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(71) Applicant (for all designated States except US): **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; S.C.O. No. 850, Shivalik Enclave, Nac Manimajra, Chandigarh 160 101 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SINGH, Gajendra** [IN/IN]; Ind-Swift Laboratories Limited, S.C.O. No. 850, Shivalik Enclave, Nac Manimajra, Chandigarh 160 101 (IN). **SINGH, Satyendra, Pal** [IN/IN]; Ind-Swift Laboratories Limited, S.C.O. No. 850, Shivalik Enclave, Nac Manimajra, Chandigarh 160 101 (IN). **WADHWA, Lalit** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phase-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN).

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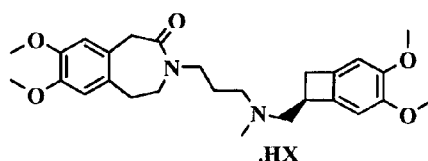
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(54) Title: ACID ADDITION SALTS OF IVABRADINE AND PREPARATION THEREOF



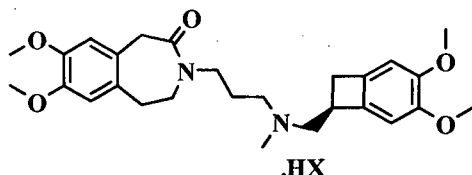
(57) Abstract: The present invention provides novel acid addition salts of ivabradine of formula (I), including their hydrates, solvates, anhydrous form, and non solvated form, both in amorphous and crystalline forms.



ACID ADDITION SALTS OF IVABRADINE AND PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to acid addition salts of ivabradine of formula I,

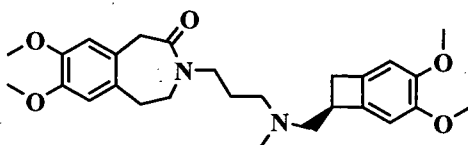


Formula I

including their hydrates, solvates, anhydrous form, and non solvated form, both in amorphous and crystalline forms, processes for their preparation and pharmaceutical compositions containing them and their use in medicine.

BACKGROUND OF THE INVENTION

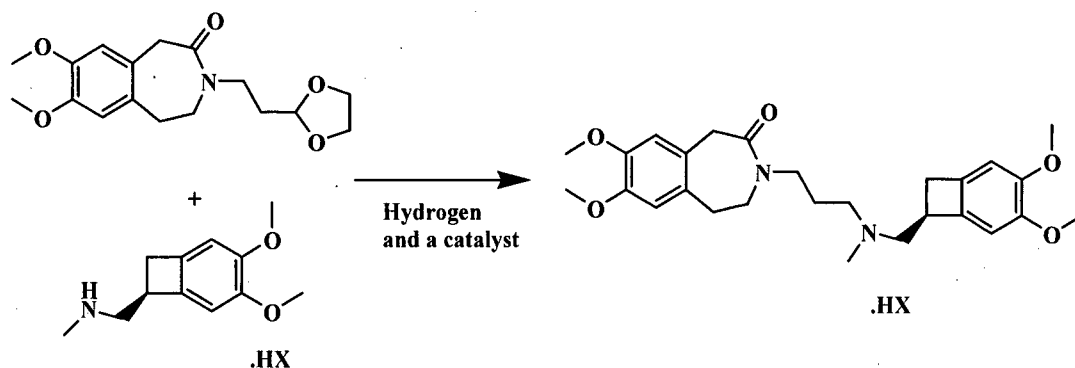
Ivabradine, 3-[3-({[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl} (methyl)amino)propyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one, having the following formula:



and addition salts thereof with a pharmaceutically acceptable acid have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

Ivabradine and its acid addition salts thereof with a pharmaceutically acceptable acid were first described in US patent 5,296,482. The patent discloses generically several acid addition salts for the (benzocycloalkyl)alkylamines compounds. These are hydrochloric, hydrobromic, sulfuric, nitric acid, phosphoric acid; acetic acid, propionic, maleic, fumaric, tartaric acid, oxalic, benzoic, methansulfonic, isethionic, benzenesulfonic acids. However, out of the listed salts, patent specifically exemplified the preparation of only two salts of ivabradine namely, dibenzoyltartrate salts and hydrochloride salt (mono-hydrochloride and di-hydrochloride salts). The disclosure of the patent is silent about the preparation of other salts for ivabradine as disclosed in the patent.

US patent 7,176,197 discloses a process for the preparation of various acid addition salts of ivabradine with a pharmaceutically acceptable acid, and hydrates thereof by the reaction of 3-(2-[1,3]dioxolan-2-yl-ethyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[d]azepin-2-one with acid addition salt of (3,4-dimethoxy-bicyclo[4.2.0]octa-1,3,5-trien-7-ylmethyl)-methyl-amine in the presence of hydrogen and a catalyst as shown in the following scheme,



Similar to the above patent, this patent also specifically describes the synthesis of ivabradine hydrochloride using hydrochloride salt of secondary amine intermediate and silent about the synthesis of other acid addition salts of ivabradine. Patent particularly describes the synthesis of α -crystalline form of ivabradine hydrochloride.

US patents 7,176,197; 7,361,650; 7,361,651; 7,361,649; 7,361,652; 7,358,240; 7,384,932; and PCT publications WO 2008/065681 and WO2008/125006 describe different polymorphic forms of ivabradine hydrochloride and process of preparation thereof.

PCT publication WO 2008/146308 discloses the amorphous ivabradine hydrochloride and process for preparation thereof. Application also discloses ivabradine oxalate and method of its preparation.

PCT publication WO 2009/124940 discloses ivabradine hydrobromide in amorphous, crystalline and dissolved state and process for preparation thereof.

There is no prior art reference which describes the preparation of ivabradine salts other than hydrochloride, hydrobromide, dibenzoyltartrate, and oxalate. Although ivabradine hydrochloride provides good pharmaceutical activity but it would be beneficial to find other acid addition salts of ivabradine, which can be easily exploited on industrial scale. Therefore, present invention provide certain new acid addition salts of ivabradine both in crystalline and amorphous forms, including their hydrates, solvates, anhydrous form and non solvated form which can be easily employed on industrial scale.

OBJECT OF THE INVENTION

It is therefore, an object of the present invention to provide new acid addition salts of ivabradine including their hydrates, solvates, anhydrous form and non solvated form, in crystalline and amorphous forms.

Another object of the present invention is to provide processes for preparing the new acid addition salts of ivabradine including their hydrates, solvates, anhydrous form and non solvated form, in crystalline and amorphous forms.

Another object of the present invention is to provide ivabradine tartrate including its hydrates, solvates, anhydrous form and non-solvated form, in crystalline and amorphous forms, and process for preparation thereof.

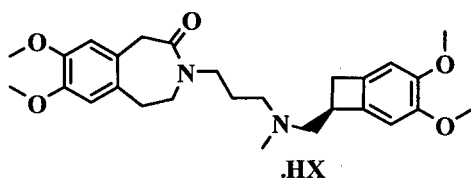
Another object of the present invention is to provide ivabradine citrate including its hydrates, solvates, anhydrous form and non-solvated form, in crystalline and amorphous forms, and process for preparation thereof.

