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(54) Title: CRYSTALLINE FORMS OF DOLASETRON BASE AND PROCESSES FOR PREPARATION THEREOF

(57) Abstract: The present invention provides crystalline polymorphic forms of Dolasetron base. Also provided are methods of preparing the crystalline polymorphic forms of Dolasetron base.



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CRYSTALLINE FORMS OF DOLASETRON BASE AND PROCESSES FOR PREPARATION THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

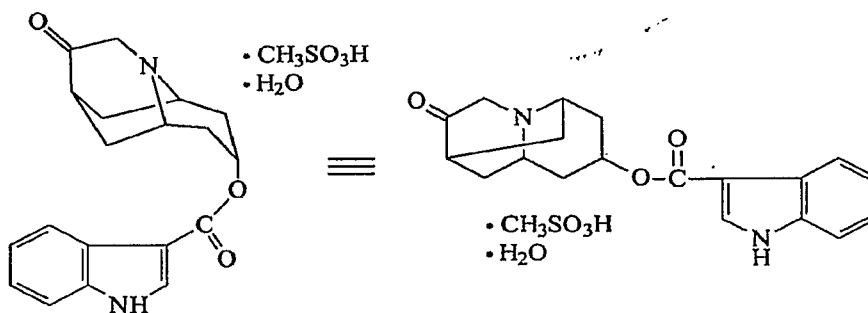
[0001] The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/756,690, filed January 5, 2006; 60/800,884, filed May 15, 2006; 60/838,758, filed August 17, 2006; 60/861,354, filed November 27, 2006; 60/802,842, filed May 22, 2006; 60/818,934, filed July 5, 2006; 60/833,515, filed July 24, 2006; 60/836,432, filed August 7, 2006; 60/763,683, filed January 30, 2006; 60/784,248, filed March 20, 2006; 60/815,199, filed June 19, 2006; 60/852,887, filed October 18, 2006. The contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to crystalline polymorphic forms of Dolasetron base, processes for preparing said crystalline forms.

BACKGROUND OF THE INVENTION

[0003] Dolasetron base is the key intermediate of Dolasetron salts, such as, Dolasetron Mesylate monohydrate. Dolasetron mesylate monohydrate, (2 α ,6 α ,8 α ,9 α β)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate monohydrate (referred to as DLS-MsOH·H₂O), a compound having the chemical structure



is a serotonin receptor (5-HT₃) antagonist used as an antiemetic and antinauseant agent in chemo- and radiotherapies.

[0004] Dolasetron mesylate (DLS-MsOH) developed by Merrell Dow Pharmaceuticals is marketed as tablets for oral administration and as sterile solution for intravenous administration by Aventis, under the name Anzemet®.

[0005] EP patent No. 0339669 describes the preparation of Dolasetron-base and its crystallization from a mixture of ethyl acetate and hexane.

[0006] Further, a publication with reference number IPCOM000144657D reports anhydrous dolasetron mesylate form F and preparation thereof.

[0007] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Dolasetron base, may give rise to a variety of crystalline forms having distinct crystal structures and physical properties like melting point, x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One crystalline form may give rise to thermal behavior different from that of another crystalline form. Thermal behavior can be measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis ("TGA"), and differential scanning calorimetry ("DSC"), which have been used to distinguish polymorphic forms.

[0008] The difference in the physical properties of different crystalline forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantageous physical properties compared to other crystalline forms of the same compound or complex.

[0009] One of the most important physical properties of pharmaceutical compounds is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal tract is slow, it is often desirable for a drug that is unstable to conditions in the patient's stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. Different crystalline forms or polymorphs of the same pharmaceutical compounds can and reportedly do have different aqueous solubilities.

[0010] The discovery of new polymorphic forms of Dolasetron base provides a new opportunity to improve the performance of the synthesis of the active pharmaceutical ingredient (API), Dolasetron mesylate, by producing crystalline forms of Dolasetron base having improved characteristics, such as flowability, and solubility. Thus, there is a need in the art for polymorphic forms of Dolasetron base.

SUMMARY OF THE INVENTION

[0011] In one embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 12.9, 14.1, and 15.2 ± 0.2 degrees 2-theta.

[0012] In another embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 13.6, 16.4, and 23.4 ± 0.2 degrees 2-theta.

[0013] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 8.2, 11.7 and 13.9 ± 0.2 degrees 2-theta.

[0014] In one embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 14.3, 16.1, 16.5 and 18.5 ± 0.2 degrees 2-theta.

[0015] In another embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 13.9, 16.9 and 21.8 ± 0.2 degrees 2-theta.

[0016] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 7.6, 12.1, and 13.7 ± 0.2 degrees 2-theta and without the peaks selected from a group consisting of peaks at: 11, 14.8, and 22.2 ± 0.2 degrees 2-theta, and mixtures thereof.

[0017] In another embodiment, the present invention provides an anhydrous crystalline Dolasetron base.

