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(54) Title: CRYSTALLINE FORM OF PRASUGREL HYDROBROMIDE, PREPARATION AND APPLICATION THEREOF

(57) Abstract: A crystalline form of prasugrel hydrobromide, the preparation method and application thereof are provided. The crystalline prasugrel hydrobromide is prepared by precipitation of prasugrel with hydrobromic acid in solvents. The prasugrel hydrobromide can be converted into prasugrel hydrochloride or used as a component of a pharmaceutical composition.



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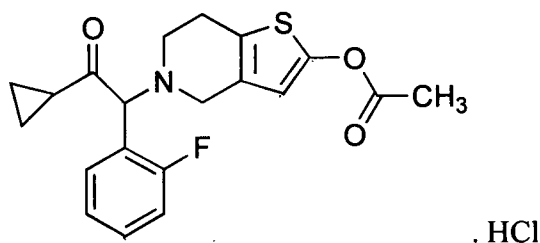
CRYSTALLINE FORM OF PRASUGREL HYDROBROMIDE, PREPARATION AND APPLICATION THEREOF

FIELD OF THE INVENTION

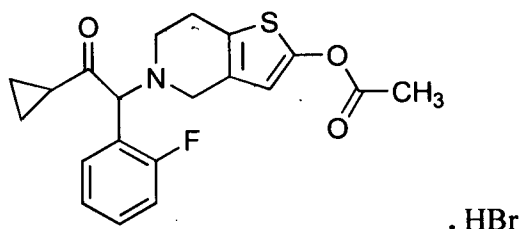
The present invention relates to crystalline form of prasugrel hydrobromide and process for the preparation thereof. The present invention also relates to a pharmaceutical composition comprising crystalline form of prasugrel hydrobromide.

BACKGROUND OF THE INVENTION

Prasugrel is a P2Y12 (P2T) antagonist which has been filed for regulatory approval in the U.S. and approved in Europe for the secondary prevention of thrombotic cardiovascular complications. Prasugrel hydrochloride is chemically described as 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate and is represented by the structural formula below;



Prasugrel hydrobromide is chemically described as 2-acetoxy-5-(.alpha.-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrobromide and can be represented by structural formula:



U.S. Patent No. 5,288,726 describes tetrahydrothienopyridine derivatives, including prasugrel and their pharmaceutically acceptable salts, a pharmaceutical composition and method of treatment.

5 U.S. Patent No. 6,693,115 discloses crystal A, crystal B1 and crystal B2 of prasugrel hydrochloride and processes for the preparation thereof.

European Patent No. 2003136 describes crystal A, crystal B1 and crystal B2 of prasugrel hydrochloride and processes for the preparation thereof.

10 The present invention provides crystalline form of prasugrel hydrobromide and a process for the preparation thereof.

The process of the present invention is simple, ecofriendly, robust, and well suited on commercial scale.

SUMMARY OF THE INVENTION

15 The present invention relates to prasugrel hydrobromide and a process for the preparation thereof. More particularly, the present invention relates to a crystalline form of prasugrel hydrobromide.

In one aspect, the present invention provides a crystalline form of prasugrel hydrobromide characterized by an X-ray powder diffraction pattern with characteristic peaks at about 7.06, 8.31, 10.08, 11.46, 12.19, 12.82, 13.73, 14.17, 15.8, 16.7, 16.98, 20 17.23, 17.73, 18.36, 18.70, 21.60, 23.42, 23.69, 24.21, 24.39, 24.9, 25.14, 25.82, 26.50, 27.0, 29.89, 30.31 and 37.2 ± 0.2 degrees two-theta, which is substantially in accordance with Fig. 1.

The present invention provides the crystalline form of prasugrel hydrobromide characterized by differential scanning calorimetry with an endotherm curve at about 25 138.25°C with an onset at about 128.29°C and an endset at about 146.34°C, which is substantially in accordance with Fig. 2.

The present invention provides crystalline form of prasugrel hydrobromide further characterized by an infrared absorption spectrum, which is substantially in accordance with Fig. 3.

The present invention provides the crystalline form of prasugrel hydrobromide further characterized by an mass spectrum, which is substantially in accordance with Fig. 4.

In yet another aspect, the present invention provides a process for preparing crystalline form of prasugrel hydrobromide comprising:

- (a) providing a solution of prasugrel and hydrobromic acid in one or more solvents or aqueous mixtures thereof; and
- (b) precipitating the solid prasugrel hydrobromide; and
- (c) recovering the prasugrel hydrobromide substantially in crystalline form.

In yet another aspect, the present invention provides a process for conversion of prasugrel hydrobromide into prasugrel hydrochloride comprising:

- (a) providing a suspension of prasugrel hydrobromide in one or more solvents or aqueous mixtures thereof;
- (b) adding a base to the suspension of a) followed by adding hydrochloric acid; and
- (c) recovering the prasugrel hydrochloride substantially in solid state.