Another object of the present invention is to provide ivabradine hydrogen sulfate including its hydrates, solvates, anhydrous form and non-solvated form, in crystalline and amorphous forms, and process for preparation thereof.

Still another object of the present invention is to provide pharmaceutical composition comprising new acid addition salts of ivabradine.

SUMMARY OF THE INVENTION

According to one embodiment, the present invention provides novel acid addition salts of ivabradine of formula I,



Formula I

wherein HX is selected from inorganic acid such as sulfuric acid, phosphoric acid, nitric acid, or organic acid such as tartaric acid, citric acid, acetic acid, propionic acid, maleic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, oxalic acid, benzoic acid, ascorbic acid, trifluoroacetic acid, methansulfonic acid, naphthalene sulfonic acid, malic acid, isethionic acid, benzenesulfonic acid, camphoric acid, toluene sulfonic acid and the like

including their hydrates, solvates, anhydrous form and non solvated form, both in crystalline and amorphous forms.

According to another embodiment, present invention provides a process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:

- a). providing a solution of ivabradine in a suitable solvent;
- b). treating the same with a source of suitable acid;
- c). removing the solvents from the reaction mixture;
- d). adding a second solvent to the resulting residue; and
- e). filtering the reaction mixture to isolate ivabradine acid addition salt of formula I there from.

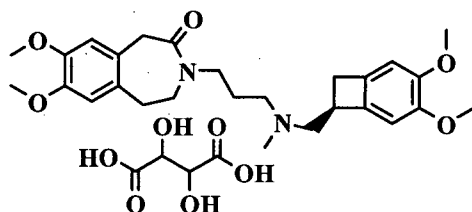
According to yet another embodiment, present invention provides a process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:

- a). providing a solution of ivabradine in a suitable solvent;
- b). treating the same with a source of suitable acid; and
- c). filtrating the precipitate of ivabradine acid addition salts of formula I there from.

According to yet another embodiment, present invention provides a process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:

- a). providing a solution of ivabradine in a suitable solvent;
- b). treating the same with a source of suitable acid to obtain clear solution;
- c). inducing precipitation of ivabradine acid addition salt; and
- d). isolating ivabradine acid addition salt of formula I there from.

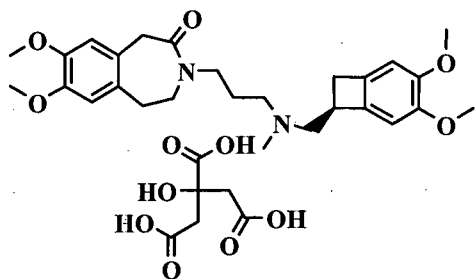
In one embodiment, the invention provides tartrate salt of ivabradine of formula II,



Formula II

including their hydrates, solvates, anhydrous form and non solvated form, both in crystalline and amorphous forms.

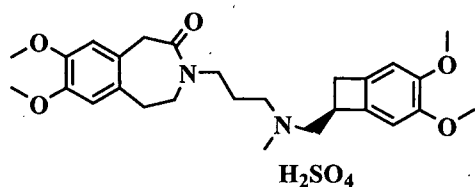
In another embodiment, the invention provides citrate salt of ivabradine of formula III,



Formula III

including their hydrates, solvates, anhydrous form and non solvated form, both in crystalline and amorphous forms.

In still another embodiment, the invention provides hydrogen sulfate salt of ivabradine of formula IV,



Formula IV

including their hydrates, solvates, anhydrous form and non solvated form, both in crystalline and amorphous forms.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an X-ray powder diffraction pattern of amorphous ivabradine tartrate

Figure 2 is infrared spectrum of ivabradine tartrate

Figure 3 is a X-ray powder diffraction pattern of amorphous ivabradine citrate

Figure 4 is infrared spectrum of ivabradine citrate

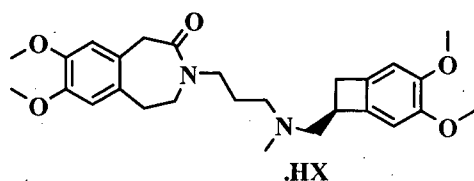
Figure 5 is an X-ray powder diffraction pattern of ivabradine hydrogen sulfate

Figure 6 is infrared spectrum of ivabradine hydrogen sulfate

DETAILED DESCRIPTION OF THE INVENTION

As used herein, ivabradine acid addition salt includes their hydrates, solvate, anhydrous form, and non-solvated form, both in amorphous as well as crystalline form.

The present invention provides new acid addition salts of ivabradine of formula I,

**Formula I**

wherein *HX* is selected from inorganic acid such as sulfuric acid, phosphoric acid, nitric acid, or organic acid such as tartaric acid, citric acid, acetic acid, propionic acid, maleic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, oxalic acid, benzoic acid, ascorbic acid, trifluoroacetic acid, methansulfonic acid, naphthalene sulfonic acid, malic acid, isethionic acid, benzenesulfonic acid, camphoric acid, toluene sulfonic acid and the like

including their solvate, hydrates, anhydrous form, non-solvated form, both in amorphous as well as crystalline form.

According to another embodiment, present invention provides a process for the preparation of ivabradine acid addition salt of formula I.

Generally, acid addition salts of ivabradine can be prepared by reacting solution of ivabradine free base in a suitable solvent with a suitable source of corresponding acid at a temperature ranging from 20 ° C to reflux temperature, preferably from 20 °C to 60 ° C for few minutes to few hours, more preferably till the completion of salt formation. Solution of ivabradine in a suitable solvent can be prepared by using a solvent that includes but not limited to ketone such as acetone; alcohol such as methanol, ethanol, isopropanol; nitrile such as acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as dichloromethane, dichloroethane, chloroform and the like or mixture thereof. Preferably, the solvent employed for the reaction includes those in which ivabradine has high solubility. The mixture of ivabradine in a solvent can be optionally heated.

The acid employed for the reaction includes inorganic acid such as sulfuric acid, phosphoric acid, nitric acid and the like; or organic acid such as tartaric acid, citric acid, acetic acid, propionic acid, maleic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, oxalic acid, benzoic acid, ascorbic acid, trifluoroacetic acid, methanesulfonic acid, naphthalene sulfonic acid, isethionic acid, benzenesulfonic acid, camphoric acid, toluenesulfonic acid and the like, preferably sulfuric acid, tartaric acid, citric acid, malic acid and the like or other suitable source thereof can be used for the salt formation that can effectively yields the respective salt of ivabradine. Acid used for the salt formation can be used as such or in solution with a suitable solvent which includes esters such as ethyl acetate; alcohol such as methanol, ethanol, isopropanol; ketone such as acetone, methyl

isobutyl ketone; and the like or other source of acids, which includes but not limited to alkali metal salt of corresponding acid such as sodium citrate, sodium tartrate, concentrated or aqueous sulfuric acid and the like may be used for the salt formation.