[0018] In yet another embodiment, the present invention provides a crystalline Dolasetron base monohydrate.

[0019] In another embodiment, the present invention provides a crystalline Dolasetron base nitromethane solvate.

[0020] In another embodiment, the present invention provides a process for preparing Dolasetron salt, by preparing any of the above crystalline Forms of Dolasetron base, and mixtures thereof, and converting them to Dolasetron salt.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a powder XRD pattern of crystalline Dolasetron base Form A.

Figure 2 shows a powder XRD pattern of crystalline Dolasetron base Form B.

Figure 3 shows a powder XRD pattern of crystalline Dolasetron base Form C..

Figure 4 shows a powder XRD pattern of crystalline Dolasetron base Form D.
Figure 5 shows a powder XRD pattern of crystalline Dolasetron base Form E.
Figure 6 shows a powder XRD pattern of pure crystalline Dolasetron Form F.

DETAILED DESCRIPTION OF THE INVENTION

[0021] As used herein, the term "anhydrous" refers to a substance that contains no more than 1% by weight of water or of any solvent.

[0022] As used herein the term "room temperature" refers to a temperature of about 20°C to about 30°C

[0023] The present invention provides a crystalline form of Dolasetron base, designated Form A, characterized by a powder XRD pattern with peaks at about 12.9, 14.1, and 15.2. ± 0.2 degrees 2-theta. Form A may be further characterized by a powder XRD pattern with peaks at about 7.6, 16.2, 16.5, 18.8, 21.2, 22.8, 26.9 ± 0.2 degrees 2-theta. Form A may also be substantially identified by the powder XRD pattern as depicted in figure 1. Form A may also be characterized by a weight loss of less than about 0.1%, at temperatures up to about 100°C, as measured by TGA. Form A may also be characterized by a DSC thermogram having a sharp endothermic peak at about 234°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. Form A is an anhydrous form of Dolasetron base.

[0024] The present invention further provides a crystalline Form A of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Preferably, the crystalline Form A of Dolasetron base comprises less than about 10% of any one of the crystalline forms B, C, D, E, and chemically pure crystalline form F of Dolasetron base, preferably, with less than about 5%, most preferably, with less than about 1%, as measured by XRD.

[0025] The present invention further provides a process for preparing Dolasetron base Form A comprising crystallizing Dolasetron base from iso-butyl acetate

[0026] The crystallization comprises providing a solution of Dolasetron base in iso-butyl acetate, and precipitating the said crystalline form of Dolasetron base therefrom.

[0027] Preferably, the solution of Dolasetron base in iso-butyl acetate is provided by combining the starting Dolasetron base and iso-butyl acetate, and heating this mixture. The starting Dolasetron may be any form of Dolasetron base, preferably, the a mixture of crystalline forms B and D. Preferably, the mixture of Dolasetron base and iso-butyl acetate is heated to a temperature of about 40°C to about 120°C, more preferably to about 70°C to about 110°C, most preferably to about 100°C, to obtain the solution.

[0028] Optionally, the solution is treated with charcoal, prior to precipitation of the crystalline form. After treating the solution with charcoal, it is filtered.

[0029] Preferably, precipitation is carried out by a process comprising concentrating the solution; and cooling the concentrated solution to obtain a suspension comprising the said crystalline form of Dolasetron base. Cooling is, preferably, gradual. The gradual cooling comprises first cooling to a temperature of about 15°C to about 35°C, more preferably to about room temperature, and subsequently further cooling to a temperature of about 0°C to about 10°C, more preferably of about 2°C to about 8°C. Preferably, the subsequent cooling is conducted for a period of about 8 hours to about 24 hours, more preferably for about 10 to about 16 hours.

[0030] The process for preparing crystalline form A may further comprise recovering the crystalline form from the suspension. The recovery may be done by any method known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0031] The present invention also provides a crystalline form of Dolasetron base, designated Form B, characterized by a powder XRD pattern with peaks at about 13.6, 16.4, and 23.4. ± 0.2 degrees 2-theta. Form B may be further characterized by a powder XRD pattern with peaks at about 9.4, 10.4, 14.9, 15.5, 17.9, 18.8, 28.4 ± 0.2 degrees 2-theta. Form B may also be substantially identified by the powder XRD pattern as depicted in figure 2. Form B may also be characterized by a weight loss of about 5.5%, at temperatures up to about 140°C, as measured by TGA. Form B may also be characterized by a DSC thermogram having a first endothermic peak at about 140°C and a second at 226°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. Form B is a

hydrated form of Dolasetron base, preferably, monohydrate. Preferably, the amount of water as measured by KF is of about 5.2% by weight.

[0032] The present invention further provides a crystalline Form B of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Preferably, the crystalline Form B of Dolasetron base comprises less than about 10% of any one of the crystalline forms A, C, D, E, and chemically pure crystalline form F of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD.