In a further aspect, the present invention provides a pharmaceutical composition comprising crystalline form of prasugrel hydrobromide and at least a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Fig. 1: X-ray powder diffraction pattern of prasugrel hydrobromide crystalline form, as prepared by Example 1.

Fig. 2: Differential scanning calorimetry of prasugrel hydrobromide crystalline form, as prepared by Example 1.

Fig. 3: infrared absorption spectrum of prasugrel hydrobromide crystalline form, as prepared by Example 1.

Fig. 4 : MASS spectrum of prasugrel hydrobromide, as prepared by Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to prasugrel hydrobromide and a process for the preparation thereof. More particularly, the present invention relates to a crystalline form of prasugrel hydrobromide.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. The solubility of each polymorph may vary, which makes identifying the existence of pharmaceutical polymorphs essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory, by methods, known in the art, which include X-ray diffraction spectroscopy and infrared spectrometry.

Such discoveries 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.

Additionally, the polymorphic forms of the same drug substance or active pharmaceutical ingredient can be administered by itself or formulated as a drug product (also known as the final or finished dosage form), and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products.

The present invention provides the crystalline form of prasugrel HBr and a process for its preparation, which is simple, ecofriendly, inexpensive, reproducible, robust and well suited on commercial scale.

The present invention provides a crystalline form of prasugrel hydrobromide characterized by an X-ray powder diffraction pattern with characteristic peaks at about

7.06, 8.31, 10.08, 11.46, 12.19, 12.82, 13.73, 14.17, 15.8, 16.7, 16.98, 17.23, 17.73, 18.36, 18.70, 21.60, 23.42, 23.69, 24.21, 24.39, 24.9, 25.14, 25.82, 26.50, 27.0, 29.89, 30.31 and 37.2 ± 0.2 degrees two-theta, which is substantially in accordance with Fig. 1.

5 The present invention further provides the crystalline form of prasugrel hydrobromide as characterized by differential scanning calorimetry with an endotherm curve at about 138.25°C, with an onset at about 128.29°C and an endset at about 146.34°C, which is substantially in accordance with Fig. 2.

10 The present invention provides the crystalline form of prasugrel hydrobromide characterized by an infrared absorption spectrum, which is substantially in accordance with Fig. 3.

The present invention provides the crystalline form of prasugrel hydrobromide further characterized by a mass spectrum, which is substantially in accordance with Fig. 4.

15 In yet another aspect, the present invention provides a process for preparing crystalline form of prasugrel hydrobromide comprising:

- (a) providing a solution of prasugrel and hydrobromic acid in one or more solvents or aqueous mixtures thereof; and
- (b) precipitating the solid prasugrel hydrobromide; and
- (c) recovering the prasugrel hydrobromide substantially in crystalline form.

20 The solution of prasugrel and hydrobromic acid can be obtained by dissolving prasugrel and hydrobromic acid, either separately or together in a solvent or mixture of solvents or their aqueous mixtures, either by agitation at room temperature or at elevated temperatures.

25 As used herein, a solvent is any liquid substance capable of dissolving prasugrel and hydrobromic acid.

As used herein a mixture of solvents refers to a composition comprising of more than one solvent.

30 The solvents that can be used include, but are not limited to water, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and tertiary butyl alcohol and the like; ketonic solvents such as acetone, methyl ethyl ketone, methyl

isobutyl ketone, 2-butanone and the like; nitrile solvents such as acetonitrile, propionitrile and the like; or mixtures thereof or their aqueous mixtures in various proportions without limitation. Preferably, acetone or acetonitrile or their aqueous mixtures.

5 The volume of the solvent used to solubilize prasugrel and hydrobromic acid can range from about 2 volumes to about 20 volumes of the weight of the prasugrel free base taken, preferably from about 15 volumes to about 18 volumes.

The molar ratio of hydrobromic acid to prasugrel is preferably about 1:1 to about 1.2:1.

10 The hydrobromic acid used herein can be of any percentage and in any form, either as a gas or in solution.

The temperature for obtaining a clear and homogenous solution can range from about 25°C to about 75°C or the boiling point of the solvent/s used, preferably from about 25°C to about 40°C.

15 The solution obtained is optionally filtered through celite or diatomaceous earth to separate the extraneous matter present or formed in the solution by using conventional filtration techniques known in the art.

20 The solid prasugrel hydrobromide is then precipitated out from the solution by maintaining the solution at room temperature or below with or without stirring or by addition of an anti-solvent to the solution. The anti-solvent is a solvent which is capable of inducing precipitation of the solid prasugrel hydrobromide from the solution.

In one embodiment the solid prasugrel hydrobromide is precipitated out from the solution by stirring at about room temperature for a period of about 1 hour to about 3 hours.

25 Recovery of crystalline form of prasugrel hydrobromide obtained by the above process, can be performed by any conventional method, known in the art, such as filtration, decantation and centrifugation.

Preferably, recovery comprises filtering, washing, and drying the solid. Washing is usually done with the same solvent used in the reaction.