For preparing ivabradine acid addition salt, generally a mixture of acid, suitable solvent and ivabradine may be contacted together to give corresponding ivabradine acid addition salt or in another way, both ivabradine and acid may be separately combined with a solvent prior to being reacted together, whereby the solvent used for the acid and ivabradine can be identical or different. When two or more solvents are used, a two phase reaction scheme may be used wherein the ivabradine and acid are primarily in one phase and the resulting ivabradine acid addition salt is primarily present in other phase due to, inter alia, solubility difference.

Preferably, prior to the addition of acid, ivabradine can be optionally stirred in a suitable solvent to obtain clear solution. The addition of suitable acid or its source to the mixture containing ivabradine may result in the formation of hazy solution, gummy mass, oily mass or clear solution depending upon the nature of acid employed as well as on the nature of solvent used. The reaction mixture, if required, may be heated to a temperature of 20°C to reflux temperature of solvent. The reaction mixture is then distilled off to remove the solvents present in the reaction mixture. It is advantageous to remove the traces of the solvent present in the reaction mixture by adding another solvent to the reaction mixture followed by solvent distillation. The product, thus obtained, can be isolated from the resulting reaction mass by further addition of a second solvent, in which ivabradine acid addition salt have low solubility or no solubility. The second solvent can be selected depending upon the nature of acid employed for the reaction, and includes but not limited to ketones such as acetone, methyl isobutyl ketone; esters such as ethyl acetate, isopropyl acetate and the like. Reaction mixture can be optionally stirred for 0.5 to 3 hours to complete precipitation. The solid, thus precipitated out, can be isolated from the reaction mass using conventional techniques known in the art such as filtration, centrifugation or decantation and the like.

According to still another embodiment, present invention provides a process for the preparation of ivabradine acid addition salts of formula I.

Generally, the process involves the addition of a suitable acid to the solution of ivabradine free base at a temperature ranging from 20°C to reflux temperature of solvent used for few minutes to few hours. Solution of ivabradine in a suitable solvent can be prepared in a suitable solvent that includes but not limited to ketone such as acetone; alcohol such as methanol, ethanol, isopropanol; nitrile such as

acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as dichloromethane, dichloroethane, chloroform and the like or mixture thereof. Preferably, the solvent employed for the reaction includes those in which ivabradine has high solubility.

The acid employed for the reaction is same as defined above. Acid used for the salt formation can be used as such or in solution with a suitable solvent or other source of acids, includes but not limited to alkali metal salt of corresponding acid such as sodium citrate, sodium tartrate, concentrated or aqueous sulfuric acid and the like may be used for the salt formation.

The solvent employed for making solution of acid can be selected from the solvents in which ivabradine acid addition salt has less solubility or no solubility. The solvent system is preferably selected so as to facilitate the salt formation and to allow the precipitation of salt subsequently. Advantageously, both ivabradine and the suitable acid are dissolvable, at least partly, in the solvent system, optionally by heating. Preferably, suitable acid in solution form is added to the clear solution of the ivabradine in a suitable solvent at a temperature of 20°C to reflux temperature of solvent used. The addition of solution of acid may result in the formation of hazy solution or gummy material depending upon the nature of acid employed as well as on the nature of solvent used. If, the addition of acid to the reaction mixture results in gummy material then reaction mixture is stirred to make easy recovery of the desired ivabradine acid addition salt from the reaction mixture. Usually, precipitation starts with the addition of acid to solution of ivabradine. The product thus formed can be isolated from reaction mixture by stirring the reaction mixture for 0.5 to 3 hours. The reaction mixture, if required, may be heated to a temperature of 20°C to reflux temperature of solvent used and preferably 20 to 60°C. The solid thus precipitated out, can be isolated from the reaction mass using conventional techniques known in the art such as filtration, centrifugation or decantation and the like.

According to still another embodiment, present invention provides a process for the preparation of ivabradine acid addition salts of formula I, by inducing the precipitation either by cooling or by adding anti solvent.

Generally, the process involves the reaction of ivabradine free base with the a source of corresponding acid in a suitable solvent, at a temperature ranging from 20°C to reflux temperature of solvent used and preferably at 20° C to 60° C for few minutes to few hours, more preferably till clear solution is obtained. Solution of ivabradine in a suitable solvent can be prepared by using a solvent that includes but not limited to ketone such as acetone; alcohol such as methanol, ethanol, isopropanol, butanol; nitrile such as acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as

dichloromethane, dichloroethane, chloroform and the like or mixture thereof. Preferably, the solvent employed for the reaction includes those in which ivabradine has high solubility.

Advantageously, both ivabradine and the suitable acid are dissolvable in the solvent system, optionally by heating. In the process, ivabradine, acid and solvent may be contacted together or in another way, both ivabradine and acid may be separately combined with a solvent prior to being reacted together, whereby the solvent used for the acid and ivabradine can be identical or different. Solvent system employed for the reaction is preferably selected from the solvents in which ivabradine base as well its acid addition salt has solubility.

The acid employed for the reaction is same as defined above. Acid used for the salt formation can be used as such or in solution with a suitable solvent or other source of acids, includes but not limited to alkali metal salt of corresponding acid such as sodium citrate, sodium tartrate, concentrated or aqueous sulfuric acid and the like may be used for the salt formation.

Preferably, suitable acid is added to the clear solution of the ivabradine in a suitable solvent at a suitable temperature and stirred for few minutes to few hours, preferably to obtain clear solution. The reaction mixture, if required, may be heated for obtaining the clear solution. The precipitation may be spontaneous depending upon the solvent system employed and nature of acid. The precipitation of the desired salt can be induced by reducing the temperature of the reaction mixture or by adding anti solvent. Anti solvent is selected from the solvent in which ivabradine acid addition salt has no solubility or very less solubility, preferably anti-solvent includes but not limited to ketones such as acetone, methyl isobutyl ketone; esters such as ethyl acetate, isopropyl acetate and the like or mixture thereof. The product thus precipitated can be isolated from the reaction mass using conventional techniques known in the art such as filtration, centrifugation or decantation and the like. The resulting product can be optionally washed and/or dried.

The ivabradine acid addition salts thus prepared by any of the above process can be washed with a suitable solvent and dried to give the product of desired quality. Suitable solvent for the washing includes but not limited to esters such as ethyl acetate; ketones such as acetone, methyl isobutyl ketone; nitriles such as acetonitrile and the like or mixture thereof. Drying is preferably performed under vacuum. It is also preferred to dry the product at a temperature within a range of from 35 to 65 °C, more preferably 45 to 55 °C and most preferably at about 50°C. During drying the product can be sieved to deagglomerate and/or remove lumps.