[0033] The present invention provides a process for preparing Dolasetron base Form B comprising combining Indole-3-carboxylic acid, an anhydride, an C₁₋₂ halogenated hydrocarbon, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (referred to as HQO) and a catalyst to form a reaction mixture; quenching the reaction with an inorganic base; and removing the C₁₋₂ halogenated hydrocarbon from the reaction mixture to obtain a suspension comprising of the said crystalline form.

[0034] Preferably, the C₁₋₂ halogenated hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform, more preferably dichloromethane (methylene chloride).

[0035] Preferably, the anhydride is either trifluoroacetic anhydride or methyl chlorocarbonate, more preferably trifluoroacetic anhydride.

[0036] Preferably, the catalyst is either a saturated trisubstituted amine or an aromatic amine. Preferably, the saturated trisubstituted amine is either a trialkyl amine or 4-dialkylaminopyridine amine. Preferably, the trisubstituted amine is 4-dimethylaminopyridine or diisopropylethylamine, more preferably, 4-dimethylaminopyridine (DMAP).

[0037] Preferably, Indole-3-carboxylic acid is added to a solution of trifluoroacetic anhydride in methylenechloride, prior to the addition of HQO and DMAP.

[0038] Preferably, the addition is done at a temperature of about 15°C to about 35°C, more preferably, at about room temperature.

[0039] Preferably, HQO and DMAP are added, both in one portion.

[0040] Preferably, prior to quenching, the temperature is maintained at about 15°C to about 35°C, more preferably, at about room temperature, for a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours, most preferably overnight.

[0041] Preferably, the reaction is quenched with an aqueous solution of an inorganic base. Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. The more preferred base is sodium carbonate.

[0042] Preferably, methylenechloride is removed by evaporation under reduced pressure, to obtain a suspension comprising said crystalline form.

[0043] The process for preparing crystalline form B may further comprise recovering the crystalline form from the suspension. The recovery may be done by any method known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0044] The present invention further provides a crystalline form of Dolasetron base, designated Form C, characterized by a powder XRD pattern with peaks at about 8.2, 11.7, 13.9 ± 0.2 degrees 2-theta. Form C may be further characterized by a powder XRD pattern with peaks at about 12.8, 15.0, 16.4, 16.8, 17.1, 18.1, 25.3 ± 0.2 degrees 2-theta. Form C may also be substantially identified by the powder XRD pattern as depicted in figure 3. Form C may also be characterized by a weight loss of less than about 0.1%, at temperatures up to about 133°C, as measured by TGA. Form C may also be characterized by a DSC thermogram having a first endothermic peak at about 220°C and a second at 234°C, and an exothermic peak at about 223°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. Form C is an anhydrous form of Dolasetron base.

[0045] The present invention further provides a crystalline Form C of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Preferably, the crystalline Form C of Dolasetron base comprises less than about 10% of any one of the crystalline forms A, B, D, E, and chemically pure crystalline form F of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD.

[0046] The present invention also provides a process for preparing Dolasetron base Form C comprising crystallizing Dolasetron base from a solvent mixture

comprising ethyl acetate and *n*-Hexane, in a volume to volume ratio of about 1:2 to about 1:8.

[0047] Preferably, the crystallization comprises providing a solution of Dolasetron base in a solvent mixture of ethylacetate and *n*-hexane in a volume to volume ratio of about 1:2 to about 1:8, and precipitating the said crystalline form of Dolasetron base.

[0048] The solution of Dolasetron base in a solvent mixture of ethylacetate and *n*-hexane in a volume to volume ratio of about 1:2 to about 1:8 is provided by combining the starting Dolasetron base and ethyl acetate; heating this mixture to obtain a first solution; and adding *n*-hexane to the mixture to obtain the solution. Preferably, the volume ratio of ethyl acetate and *n*-Hexane is of about 1:4, respectively. Preferably, the mixture of Dolasetron base and ethylacetate is heated to a temperature of about room temperature to about 70°C, more preferably from about 40°C to about 60°C.

[0049] Preferably, the precipitation is carried out by cooling the said solution to obtain a suspension comprising the said crystalline form of Dolasetron base. Preferably, the said solution is cooled to a temperature of about 15°C to about 35°C, more preferably, at about room temperature, providing the suspension.

[0050] The suspension is kept at such temperature to increase the yield of the crystallized product. Preferably, the suspension is kept at a temperature of about 15°C to about 35°C, more preferably, at about room temperature, for a period of about 1 hour to about 24 hours, more preferably for about 2 to about 12 hours, most preferably for about 2 hours.