30 The crystalline form of prasugrel hydrobromide obtained by the above process may be further dried in, for example, a vacuum tray dryer, a rotocon vacuum dryer, a

vacuum paddle dryer or a pilot plant rotavapor, to further lower residual solvents. When implemented, the preferred instrument is a vacuum tray dryer.

The temperature for drying can range from about 25°C to about 60°C, preferably from about 50°C to about 60°C under vacuum.

5 The drying can be carried out for any desired time, till a constant weight is obtained and time periods can range from about 1 hour to about 50 hours, preferably from about 40 hours to about 50 hours.

The prasugrel freebase used as starting material in the processes described herein above, may be of an indefinite morphology, i.e. crystalline or crude or mixtures thereof
10 resulting from synthetic process known in the art. Illustratively, these processes are disclosed in U.S. Patent Nos. 5288726 and 6693115, both of which are incorporated herein in their entirety by reference.

The characterization of the crystalline form of prasugrel hydrobromide of the present invention is analyzed by X-ray powder diffraction was performed on a Philips
15 X'pert PRO Diffractometer using Cu K α radiation (Cu K α 1=1.54060Å). The X-ray source is operated at 45 kV and 40mA. Spectra are recorded in the 2 θ range of 2-50°, a step size 0.0167° with a "time-per-step" optimized to 1000 seconds.

While the Differential scanning calorimetry (DSC) characterization of the crystalline form of prasugrel hydrobromide was as follows:

20 Approximately 1-2mg sample was accurately weighed into an Aluminum DSC pan with pin hole lid and the sample was placed into the Mettler Toledo DSC822° equipped with a nitrogen cooling unit and allowed to equilibrate at 30°C until the stable heat flow reference was seen. A dry nitrogen purge gas at a flow rate of 50ml/minute was used to produce inert atmosphere to prevent oxidation of sample during the heating. The
25 sample was scanned from about 30°C to about 350°C at rate of 10°C/min and the resulting heat flow response was measured against temperature.

FTIR method: IR is measured by using instrument Perkin Elmer by KBr mode.

The present invention provides substantially pure crystalline form of prasugrel
30 hydrobromide having less than 20% of amorphous form of prasugrel hydrobromide as determined by x-ray powder diffraction. More preferably less than 10% of amorphous

form of prasugrel hydrobromide as determined by x-ray powder diffraction. Even more preferably less than about 5% of amorphous form of prasugrel hydrobromide as determined by x-ray powder diffraction and most preferably less than 1 % of amorphous form of prasugrel hydrobromide as determined by x-ray powder diffraction

5 In one example, the x-ray powder diffraction (PXRD) pattern of the pure crystalline form of prasugrel hydrobromide is substantially in accordance with Fig.1.

Mass spectrum analysis was performed with Thermofinnigan, LCQ DECA XP MAX. Approximately 20 ppm Prasugrel API was prepared in methanol and solution was
10 injected in mass spectrometry using 250µl Hamilton gas tight syringe and the injection volume was 12 µl/min using nitrogen gas as nebulizer (sheath gas). The molecular mass = for prasugrel free base was detected in ESI +ve mode.

The present invention provides the crystalline prasugrel hydrobromide having a
15 purity, as measured by high performance liquid chromatography (HPLC), of at least about 98%, more preferably, at least about 99% and most preferably at least about 99.5%. Preferably, the chemical purity of the prasugrel hydrobromide is about 99% or more, more preferably about 99.5% or more, more preferably about 99.8% or more, more preferably about 99.9% or more, as measured by HPLC.

20 In one embodiment, the present invention encompasses prasugrel hydrobromide having less than about 0.20% of any single impurity as measured by HPLC. Preferably, the prasugrel or a pharmaceutically acceptable salt thereof has less than about 0.15% of any single chemical impurity as measured by HPLC.

Advantageously the prasugrel HBr is converted into a hydrochloride salt of
25 prasugrel by general methods known in the art. Illustratively, the salt transformation may be by neutralizing the HBr salt of prasugrel by using a base to give prasugrel freebase and then followed by the reaction of freebase with hydrochloric acid to give the hydrochloride salt of prasugrel which is herein described in the example 2.

In one embodiment, the present invention provides a process for the conversion of
30 prasugrel hydrobromide into prasugrel hydrochloride comprising:

(a) providing a suspension of prasugrel hydrobromide in one or more

solvents or aqueous mixtures thereof;

(b) adding a base to the suspension of a) followed by adding hydrochloric acid;

and

(c) recovering the prasugrel hydrochloride substantially in solid state.

5 The prasugrel hydrobromide is suspended in a solvent. Preferably ethyl acetate is used as a solvent. A base is then added to the suspension to obtain a clear solution. The base is selected from an organic base or inorganic base. The organic base may be selected from trimethylamine, triethylamine, tripropylamine. The inorganic base may be selected from carbonate or a hydroxide of an alkaline metal or an alkaline earth metal such as
10 sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide. Preferably triethylamine is used as a base.