The acid addition salts of ivabradine can be in isolated and/or purified form or can be part of a composition. The acid addition salts of ivabradine includes various forms of the salt including dissolved forms, solvent free form or it may be isolated as a hydrate, anhydrate or a solvate, non-solvate form, both in crystalline and amorphous. All the polymorphic form of the salts of the present invention form a novel feature of the invention. The acid addition salts of ivabradine thus prepared can exist in amorphous as well as crystalline form.

Acid addition salts of ivabradine as described by the present invention can be characterized by suitable techniques known in the art. Preferably, acid addition salts of ivabradine of the present invention can be characterized by various spectroscopic techniques like ^1H and ^{13}C Nuclear magnetic resonance (NMR), Mass spectrometry (MS), Infrared spectroscopy (IR) and X-ray diffraction chromatogram (XRD). Ivabradine acid addition salts can also be characterized by Thermo gravimetric analysis (TGA), Differential scanning calorimetry (DSC), and Karl Fischer technique.

X-ray diffraction pattern was measured on a PANalytical X'Pert Pro diffractometer with Cu radiation and expressed in terms of two-theta, d-spacings and relative intensities.

According to one embodiment, present invention provides ivabradine tartrate.

Specifically, the present invention relates to the ivabradine tartrate in a solid or dissolved state. Solid ivabradine tartrate can be in an amorphous or crystalline state.

Ivabradine tartrate forms one aspect of the present invention and is characterized by an X-ray powder diffraction pattern. It can exist in amorphous or crystalline form. The amorphous form of ivabradine tartrate displays the X-ray powder diffraction pattern as shown in Figure 1. Ivabradine tartrate is also characterized by infrared spectroscopy.

According to another embodiment, present invention provides ivabradine citrate.

Specifically, the present invention relates to the ivabradine citrate in a solid or dissolved state. Solid ivabradine citrate can be in an amorphous or crystalline state.

Ivabradine citrate forms another aspect of the present invention and is characterized by X-ray powder diffraction pattern. The amorphous form of ivabradine citrate displays the X-ray powder diffraction pattern as shown in Figure 3. Ivabradine citrate is also characterized by infrared spectroscopy.

According to yet another embodiment, present invention provides ivabradine hydrogen sulfate.

Specifically, the present invention relates to the ivabradine hydrogen sulfate in a solid or dissolved state. Solid ivabradine hydrogen sulfate can be in an amorphous or crystalline state.

Ivabradine hydrogen sulfate forms yet another aspect of the present invention and is characterized by X-ray powder diffraction pattern. The amorphous form of ivabradine hydrogen sulfate displays the X-ray powder diffraction pattern as shown in Figure 5. Ivabradine hydrogen sulfate is also characterized by infrared spectroscopy.

The present invention also provides the conversion of amorphous form of ivabradine acid addition salt to crystalline form or vice versa using a suitable method, preferably slurry or crystallization with a suitable solvent.

Acid addition salts thus prepared by the process of present invention may have moisture content less than 2.0 % w/w, preferably less than 1.5%, more preferably less than 1.0% w/w, or still more preferably free from water. Moisture content of the ivabradine acid addition salts depends upon drying conditions such as time, temperature, pressure etc. The moisture content of the resulting compound can be reduced by the increasing the time and/or temperature for the drying of the product.

The quality of the resulting ivabradine acid addition salt depends upon the purity of the ivabradine free base employed for the reaction. Ivabradine free base employed can be purified using a suitable purification method prior to be used for the reaction with a suitable solvent or ivabradine acid addition salt thus prepared can be purified to enhance the purity as well as to minimize the presence of undesired impurity present in the product.

Ivabradine base used in the present invention can be prepared by any of the method disclosed in prior art.

The present invention also relates to pharmaceutical compositions comprising as active ingredient the ivabradine acid addition salts of the present invention together with one or more appropriate carriers or auxiliary substance(s) conventionally applied in the pharmaceutical industry.

Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral (for example powders, pellets, tablets, coated tablets, capsules, orally disintegrating tablets, chewable tablets, solutions, suspensions or emulsions), parenteral (intravenous intramuscular, subcutaneous or intraperitoneal use), rectal (suppositories), transdermal (patches) or local (ointments or patches) or nasal administration. Suitable pharmaceutical

dosage form can be tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and drinkable suspensions.

The major advantage lies in the present invention that it provides new acid addition salts of ivabradine including hydrates, anhydrous form, solvate form, non-solvated form, both in crystalline or amorphous form.

The invention is illustrated by reference to the following examples. However, the examples are not intended to limit any scope of the claim anyway. 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 purpose and interest of this invention.

EXAMPLES

Example 1: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in isopropanol (100 ml) for 15 minutes at 20-25°C. A solution of tartaric acid (3.5 g) in isopropanol (30 ml) was added to the reaction mixture at 20-25°C. The reaction mixture was stirred for 1 hour at 20-25°C. The resulting product was filtered and washed with isopropanol (30 ml), dried under vacuum at 40-45°C to give 12 g of title compound having purity 99.35% by HPLC and displays infra-red spectrum as shown in figure 2.

Example 2: Preparation of ivabradine tartrate

Ivabradine (13 g) was stirred in acetone (130 ml) for 15 minutes at 25-30°C. Tartaric acid (4.55 g) was added to the resulting solution, heated to 50-55°C and maintained at same temperature for one hour. Acetone was distilled under vacuum and ethyl acetate (30 ml) was added to the resulting residue. Ethyl acetate was distilled off from the reaction mixture and again ethyl acetate (70 ml) was added to the resulting residue. The reaction mixture was stirred for 1 hour at 25-30°C and filtered. The product was washed with ethyl acetate (30 ml) and dried at 45-55°C to give 16.3 g of title compound having moisture content: 1.03% w/w.

Example 3: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in methanol (70 ml) for 15 minutes at 25-30°C. Tartaric acid (3.5 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled off. Further, ethyl acetate (50 ml) was added to the residue, stirred for 1 hour at 25-30°C and filtered. The

product was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give 13.3 g of title compound as amorphous solid having melting point 99-102°C.

Example 4: Preparation of ivabradine tartrate

Ivabradine (12 g) was stirred in ethanol (60 ml) for 15 minutes at 25-30°C to obtain clear solution. Tartaric acid (4.2 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained at 50-55 °C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (60 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The solid thus filtered was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give title compound as amorphous solid having melting point 101-105°C and moisture content: 0.84% w/w.

Example 5: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in ethyl acetate (150 ml) for 15 minutes at 25-30°C. Tartaric acid (3.5 g) in acetone (40 ml) was added to the resulting solution at 30-35°C and was stirred. Reaction mixture was heated to 55-60°C and maintained for 1 hour. Reaction mixture was slowly cooled to ambient temperature and further stirred for 1 hour. The resulting product was filtered, washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give title compound having melting point 100-105°C and moisture content: 1.0% w/w.