[0051] The process for preparing crystalline form C may further comprise recovering the crystalline form from the suspension. The recovery may be carried out by any method known to a skilled artisan. The recovery may be carried out for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0052] The present invention provides a crystalline form of Dolasetron base, designated Form D, characterized by a powder XRD pattern with peaks at about 14.3, 16.1, 16.5 and 18.5 ± 0.2 degrees 2-theta. Form D may be further characterized by a powder XRD pattern with peaks at about 9.3, 17.5, 21.4, 24.6, 27.9, 28.5 ± 0.2 degrees 2-theta. Form D may also be substantially identified by the powder XRD pattern as

depicted in figure 4. Form D may also be characterized by a weight loss of about 5.3%, at temperatures up to about 144°C, as measured by TGA. Form D may also be characterized by a DSC thermogram having a first endothermic peak at about 130°C, a second at 229°C, and a third endothermic peak at about 235°C, and an exothermic peak at about 232°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. Form D is a hydrated form of Dolasetron base, preferably, monohydrate. Preferably, the amount of water as measured by KF is of about 5.2% by weight.

[0053] The present invention further provides crystalline Form D of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Preferably, crystalline Form D of Dolasetron base comprises less than about 10% of any one of the crystalline forms A, B, C, E, and chemically pure crystalline form F of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD.

[0054] The present invention further provides a process for preparing Dolasetron base Form D comprising crystallizing Dolasetron base from a solvent mixture comprising acetonitrile and water

[0055] The crystallization comprises providing a solution of Dolasetron base in a solvent mixture comprising acetonitrile and water, and precipitating the said crystalline form of Dolasetron base.

[0056] The solution of Dolasetron base in a solvent mixture comprising acetonitrile and water may be provided by combining the starting Dolasetron base and the mixture of water and acetonitrile; and heating this mixture. Preferably, the mixture is heated to a temperature of about room temperature to about 85°C, more preferably, of about 40°C to about 85°C. When Dolasetron base is dissolved at about room temperature, it may take an overnight period to dissolve. Preferably, the acetonitrile /water ratio is about 99:1 to about 80:20. More preferably, the acetonitrile /water ratio is about 95:5.

[0057] Preferably, the precipitation is done by cooling the solution to obtain a suspension comprising said crystalline form of Dolasetron base. Cooling is, preferably, gradual. The gradual cooling comprises first cooling to a temperature of about 15°C to about 35°C, more preferably, to about room temperature, and subsequently further cooling to a temperature of about 0°C to about 10°C, more

preferably to about 2°C to about 8°C. Preferably, the subsequent cooling to a temperature of about 0°C to about 10°C, more preferably to about 8°C to about 2°C is carried out for a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours, most preferably overnight.

[0058] The process for preparing crystalline form D may further comprise recovering the crystalline form from the suspension. The recovery may be done by any method known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0059] The present invention further provides another process for preparing Dolasetron base Form D comprising suspending Dolasetron base Form A in a mixture comprising acetone and water.

[0060] Preferably, the suspension is provided at about 15°C to about 55°C, more preferably, at about 15°C to about 35°C, most preferably at about room temperature. Preferably, the acetone /water ratio is of about 99:1 to about 80:20. More preferably, the acetone /water ratio is of about 95:5.

[0061] Preferably, suspending Dolasetron base form A is carried out while stirring.

[0062] Preferably, the suspension is kept at such temperature, preferably while stirring, for a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours, most preferably overnight.

[0063] The process for preparing the crystalline form D may further comprise recovering the crystalline form the suspension. The recovery may be done by any process known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0064] The present invention also provides a process for preparing a mixture of crystalline forms of Dolasetron base, containing crystalline form B and D, comprising combining Indole-3-carboxylic acid, an anhydride, an organic solvent, HQO and a catalyst forming a reaction mixture; quenching the reaction with an inorganic base by addition of the inorganic base to the reaction mixture; and removing the organic solvent from the reaction mixture.

[0065] Preferably, the organic solvent is selected from the group consisting of a C₁₋₂ halogenated hydrocarbon, a C₆₋₈ aromatic hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkyl cyanide, trifluoroacetic acid and mixtures thereof. A preferred C₁₋₂ halogenated

hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform, more preferably dichloromethane (methylene chloride). A preferred C₆₋₈ aromatic hydrocarbon is benzene, toluene or xylol, more preferably toluene. Preferably, the C₁₋₄ nitroalkane is a C₁₋₂ nitroalkane, either nitromethane or nitroethane, more preferably nitromethane. Preferably, the C₁₋₄ alkyl cyanide is a C₁₋₂ alkyl cyanide, either acetonitrile or propionitrile, more preferably acetonitrile. A preferred organic solvent is either methylene chloride or a mixture of toluene and trifluoroacetic acid.

[0066] Preferably, the anhydride is either trifluoroacetic anhydride or methyl chlorocarbonate, more preferably, trifluoroacetic anhydride.

[0067] Preferably, the catalyst is either a saturated trisubstituted amine or an aromatic amine. Preferably, the saturated trisubstituted amine is either a trialkyl amine or 4-dialkylaminopyridine amine. Preferably, the trisubstituted amine is 4-dimethylaminopyridine or diisopropylethylamine, more preferably, 4-dimethylaminopyridine (DMAP).