 The hydrochloric acid is then added to the clear solution and the obtained prasugrel hydrochloride is recovered by standard techniques. Alternatively, after the
15 addition of the base is complete, and prior to the addition of hydrochloric acid the reaction mixture is washed with water and the organic layer containing the product is separated. Optionally the organic solvent is distilled out and one or more solvents like alcohol is added to the residue and removed. The solid obtained is dissolved in a solvent like acetone to obtain a clear solution. The hydrochloric acid is then added to the clear
20 solution and the obtained prasugrel hydrochloride is recovered by standard techniques.

 Prasugrel hydrobromide obtained by the process described above, has residual organic solvents or organic volatile impurities comprises less than the amount recommended for pharmaceutical products, as set forth for example in ICH guidelines and U.S. pharmacopoeia; less than about 600ppm of dichloromethane, less than about
25 5000ppm of ethanol, acetone, ethyl acetate, isopropyl alcohol, less than about 890 ppm of toluene and less than about 290ppm of n-hexane.

 Accordingly, D₉₀ particle size of the unformulated crystalline prasugrel hydrobromide salt obtained by the process of present invention is used as starting material in preparing a pharmaceutical composition generally is less than 400 microns
30 preferably less than about 200 microns, more preferably less than 150 microns, still more

preferably less than about 50 microns and still more preferably less than about 15 microns.

Any milling, grinding micronizing or other particle size reduction method known in the art can be used to bring the crystalline prasugrel hydrobromide into any desired particle size range as set forth above.

In another embodiment, the present invention provides a pharmaceutical composition comprising crystalline form of prasugrel hydrobromide and at least a pharmaceutically acceptable carrier.

Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The prasugrel or its pharmaceutically acceptable salts obtained by the process disclosed herein also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The most preferred route of administration of the prasugrel or its pharmaceutically acceptable salts is oral. The dosage forms may contain the prasugrel or its pharmaceutically acceptable salts as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients.

Capsule dosages will contain the prasugrel or its pharmaceutically acceptable salts which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the

compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl hydrobromide; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The process for the preparation of crystalline prasugrel hydrobromide of the present invention is simple, eco-friendly and easily scaleable.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

**EXAMPLE 1: PREPARATION OF CRYSTALLINE FORM OF PRASUGREL
HYDROBROMIDE**

75.0 ml of acetone and 5.0 g prasugrel base were charged in a clean and dry 4 neck round-bottom-flask (RBF) followed by stirring for about 15 minutes. 2.7 g of Hydrobromic acid (48%v/v) was added dropwise at about 25°C to about 30°C over about 10 minutes. The resultant reaction solution was stirred at about 25°C to about 30°C for about 3 hours. The separated solid was filtered and the solid obtained was washed with 2×20 ml of acetone. The solid obtained was dried at about 50°C to about 60°C under vacuum for about 48 hours to afford 4.7 g of the title compound.

Purity by HPLC: 99.5%

All known and Unknown impurities = 0.5%.

MASS (M/S): 374.15 a.m.u

Content of HBr (%w/w by titrimetry): 17%w/w.

Target compound has an X- ray powder diffraction (XRD) pattern with characteristic peaks at about 7.06, 8.31, 10.08, 11.46, 12.19, 12.82, 13.73, 14.17, 15.8, 16.7, 16.98, 17.23, 17.73, 18.36, 18.70, 21.60, 23.42, 23.69, 24.21, 24.39, 24.9, 25.14, 25.82, 26.50, 27.0, 29.89, 30.31 and 37.2 ± 0.2 degrees two-theta, which is substantially in accordance with Fig1.

Differential scanning calorimetry (DSC) endotherm curve at about 138.25°C with an onset at about 128.29°C and an endset at about 146.34°C, which is substantially in accordance with Fig. 2.

And Fourier Transform Infrared (FTIR) frequencies by infrared absorption which is substantially in accordance with Figure 3.

EXAMPLE-2: PROCESS FOR CONVERSION OF PRASUGREL

HYDROBROMIDE TO PRASUGREL HYDROCHLORIDE

10 gm of prasugrel hydrobromide and 100ml of ethyl acetate in a clean and dry 4 neck RBF followed by stirring for about 15 minutes. 12 ml of triethyl amine was added slowly over about 10 minutes. Organic layer was washed with 20 ml of water followed by 20 ml of brine solution. Organic layer was separated and the dried over 2gm of anhydrous sodium sulphate. Organic layer was distilled completely at about 45°C under

vacuum of about 700mm of Hg. 50ml of methanol was charged and distilled completely. 10 ml of methanol was charged and stirred for about 1 hour. The solid separated was filtered and the solid was washed with 2x10ml of methanol. The solid obtained was dried at about 55°C under vacuum over about 12 hours. To the solid (6.5gm) obtained 97.5 ml of Acetone was charged and stirred for about 15 minutes to obtain clear solution. 1.5ml of concentrated HCl was added followed by stirring 4 hrs. Solid separated was filtered and the solid was washed with 2x10ml of acetone. The solid obtained was dried at about 55°C under vacuum for about 12 hrs to afford about 4gm to about 5.5gm of the title compound.