Example 6: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in acetonitrile (60 ml) for 15 minutes at 25-30°C. Tartaric acid (3.5 g) was added to the resulting solution and heated to 50-55°C. The reaction mixture was maintained at 50-55°C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the residue and distilled. Further, ethyl acetate (60 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and filtered. The solid thus filtered was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give 12.6 g of title compound having melting point 101-104°C and moisture content 1.08% w/w.

Example 7: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in tetrahydrofuran (50 ml) for 15 minutes at 25-30°C. Tartaric acid (3.5 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained at 50-55 °C for one hour. The reaction mixture was cooled to 25-30 °C and then distilled under vacuum. Ethyl acetate (30 ml) was added to the residue and distilled. Further, ethyl acetate (70 ml) was added

to the resulting residue, stirred for 1 hour at 25-30°C and filtered. The filtered solid was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give 13.7 g of title compound having melting point 102-106°C.

Example 8: Preparation of ivabradine tartrate

Ivabradine (10 g) was stirred in methyl isobutyl ketone (200 ml) for 15 minutes at 25-30°C. Solution of tartaric acid (3.5 g) in acetone (30 ml) was added to the resulting mixture at 25-30°C. The reaction mixture was stirred for 1 hour and filtered. The resulting product was washed with methyl isobutyl ketone (20 ml) and dried under vacuum at 45-55 °C to give title compound having moisture content 1.42% w/w.

Example 9: Preparation of ivabradine tartrate

Ivabradine (12 g) was stirred in dichloromethane (50 ml) for 15 minutes at 25-30°C. A solution of tartaric acid (4.3 g) in methanol (20 ml) was added to the resulting solution and maintained for hour at 25-30 °C. The solvent were distilled at atmospheric pressure off. Ethyl acetate (30 ml) was added to the residue and distilled off. Further, ethyl acetate (50 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and filtered. The filtered solid was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give 15.8 g of title compound having melting point: 101-106°C and moisture content: 0.73% w/w

Example 10: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in ethyl acetate (170 ml) for 15 minutes at 20-25°C. A solution of citric acid (4.5 g) in ethyl acetate (60 ml) was added to the reaction mixture at 25-30°C. The reaction mixture was stirred for 1.5 hour at 25-30°C. The resulting product was filtered and washed with ethyl acetate (50 ml), dried under vacuum at 40-45°C to give 14 g of title compound having purity 99.26% by HPLC; melting point 100-105°C.

Example 11: Preparation of ivabradine citrate

Ivabradine (20 g) was stirred in ethyl acetate (340 ml) for 15 minutes at 20-25°C. A solution of citric acid (9.0 g) in ethyl acetate (120 ml) was added to the reaction mixture at 25-30°C. The reaction mixture was stirred for 1.5 hour at 25-30°C. The resulting product was filtered and washed with ethyl acetate (100 ml), dried under vacuum at 40-45°C to give title compound as amorphous solid having melting point 101-105°C.

Example 12: Preparation of ivabradine citrate

Ivabradine (13 g) was dissolved in acetone (100 ml) for 15 minutes at 25-30°C. Citric acid (4.85 g) was added to the resulting solution, heated to 50-55°C. Reaction mixture was maintained at 50-55°C for one hour and solvent was distilled under vacuum. Ethyl acetate (20 ml) was added to the resulting residue and distilled off. Further, ethyl acetate (70 ml) was added to the resulting residue. The reaction mixture was stirred for 1 hour at 25-30°C and filtered. The product was washed with ethyl acetate (20 ml) and dried at 50-55°C to give title compound having moisture content: 1.9% w/w.

Example 13: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in methanol (70 ml) for 15 minutes at 25-30°C. Citric acid (4.5 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled off. Further, ethyl acetate (50 ml) was added to the residue, stirred for 1 hour at 25-30°C and filtered. The filtered product was washed with ethyl acetate (20 ml) and dried under vacuum at 45-55°C to give 13.3 g of title compound having moisture content: 0.76 % w/w.

Example 14: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in ethanol (50 ml) for 15 minutes at 25-30°C to obtain clear solution. Citric acid (4.5 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained at 50-55 °C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (50 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The solid thus filtered was washed with ethyl acetate (30 ml) and dried under vacuum at 45-55°C to give title compound having melting point: 100-105°C and moisture content: 0.98%w/w.

Example 15: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in isopropanol (70 ml) for 15 minutes at 25-30°C. Citric acid (4.5 g) was added to the resulting solution and heated to 50-55°C. Reaction mixture was maintained at 50-55 °C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (60 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The solid thus filtered was washed with ethyl acetate (30 ml) and dried under vacuum at 45-55°C to give 13.7 g of title compound as amorphous solid having melting point 100-104°C.

Example 16: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in acetonitrile (70 ml) for 15 minutes at 25-30°C. Citric acid (4.5 g) was added to the resulting solution and heated to 55-60°C. Reaction mixture was maintained at 50-55 °C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (70 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The filtered solid was washed with ethyl acetate (30 ml) and dried under vacuum at 45-50°C to give title compound having melting point: 101-105°C and moisture content: 0.76% w/w.

Example 17: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in tetrahydrofuran (50 ml) for 15 minutes at 25-30°C. Citric acid (4.5 g) was added to the resulting solution and heated to 55-60°C. Reaction mixture was maintained at 50-55 °C for one hour and distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (70 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The filtered solid was washed with ethyl acetate (20 ml) and dried under vacuum at 45-50°C to give 13.3 g of title compound having melting point: 99-103°C and moisture content: 0.80% w/w.

Example 18: Preparation of ivabradine citrate

Ivabradine (10 g) was stirred in methyl isobutyl ketone (200 ml) for 15 minutes at 25-30°C to obtain clear solution. A solution of citric acid (4.5 g) in acetone (30 ml) was added to the resulting solution and stirred for 1 hour. Reaction mixture was filtered and filtered solid was washed with methyl isobutyl ketone (20 ml) and dried under vacuum at 45-50°C to give title compound having melting point 101-104°C, moisture content: 0.99% w/w and display infrared spectrum as shown in figure 4.

Example 19: Preparation of ivabradine citrate

Ivabradine (12 g) was stirred in dichloromethane (80 ml) for 15 minutes at 25-30°C. A solution of citric acid (5.4 g) in acetone (30 ml) was added to the resulting solution. Reaction mixture was maintained at 25-30 °C for one hour and solvents were distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled. Further, ethyl acetate (50 ml) was added to the resulting residue, stirred for 1 hour at 25-30°C and reaction mixture was filtered. The filtered solid was washed with ethyl acetate (30 ml) and dried under vacuum at 45-50°C to give 16.7 g of title compound as amorphous solid having melting point 100-105°C & moisture content 0.60% w/w.

Example 20: Preparation of ivabradine hydrogen sulfate

Ivabradine (20 g) was stirred in ethyl acetate (300 ml) for 15 minutes at 20-25°C. A solution of hydrogen sulphate (5.0 g) in ethyl acetate (40 ml) was slowly added to the reaction mixture at 20-25°C. The reaction mixture was stirred for 1.5 hour at 20-25°C. The resulting product was filtered, washed with ethyl acetate (60ml), dried under vacuum at 40-45°C to give 22 g of title compound as amorphous solid having melting point 150-155°C.