[0068] When the organic solvent is methylene chloride, Indole-3-carboxylic acid is preferably added to a solution of trifluoroacetic anhydride in methylene chloride, prior to the addition of HQO and DMAP. Preferably, the addition is done at a temperature of about 15°C to about 35°C, more preferably, at room temperature. Preferably, HQO and DMAP are added, both, in one portion. Further, a second portion of the trifluoroacetic anhydride is preferably added following the addition of HQO and DMAP. Preferably, prior to the second addition of trifluoroacetic anhydride, the temperature is maintained at about 15°C to about 35°C, more preferably, at about room temperature, for a period of about 1 to about 4 hours, more preferably for about 2 hours. Preferably, trifluoroacetic anhydride is added in one portion, prior to quenching. Further, prior to quenching the mixture is maintained at a temperature of about 15°C to about 35°C, more preferably about room temperature, for a period of about 1 to about 4 hours, more preferably for about 2 hours.

[0069] When the organic solvent is a mixture of toluene and trifluoroacetic acid, Indole-3-carboxylic acid is preferably added to a solution of trifluoroacetic anhydride in a mixture of toluene and trifluoroacetic acid, prior to the addition of HQO without the addition of a catalyst. Preferably, the addition is done at a temperature of about 15°C to about 35°C, more preferably, at room temperature. Preferably, HQO is added in one portion. Preferably, prior to quenching, the

temperature is maintained at about 15°C to about 35°C, more preferably at about room temperature, for a period of about 1 to about 4 hours, more preferably for about 2 hours. Preferably, prior to quenching trifluoroacetic acid is removed by evaporation.

[0070] Preferably, the reaction is quenched by using an aqueous solution of an inorganic base. Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. The more preferred base is sodium carbonate. Preferably, organic solvent is removed by evaporation under reduced pressure, to obtain a suspension comprising of the said crystalline form.

[0071] The process for preparing the mixture of crystalline form D and B may further comprise recovering the said mixture of the crystalline forms from the suspension. The recovery may be done by any process known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0072] The present invention provides a crystalline form of Dolasetron base, designated Form E, characterized by a powder XRD pattern with peaks at, 13.9, 16.9, and 21.8 ± 0.2 degrees 2-theta. Form E may be further characterized by a powder XRD pattern with peaks at about 6.5, 8.0, 10.3, 10.8, 14.6, 19.4, 21.4 ± 0.2 degrees 2-theta. Form E may also be substantially identified by the powder XRD pattern as depicted in figure 5. Form E may also be characterized by a weight loss of about 6.4%, at temperatures up to about 145°C, as measured by TGA. Preferably, the amount of water as measured by KF is less than about 0.1%, by weight. Form E may also be characterized by a DSC thermogram having a first endothermic peak at about 94°C, a second at 225°C, and a third endothermic peak at about 235°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. Form E is a solvated form of Dolasetron base, preferably a nitromethane solvate. Preferably, the amount of nitromethane, as measured by TGA is of about 6.5% to about 8%, by weight.

[0073] The present invention further provides a crystalline Form E of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, with than about 1%, as measured by XRD. Preferably, the crystalline Form E of Dolasetron base comprises less than about 10% of any one of the crystalline forms A, B, C, D, and chemically

pure crystalline form F of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. More preferably, the crystalline Form E of Dolasetron base comprises less than about 10% of crystalline Form B of Dolasetron base, more preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD.

[0074] The present invention further provides a process for preparing Dolasetron base Form E comprising crystallizing Dolasetron base from nitromethane.

[0075] The crystallization comprises providing a solution of Dolasetron base in nitromethane; and precipitating the said crystalline form of Dolasetron base.

[0076] The solution of Dolasetron base in nitromethane is provided by combining Dolasetron base and nitromethane, at a temperature of about 15°C to about 35°C, more preferably, at room temperature.

[0077] Preferably, precipitation is done by concentrating the solution to obtain a suspension. Typically, the solution is concentrated to induce crystallization, thus obtaining a suspension, which may be further cooled to increase the yield of the precipitated product. Preferably, the suspension is cooled to a temperature of about 0°C to about 10°C, more preferably of about 2°C to about 8°C. Preferably, cooling is conducted over a period of about 8 to about 24 hours, more preferably of about 10 to about 16 hours, most preferably overnight.

[0078] The process for preparing crystalline form E may further comprise recovering the crystalline form from the suspension. The recovery may be done by any method known to a skilled artisan. The recovery may be done for example by filtering the suspension, washing the filtered precipitate of the crystalline form and drying.