EXAMPLE 3: PRASUGREL TABLETS

Sr. No.	Ingredients	Qty/tablet (in mg)
A	Prasugrel HBr	10.00
B	Mannitol (Pearlitol® SD 200)	50-150
C	Microcrystalline Cellulose (Avicel® PH112)	25-125
D	HPMC 6 cps	2-15
E	Croscarmellose Sodium	4-35
F	Magnesium Stearate	4-20

Process:

Sift A, B, part of C, D and part of E through ASTM #30 and blend the mixture in a blender followed by lubrication with part of F. Roll compact the lubricated blend followed by milling and sifting to the desired granule size. Blend these granules with the remaining part of C and E in blender followed by lubrication with remaining part of F in blender. Compress this final lubricated blend in to tablets using suitable punches.

Claims

1. A crystalline form of prasugrel hydrobromide.
- 5 2. The crystalline form of prasugrel hydrobromide as claimed in claim 1, characterized by X- ray powder diffraction pattern with characteristic peaks at about 7.06 , 8.31, 10.08, 11.46, 12.19, 12.82, 13.73, 14.17, 15.8, 16.7, 16.98, 17.23, 17.73, 18.36, 18.70, 21.60, 23.42, 23.69, 24.21, 24.39, 24.9, 25.14, 25.82, 26.50, 27.0, 29.89, 30.31 and 37.2 ± 0.2 degrees two-theta.
- 10 3. The crystalline form of prasugrel hydrobromide as claimed in claim 1, characterized by an PXRD spectrum, which is substantially in accordance with Fig. 1.
- 15 4. The crystalline prasugrel hydrobromide as claimed in claim 1, characterized by differential scanning calorimetry endotherm substantially in accordance with Fig. 2.
- 20 5. The crystalline prasugrel hydrobromide as claimed in claim 1, characterized by infrared absorption spectrum substantially in accordance with Fig. 3.
6. A process for preparing crystalline form of prasugrel hydrobromide comprising:
 - (a) providing a solution of prasugrel and hydrobromic acid in one or more solvents or aqueous mixtures thereof;
 - (b) precipitating the solid prasugrel hydrobromide; and
 - 25 (c) recovering the prasugrel hydrobromide substantially in crystalline form.
7. The process as claimed in claim 6, wherein the crystalline form of prasugrel hydrobromide has an X- ray powder diffraction pattern 2-theta peaks as claimed in claim 2.
- 30 8. The process as claimed in claim 7, wherein the solvent is selected from alcoholic

solvents like methanol, ethanol, isopropyl alcohol, n-butanol, tertiary butyl alcohol; ketones like acetone, methyl ethyl ketone, methyl isobutyl ketone; nitriles like acetonitrile, propionitrile, and mixtures and aqueous mixtures thereof.

5 9. The process as claimed in claim 8 wherein the solvent used is acetone or acetonitrile.

10. A process for conversion of prasugrel hydrobromide into prasugrel hydrochloride comprising:

- 10 (a) providing a suspension of prasugrel hydrobromide in one or more solvents or aqueous mixtures thereof;
- (b) adding a base to the suspension of a) followed by adding hydrochloric acid; and
- (c) recovering the prasugrel hydrochloride substantially in solid state.