Example 21: Preparation of ivabradine hydrogen sulfate

Ivabradine (10 g) was dissolved in isopropyl alcohol (70 ml) and stirred for 15 minutes at 25-30°C. A solution of sulfuric acid (2.5 g) in isopropyl alcohol (20 ml) was added to the resulting solution at 30-35°C and stirred for 1 hour to obtain clear solution. Ethyl acetate (40 ml) was added to the resulting solution and stirred for 1 – 2 hours. The solid thus precipitated was filtered, washed with ethyl acetate (30 ml) and dried at 45-50°C to give title compound having purity 99.77% by HPLC, melting point 150-155°C; and moisture content: 0.55% w/w.

Example 22: Preparation of ivabradine hydrogen sulfate

Ivabradine (10 g) was stirred in acetone (50 ml) for 15 minutes at 25-30°C to obtain clear solution. A solution of sulfuric acid (2.5 g) in ethyl acetate (30 ml) was added to the resulting solution and reaction mixture was maintained at room temperature for one hour. Reaction mixture was heated to 45-50°C and solvent were distilled under vacuum. Acetone (70 ml) was added to the resulting residue and stirred for 30 minutes. The reaction mixture was cooled to 25-30 °C and further to 10-15 °C. The reaction mixture was further stirred for 30 minutes at 10-15°C and filtered. The resulting solid was washed with acetone (20 ml) and dried at 45-50°C to give 10.6 g of title compound as amorphous solid having purity 99.48 % by HPLC and moisture content: 1.13% w/w.

Example 23: Preparation of ivabradine hydrogen sulfate

Ivabradine (10 g) was stirred in ethanol (70 ml) for 15 minutes at 25-30°C. A solution of sulfuric acid (2.5 g) in ethanol (10 ml) was added to the resulting solution and reaction mixture was stirred for 30 minutes to obtain clear solution. Reaction mixture was heated to 55-60 °C and solvent were distilled under vacuum. Ethyl acetate (30 ml) was added to the resulting residue and distilled under vacuum. Further, ethyl acetate (70 ml) was added to the resulting residue and stirred for 1 hour at 25-30°C. The resulting solid was filtered, washed with ethyl acetate (30 ml) and dried at 45-50°C to give title

compound having melting point 150-155°C and moisture content: 0.88% w/w. The product display infrared spectrum as shown in figure 6.

Example 24: Preparation of ivabradine hydrogen sulfate

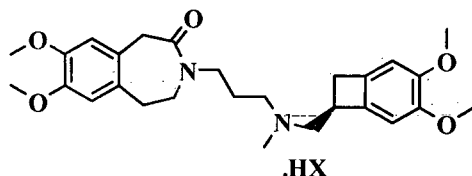
Ivabradine (10 g) was stirred in methanol (60 ml) for 15 minutes at 25-30°C. A solution of sulfuric acid (2.5 g) in methanol (10 ml) was added to the resulting solution to obtain a clear solution and reaction mixture was stirred for 1 hour at 25-30 °C. Solvent was distilled under vacuum. Ethyl acetate (30 ml) was added to the residue and distilled under vacuum to remove traces of methanol. Further, ethyl acetate (70 ml) was added to the resulting residue and stirred for 1 hour at 25-30°C. The resulting solid was filtered, washed with ethyl acetate (20 ml) and dried at 45-50°C to give title compound.

Example 25: Preparation of ivabradine hydrogen sulfate

Ivabradine (10 g) was stirred in methyl isobutyl ketone (50 ml) for 15 minutes at 25-30°C to obtain clear solution. A solution of sulfuric acid (2.5 g) in methyl isobutyl ketone (10 ml) was added to the resulting solution and stirred for 1 hour at 25-30°C. Solid thus precipitated was filtered, washed with methyl isobutyl ketone (20 ml) and dried under vacuum at 45-50°C to give title compound having melting point: 150-155°C.

WE CLAIM:

1. An acid addition salt of ivabradine of formula I,

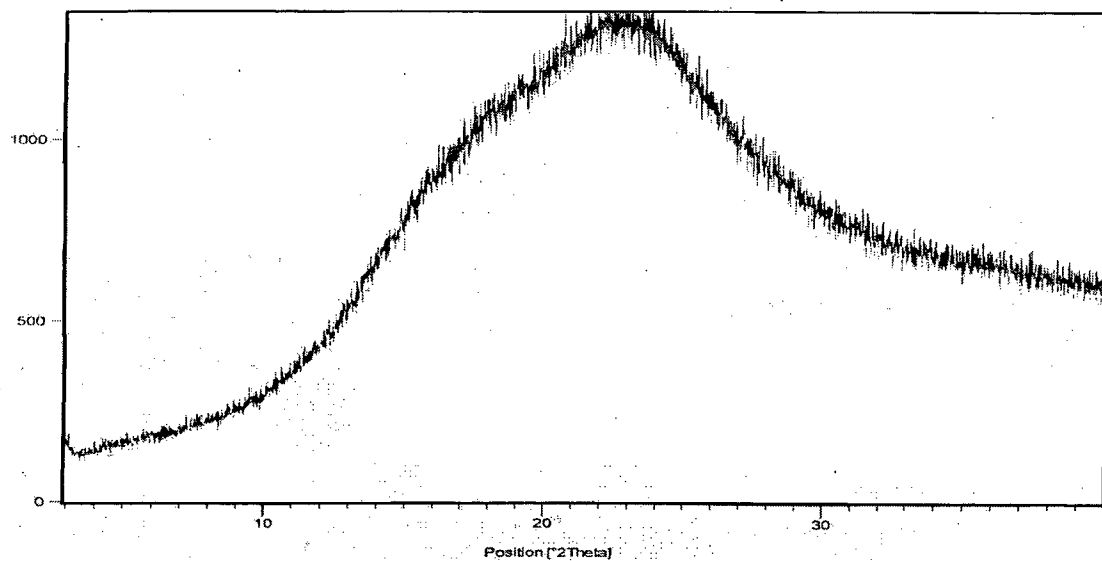
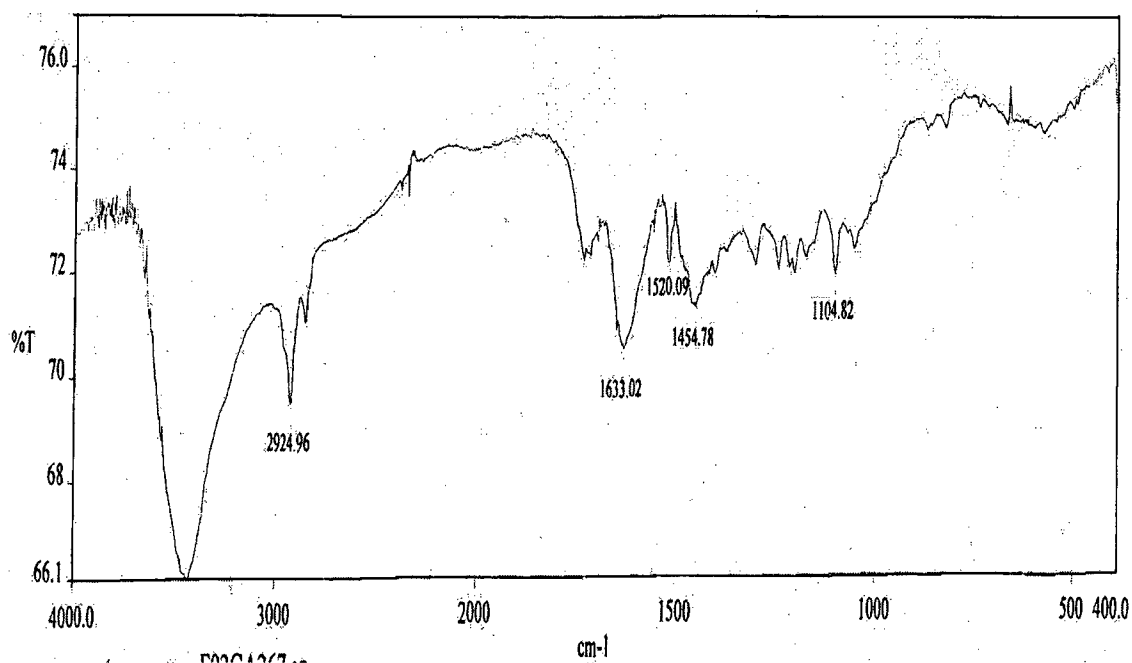
**Formula I**