[0079] The present invention also provides a crystalline form of Dolasetron base, designated as chemically pure form F, characterized by a powder XRD pattern with peaks at 7.6, 12.1 and 13.7 ± 0.2 degrees 2-theta, and without one or more of the peaks selected from the group consisting of: 11, 14.8, and 22.2 ± 0.2 degrees 2-theta, and combination thereof. Preferably, the absent peaks at about 11, 14.8, and 22.2 ± 0.2 degrees 2-theta are absent when the analysis is done at a scan rate slow enough for detection, according to the common knowledge of the skilled in the art. The scan rate used may vary from instrument to instrument, and sample preparation. The peaks identified as absent peaks represent X-ray diffractions derived from one or more

chemical impurities in the Dolasetron base of the invention not from another crystalline form. As a result the crystalline Dolasetron base characterized by a powder XRD pattern with peaks at 7.6, 12.1 and 13.7 ± 0.2 degrees 2-theta, and without one or more of the peaks selected from the group consisting of: 11, 14.8, and 22.2 ± 0.2 degrees 2-theta represents a chemically pure crystalline form of Dolasetron base.

[0080] In addition, the chemically pure crystalline form F of Dolasetron base may be further characterized by a powder XRD pattern with peaks at 11.3, 16.5, 18.2, 19.9, 21.3, 27.8, and 28.5 ± 0.2 degrees 2-theta. The chemically pure crystalline Form F of Dolasetron base may also be without one or more of the peaks selected from the group consisting of: 9.4, 9.8, 10.4, 15.6, 16.1 and 35.8 ± 0.2 degrees 2-theta, and combination thereof. Preferably, the absent peaks at about 9.4, 9.8, 10.4, 15.6, 16.1 and 35.8 ± 0.2 degrees 2-theta are absent wherein the analysis is done at a scan rate slow enough to detect, according to the common knowledge of the skilled in the art. Also, chemically pure crystalline form F may also be substantially identified by the powder XRD pattern as depicted in figure 6. The crystalline form can be characterized by any other method known to a skilled artisan, such as Thermographic analysis (TGA or DSC), solid state NMR, and FTIR. The crystalline form is an anhydrous form of Dolasetron base.

[0081] The present invention further provides chemically pure crystalline Form F of Dolasetron base comprising less than about 10% of any other form of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Preferably, the chemically pure crystalline Form F of Dolasetron base comprises less than about 10% of any one of the crystalline forms A, B, C, D, and E of Dolasetron base, preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD. Most preferably, the chemically pure crystalline Form F of Dolasetron base comprises less than about 10% of at least one of the crystalline forms A and C of Dolasetron base, more preferably, less than about 5%, most preferably, less than about 1%, as measured by XRD.

[0082] The present invention provides a process for preparing chemically pure Dolasetron base Form F comprising crystallizing Dolasetron base from a mixture comprising tetrahydrofuran and water, and drying the crystalline product.

[0083] The crystallization comprises providing a solution of Dolasetron base in a mixture of tetrahydrofuran and water; and precipitating the said crystalline form of Dolasetron base.

[0084] The solution of Dolasetron base in a mixture of tetrahydrofuran and water is provided by combining Dolasetron base with a mixture of tetrahydrofuran and water; and heating the resulting mixture. Preferably, heating the resulting mixture is to a temperature of about 40°C to about the reflux temperature, preferably to a temperature of about 40°C to about 70°C.

[0085] Preferably, the tetrahydrofuran /water ratio is about 99:1 to about 80:20, more preferably about 95:5.

[0086] Preferably, precipitation is carried out by cooling the obtained solution to obtain a suspension comprising the said crystalline form. Cooling is, preferably, gradual. The gradual cooling comprises first cooling to a temperature of about 15°C to about 35°C, more preferably to about room temperature, and subsequently further cooling to a temperature of about 0°C to about 10°C, more preferably to about 2°C to about 8°C. Preferably, the subsequent cooling to a temperature of about 0°C to about 10°C, more preferably to about 2°C to about 8°C is carried out for a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours, most preferably overnight.

[0087] The resulting suspension is, preferably filtered, prior to drying the obtained crystalline form. Preferably, drying is done at a temperature of about 20°C to about 80°C, more preferably, at about 40°C. Preferably, the drying is done under reduced pressure. Preferably, drying is done for about 2 to about 24 hours.

[0088] The present invention further provides another process for the preparation of chemically pure Dolasetron base form F comprising heating crystalline Dolasetron base selected from the group consisting of: crystalline Dolasetron base Form D, crystalline Dolasetron base form B, and mixtures thereof, to a temperature of about 60°C to about 130°C. Preferably, heating of the crystalline Dolasetron base is to a temperature of about 80°C to about 120°C. Preferably, when the crystalline Dolasetron base form B is the starting material, heating of the crystalline Dolasetron base is to a temperature of about 80°C to about 100°C, more preferably to about 80°C. Preferably, when the crystalline Dolasetron base form D is the starting material, heating is to a temperature of about 110°C to about 130°C, more preferably to about 120°C. Preferably, when the starting material is crystalline form B, heating is

conducted for a period of about 1 to 24 hours, more preferably for about 10 to about 16 hours, most preferably overnight. Preferably, heating crystalline Dolasetron base form B is done under reduced pressure. Preferably, when the starting material is crystalline form D, heating is conducted for about 1 to about 24 hours, preferably for about 2 to about 16 hours, more preferably, for about 2 to about 5 hours.