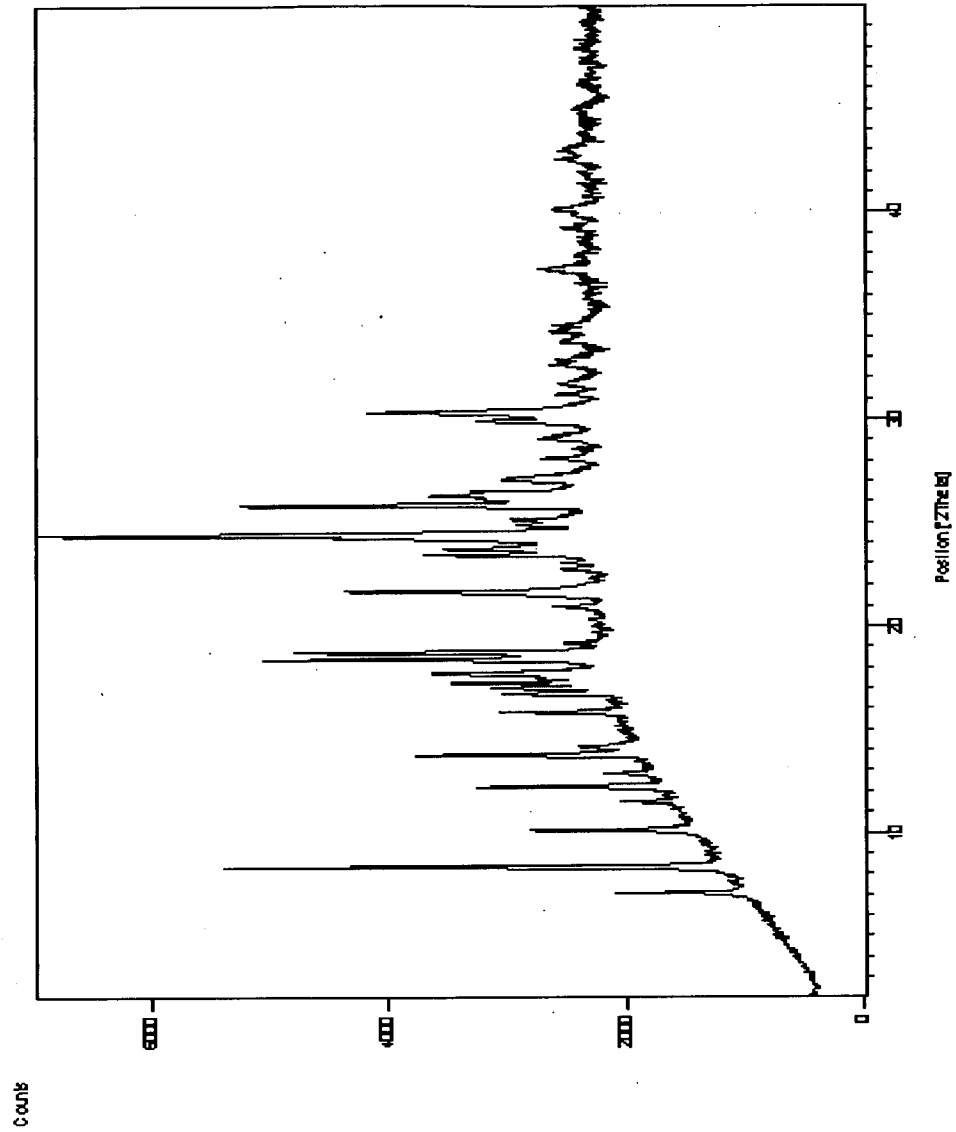
15 11) The process as claimed in claim 10, wherein the solvent used is ethyl acetate.

12) The process as claimed in claim 10, wherein the base used is triethylamine.

20 13) A pharmaceutical composition, comprising crystalline form of prasugrel hydrobromide and at least one pharmaceutically acceptable excipient.