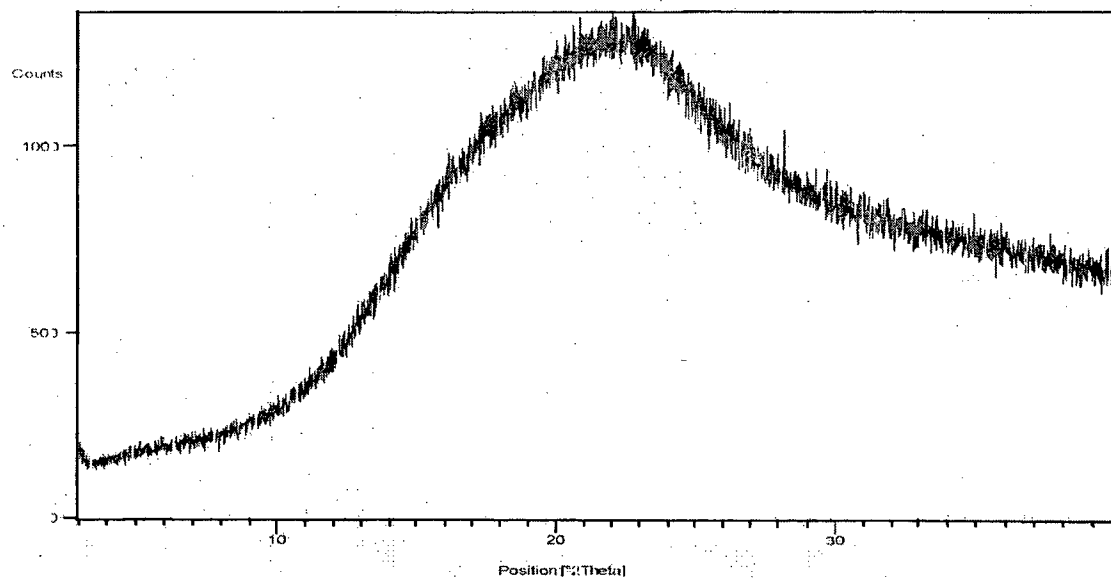
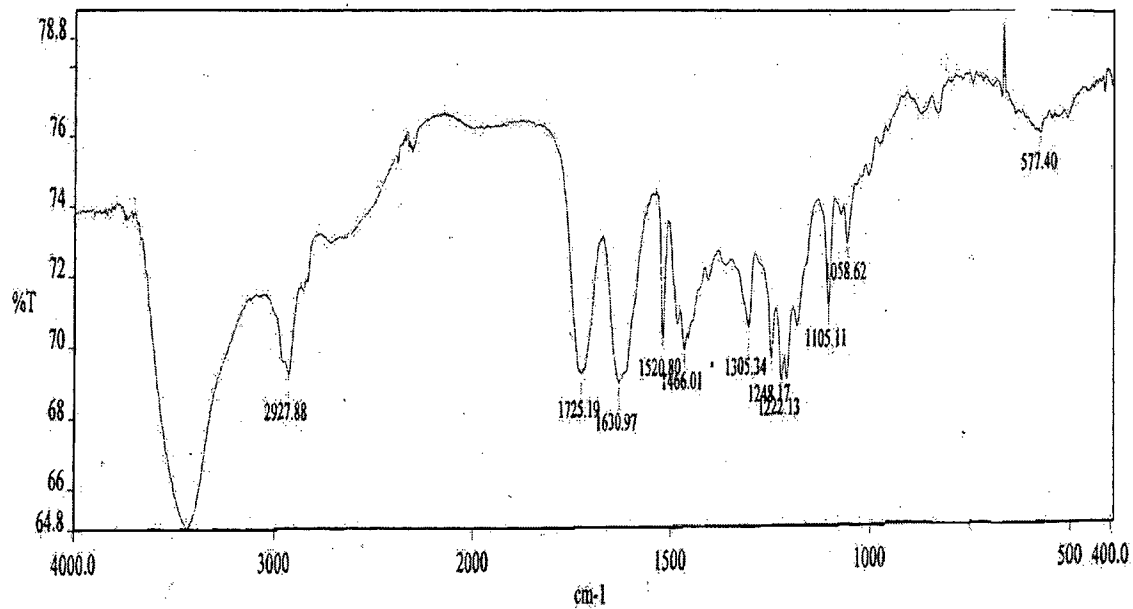
including their hydrates, solvates, anhydrous form and non solvated form, both in crystalline and amorphous forms.