[0089] The present invention provides an anhydrous crystalline Dolasetron base. Preferably, the anhydrous crystalline base is either Dolasetron base form A, Dolasetron base form C, or chemically pure Dolasetron base form F.

[0090] The present invention also provides a crystalline Dolasetron base monohydrate. Preferably, the crystalline Dolasetron base monohydrate is either Dolasetron base form B or Dolasetron base form D.

[0091] The present invention also provides a crystalline Dolasetron base nitromethane solvate. Preferably, the crystalline Dolasetron base nitromethane solvate is Dolasetron base form E.

[0092] The present invention provides a process for preparing a Dolasetron salt, comprising preparing one or more of the designated crystalline Forms A, B, C, D, E, or chemically pure crystalline form F of Dolasetron base and mixtures thereof and converting them to a Dolasetron salt. The conversion of Dolasetron base to Dolasetron salt may be carried out by reacting Dolasetron base with an acid. The reaction comprises, combining any of the designated crystalline Forms A, B, C, D, E, or chemically pure crystalline form F of Dolasetron base, preferably a mixture of forms B and D of Dolasetron base, methanesulfonic acid, and a solvent mixture comprising acetone and water. Preferably, the acid is methanesulfonic acid. Preferably, the Dolasetron salt is Dolasetron mesylate monohydrate. Preferably, methane sulfonic acid is added to a suspension of the Dolasetron base in a mixture comprising acetone and water. Preferably, the ratio of acetone and water is about 99:1 to about 80:20, preferably about 95:5.

[0093] Preferably, the addition of methane sulfonic acid transforms the suspension into a solution, in which a precipitate is formed after a few minutes.

[0094] The suspension is cooled to increase the yield of the precipitated Dolasetron mesylate monohydrate. Preferably, the suspension is cooled to a temperature of about 0°C to about 10°C, more preferably to about 2°C to about 8°C.

Preferably, cooling is conducted for a period of about an hour to about 24 hours, more preferably for about 2 to about 8 hours, most preferably for about 4 hours.

[0095] The process may further comprise recovering the Dolasetron mesylate monohydrate. The recovery may be done by any method known to a skilled artisan. Preferably, the recovery may be done for example by filtration of the cooled suspension, washing the filtered product, and drying it.

[0096] Further, as referenced herein peak positions from an X ray diffraction pattern have a variation of ± 0.2 degrees 2-theta. The accuracy of peak positions is defined as ± 0.2 degrees 2-theta due to experimental differences such as instrumentation, sample preparations etc.

[0097] Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way.

EXAMPLES

PXRD:

[0098] Powder X-ray diffraction ("PXRD") analysis using an ARL X-ray powder diffractometer model X'TRA-030, equipped with Peltier detector. The sample was introduced using round standard aluminum sample holder with round zero background quartz plate. Scanning parameters: Range: 2-40 deg. 2 θ , continuous Scan, Rate: 3 deg./min. The accuracy of peak positions is defined as ± 0.2 degrees due to experimental differences like instrumentations, sample preparations etc.

Differential Scanning Calorimetry (DSC)

[0099] DSC 822^c/700, Mettler Toledo, Sample weight: 3-5 mg.
Heating rate: 10 °C/min., Number of holes of the crucible: 3
In N₂ stream: flow rate = 40 ml/min
Scan range: 30-250°C, 10°C/ minutes heating rate.

Thermal Gravimetric Analysis (TGA)

[00100] TGA/SDTA 851^c, Mettler Toledo, Sample weight 7-15 mg.
Heating rate: 10°C/ min., In N₂ stream: flow rate = 50 ml/min
Scan range: 30-250°C.

Example 1: Preparation of Dolasetron base Form A

[00101] Dolasetron base (*B+D*) (70 g) was dissolved in iso-butyl acetate (2.2 l) at 100°C. Charcoal (7 g) was added to the solution, and after 10 minutes of stirring it was filtered off, and washed with iso-butyl acetate (0.2 l). The solution was evaporated under reduced pressure to obtain a residue weighing 0.5 kg, which was allowed to cool to room temperature, and then further cooled overnight in a fridge. The precipitated crystals were filtered off, washed with iso-butyl acetate (2×40 ml), and dried overnight at 40°C under reduced pressure. Polymorphism was determined by X-ray diffraction. Wet and dry sample were form A.