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**Figure 1**

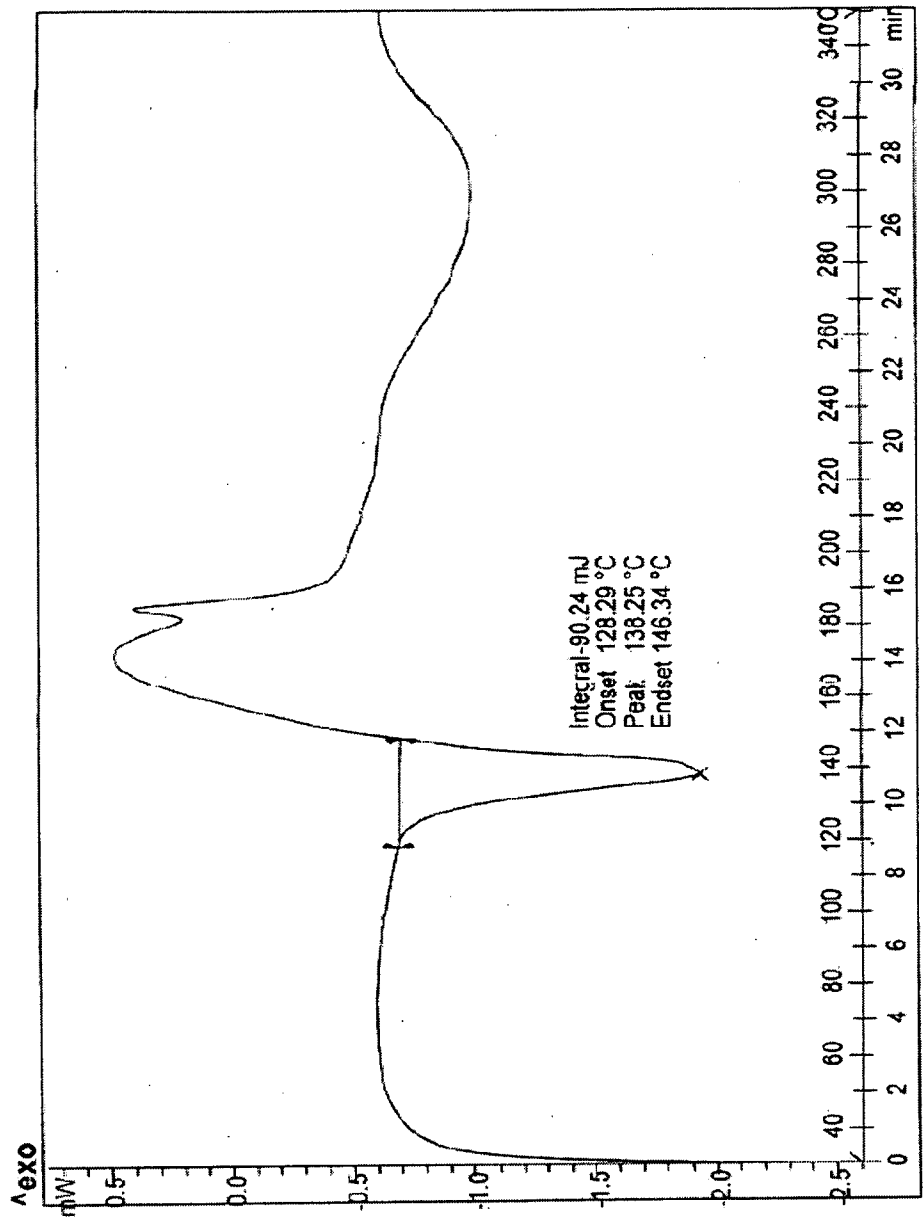
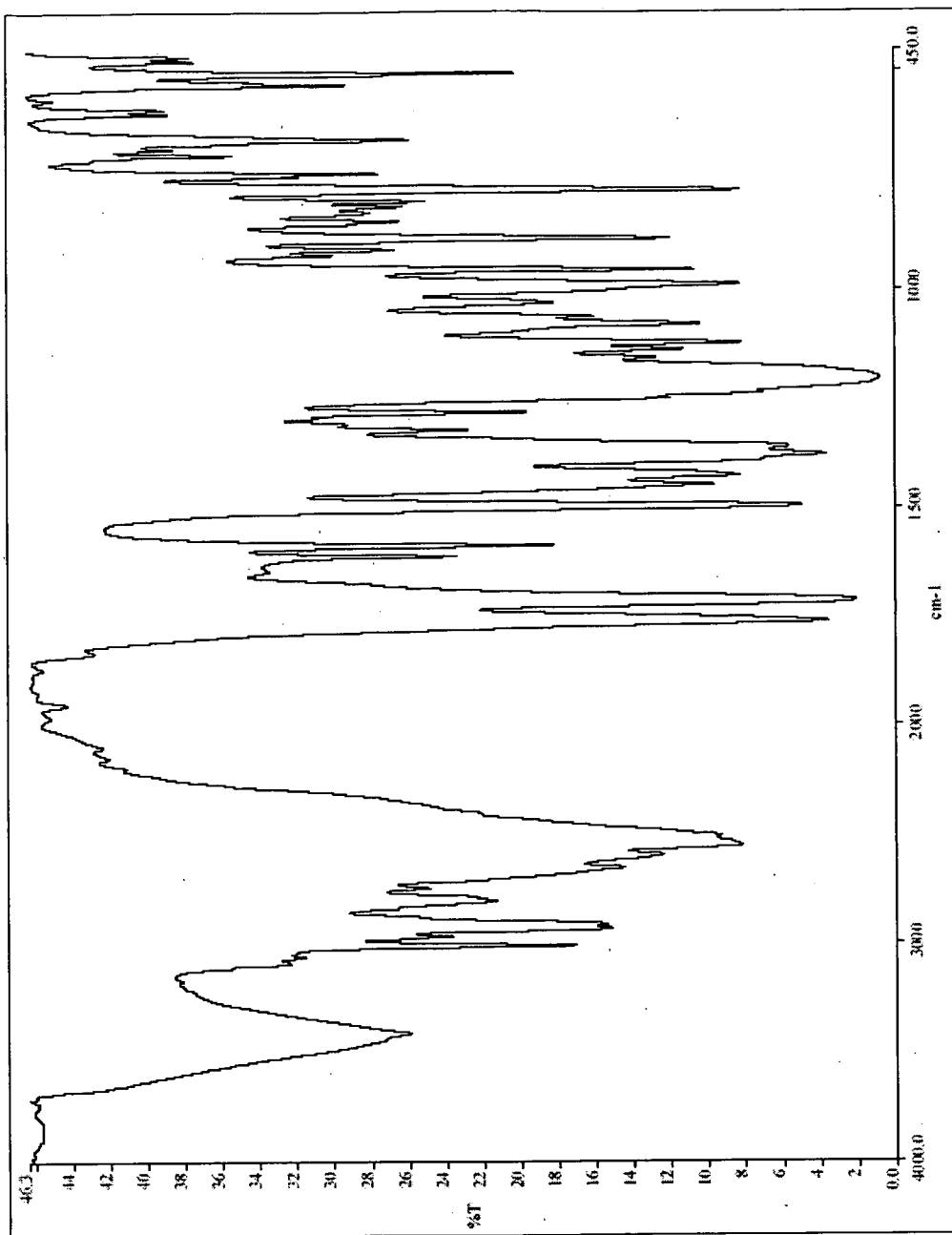