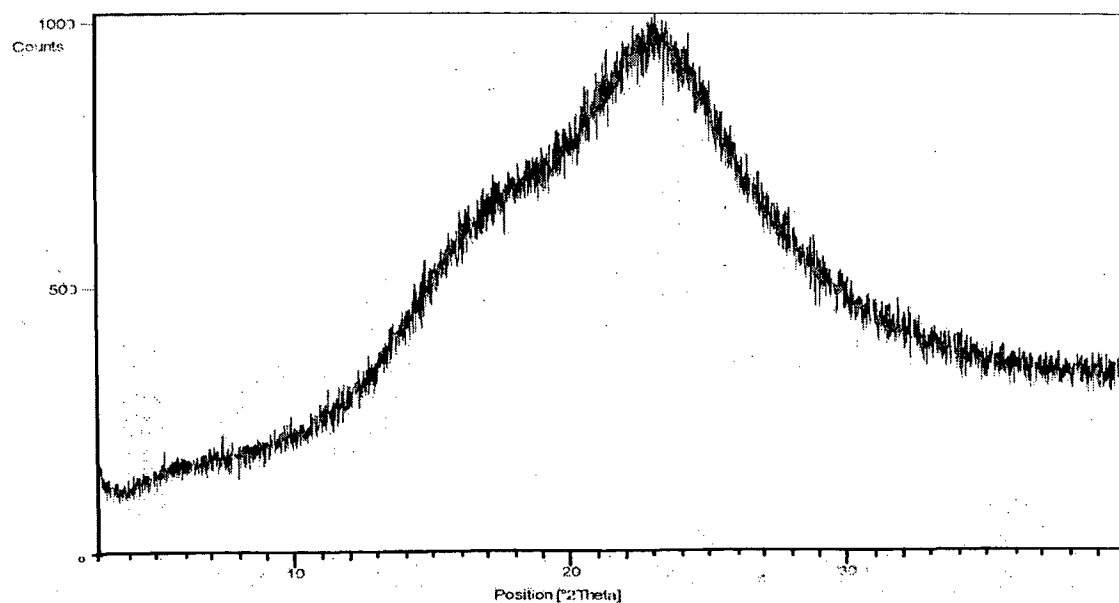
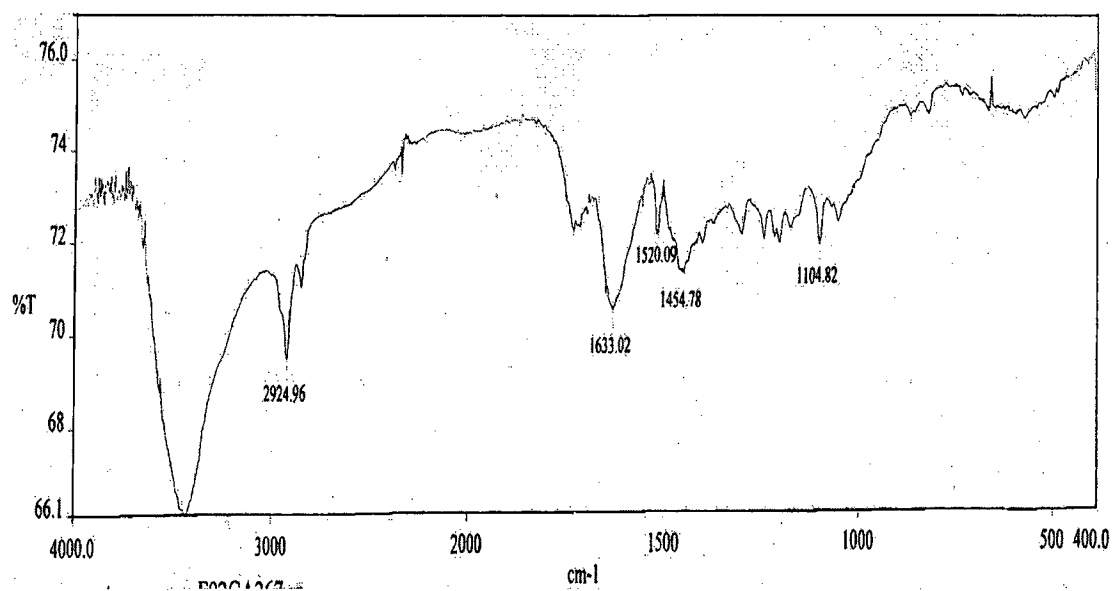
2. An acid addition salt of ivabradine according to claim 1, wherein HX is selected from citrate, tartrate and hydrogen sulfate.
3. A process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:
 - a). providing a solution of ivabradine in a suitable solvent;
 - b). treating the same with a source of suitable acid;
 - c). removing the solvents from the reaction mixture;
 - d). adding a second solvent to the resulting residue; and
 - e). filtering the reaction mixture to isolate ivabradine acid addition salt of formula I there from.
4. The process according to claim 3, wherein in step a) suitable solvent is selected from ketone such as acetone; alcohol such as methanol, ethanol, isopropanol; nitrile such as acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as dichloromethane, dichloroethane, chloroform and the like or mixture thereof; and in step b) suitable acid is selected from citric acid, tartaric acid or sulfuric acid.
5. The process according to claim 3, wherein in step d) second solvent is selected from ketones such as acetone, methyl isobutyl ketone; esters such as ethyl acetate, isopropyl acetate and the like or mixture thereof.
6. A process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:
 - a). providing a solution of ivabradine in a suitable solvent;
 - b). treating the same with a source of suitable acid; and
 - c). filtrating the precipitate of ivabradine acid addition salts of formula I there from.
7. The process according to claim 6, wherein in step a) suitable solvent is selected from ketone such as acetone; alcohol such as methanol, ethanol, isopropanol; nitrile such as acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as dichloromethane, dichloroethane, chloroform and the

like or mixture thereof; and in step b) suitable acid is selected from citric acid, tartaric acid or sulfuric acid.

8. A process for the preparation of ivabradine acid addition salts of formula I, comprises the steps of:
- a). providing a solution of ivabradine in a suitable solvent;
 - b). treating the same with a source of suitable acid to obtain clear solution;
 - c). inducing precipitation of ivabradine acid addition salt; and
 - d). isolating ivabradine acid addition salt of formula I there from.
9. The process according to claim 8, wherein in step a) suitable solvent is selected from ketone such as acetone; alcohol such as methanol, ethanol, isopropanol; nitrile such as acetonitrile; ethers such as tetrahydrofuran; halogenated solvent such as dichloromethane, dichloroethane, chloroform and the like or mixture thereof; and in step b) suitable acid is selected from citric acid, tartaric acid or sulfuric acid.
10. The process according to claim 8, wherein in step c) precipitation is induced by reducing the temperature of the reaction mixture.
11. The process according to claim 8, wherein in step c) precipitation is induced by adding anti solvent selected from ketones such as acetone, methyl isobutyl ketone; esters such as ethyl acetate, isopropyl acetate and the like or mixture thereof.
12. Ivabradine tartrate.
13. Ivabradine tartrate according to claim 12, in a solid state.
14. Ivabradine tartrate according to claim 12, in a dissolved state.
15. Ivabradine citrate.
16. Ivabradine citrate according to claim 15, in a solid state.
17. Ivabradine citrate according to claim 15, in a dissolved state.
18. Ivabradine hydrogen sulfate.
19. Ivabradine hydrogen sulfate according to claim 18, in a solid state.
20. Ivabradine hydrogen sulfate according to claim 18, in a dissolved state.

**Figure- 1****Figure -2**

**Figure- 3****Figure -4**

**Figure- 5****Figure -6**