the slurry to 0-4^{0}C and stirred for 1 hr. Filtered the product, washed with pre cooled acetone and dried under vacuum at 45-55^{0}C to afford off-white solid material of Dabigatran Etexilate bisferulate salt (5.5 g, >99.5% hplc pure).

Example 3: Preparation of Dabigatran etexilate bisferulate salt

25.0 g of Dabigatran Etexilate free base in 150 mL of acetone was heated up to 40-44^{0}C till clear solution was observed. 15.4 g of ferulic acid was added to the reaction mass and stirred the reaction mass at the same temperature for 1hr. Cooled down to 28-32^{0}C and stirred for 1hr at constant temperature. Further cooled down to 0-4^{0}C and stirred the reaction mass for 1hr at constant temperature. The solid material was filtered and washed

with pre cooled acetone. Wet product was slurred in 100 mL of acetone at 20-30^{0}C for 15 min. Cooled the slurry to 0-4^{0}C and stirred for 1hr. Filtered the product, washed with pre cooled acetone and dried under vacuum at 45-55^{0}C to afford off-white solid material of Dabigatran etexilate bisferulate salt (27 g, >99.5% hplc pure).

Example 4: Preparation of Dabigatran etexilate caffeic acid salt

5.0 g of Dabigatran Etexilate free base in 25 mL of acetone was heated up to 40-45^{0}C, till clear solution was observed. Cooled the reaction mass to 30-35^{0}C followed by gradual addition of solution of 1.43 g of caffeic acid in 45 mL of acetone over a period of 30 min. Distilled the solvent completely under vacuum. 15 mL of acetone was added to the reaction mass and raised the temperature of the reaction mass to 40-45^{0}C to get clear solution. Cooled down to 10-15^{0}C and stirred further for 2hr. Filtered the solid, washed with pre cooled acetone and dried under vacuum at 45-50^{0}C to obtain off white solid material of Dabigatran Etexilate Caffeic acid salt (4.7 g, >99.0% hplc pure).

Example 5: Preparation of Dabigatran etexilate gallic acid salt:

5.0 g of Dabigatran Etexilate free base in 25 mL of acetone was heated up to 40-45^{0}C till clear solution was observed. Cooled the reaction mass to 30-35^{0}C followed by addition of solution of 2.1 g of Gallic acid in 10 mL of acetone over a period of 15 min. Stirred the reaction mass at 30-32^{0}C for 1 hr. Gradually cooled down to 20-25^{0}C and stirred further for 1hr. Further cooled down to 10-15^{0}C and stirred for 1 hr. Gradually cooled further to 0-5°C and stirred for 2 hr. Filtered the obtained solid, washed with pre cooled acetone and dried under vacuum at 45-50^{0}C to obtain off-white solid material Dabigatran Etexilate Gallic acid salt (4.7 g, >99.5% hplc pure).

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be constructed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.

Dated this 31st day of Aug 2013

Sign----------

(CH.V.Ramana Rao)
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ABSTRACT

The present invention relates to novel acid addition salts of dabigatran etexilate, process for the preparation and pharmaceutical compositions containing the same. Further, the invention relates to uses of said compositions for post operative prophylaxis of deep vein thrombosis and the prevention of strokes.