Figure 2

**Figure 3**

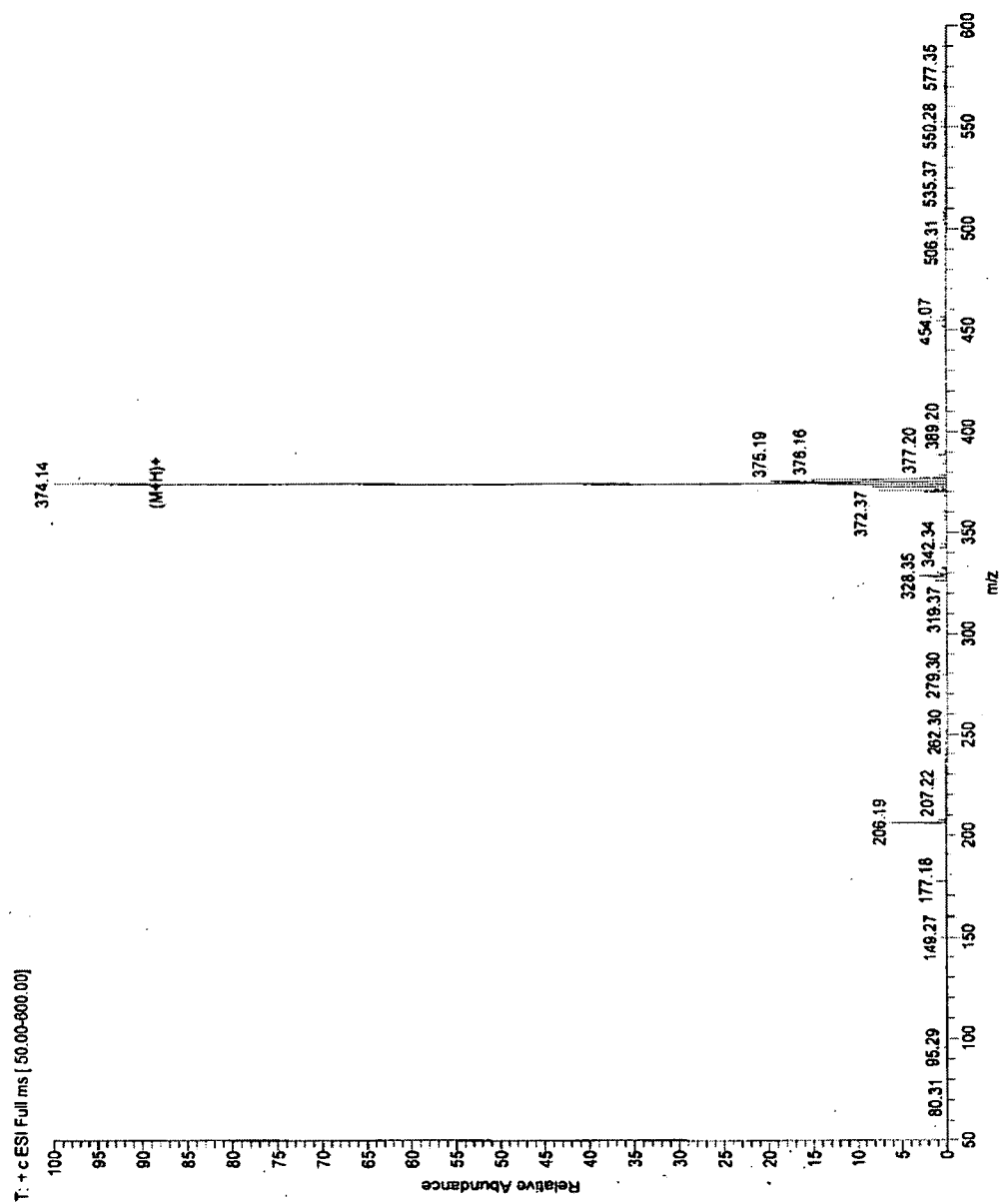


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2010/000435

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

IPC: C07D495/-; A61K31/-; A61P7/-; A61P9/-

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, WPI, EPODOC, CA:

prasugrel, thieno 3d pyridin??, hydrobromide, hydrobromic acid, hydrochloride, hydrochloric acid; +amine; base

formula in CA: C20H20FNO3S, BrH, ClH, C6H15N; CA RNS in CA: 1060616-79-6, 150322-43-3, 389574-19-0, 121-44-8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN101255169A (UNIV. SHANDONG) 03 Sep. 2008 (03.09.2008) example 1; page 1 reciprocal lines 3-4 of description; background; page 1 reciprocal paragraphs 5-9	1-13
A	US6693115B2 (SANKYO CO., LTD. et al.) 17 Feb. 2004 (17.02.2004) abstract	1-13
A	EP2003136A1 (DAIICHI SANKYO CO., LTD. et al.) 17 Dec. 2008 (17.12.2008) abstract	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 20 Oct. 2010 (20.10.2010)	Date of mailing of the international search report 02 Dec. 2010 (02.12.2010)
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Telephone No. (86-10)82245512

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2010/000435

Continuation of **CLASSIFICATION OF SUBJECT MATTER:**

C07D495/04 (2006.01) i

A61K31/4365 (2006.01) i

A61P7/02 (2006.01) n

A61P9/10 (2006.01) n

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2010/000435

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2010/000435

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