Example 2: Preparation of Dolasetron base Form B

[00102] Indole-3-carboxylic acid (56.02 g) was added in portions to a solution of trifluoroacetic anhydride (49.1 ml) in dry methylene chloride (2.7 L), at room temperature, during 15 minutes. After 5-minutes of stirring, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (48.46 g), and then 4-dimethylaminopyridine (0.33 g) were added (both in one portion). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by 10% of an aqueous solution of sodium carbonate (0.8 L). Methylene chloride was removed by evaporation under reduced pressure. The precipitated Dolasetron base was collected by filtration, washed with water (3×0.5 L), and dried overnight at 40°C under reduced pressure. The dry product weighed 88.4 g. Polymorphism was determined by X-ray diffraction.

Example 3: Preparation of Dolasetron base Form C

[00103] Dolasetron base (0.50 g) was dissolved in ethyl acetate (20 ml) at 60°C. n-Hexane (40 ml) was added to this solution, and then allowed to cool to room temperature. After 2-hour of standing at room temperature, the precipitated crystals were filtered off, and dried overnight at room temperature under normal pressure. Polymorphism was determined by X-ray diffraction.

Example 4: Preparation of Dolasetron base Form D

[00104] Dolasetron base (0.50 g) was dissolved in a mixture of acetonitrile-water 95:5 (10 ml) at reflux temperature. The solution was allowed to cool to room temperature, and then further cooled overnight in a fridge. The precipitated crystals were filtered off, and dried overnight at 40°C under reduced pressure. Polymorphism was determined by X-ray diffraction. Wet and dry samples were form D.

Example 5: Preparation of Dolasetron base Form D

[00105] Dolasetron base Form A (1.0 g) was suspended in a mixture of acetone-water 95:5 (10 ml) and stirred overnight at room temperature. The product was filtered off, obtained 0.75 g. Polymorphism is determined by X-ray diffraction. The crystal form of the sample was found form D.

Example 6: Preparation of a mixture of Dolasetron base Form B and D

[00106] Indole-3-carboxylic acid (39.71g) was added in portions to a solution of trifluoroacetic anhydride (44.3 ml) in dry methylene chloride (2.24 L), at room temperature, during 15 minutes. After 5-minutes of stirring, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (40.59 g), and then 4-dimethylaminopyridine (0.27 g) were added (both in one portion). The reaction mixture was stirred for 2 hours at room temperature. Additional (22 ml) trifluoroacetic anhydride was added in one portion. After 2 hours of stirring, the reaction was quenched by 10% of an aqueous solution of sodium carbonate (0.84 L). Methylene chloride was removed by evaporation under reduced pressure. The precipitated Dolasetron base was collected by filtration, washed with water (3×0.5 L), and dried overnight at 40°C under reduced pressure. The dry product weighed 70.36 g. Polymorphism was determined by X-ray diffraction.

Example 7: Preparation of Dolasetron base Form E

[00107] Dolasetron base (0.50 g) was dissolved in nitromethane (19 ml) at room temperature. The solution was evaporated to small volume under reduced pressure, until crystallization started. Then, it was allowed to cool to room temperature, followed by further cooling in a fridge for overnight. The precipitated crystals were filtered off, and dried overnight at 40°C under reduced pressure. Polymorphism was determined by X-ray diffraction. Wet and dry sample were form E.

Example 8: Preparation of Dolasetron base chemically pure Form F

[00108] Dolasetron base (0.50 g) was dissolved in a mixture of tetrahydrofuran-water 95:5 (5 ml) at reflux temperature. The solution was allowed to cool to room temperature, and then put into fridge overnight. The precipitated crystals were filtered off, and dried overnight at 40°C under reduced pressure. Polymorphism was determined by X-ray diffraction. Dry sample was chemically pure Form F.

Example 9: Preparation of chemically pure Form F by heating Form D

[00109] Dolasetron base form D (100 mg) was heated in an oven at 120°C for 2 hours. It was cooled down and measured by XRD and DSC.

Example 10: Preparation of Dolasetron base chemically pure Form F by heating Form B

[00110] Dolasetron base Form B (1.2 g) was dried overnight at 80°C under reduced pressure. The dry product was 1.14 g Polymorphism was determined by X-ray diffraction.

Example 11: Preparation of DLS-MsOH monohydrate

[00111] Methanesulfonic acid (2.85 ml, 1 equiv) was added to a stirred suspension of Dolasetron base (14.24 g, 43.9 mmol), A, B C, D, E or F in a mixture of acetone-water 95:5 (100 ml). The solid dissolved immediately, after some minutes the salt precipitated in crystalline form. The mixture was put into fridge, after 4 hours the salt was filtered off, washed with same solvent mixture (2×15 ml), and dried overnight in an air-ventilated oven at 40°C. The yield was 15.63 g (81 %).

Example 12: Preparation of a mixture of Dolasetron base Form D and B

[00112] Indole-3-carboxylic acid (17.7 g, 1.1 equiv.) was added in portions to a solution of trifluoroacetic anhydride (20 ml, 1.4 equiv.) in a mixture of toluene (360 ml) and trifluoroacetic acid (90 ml), at room temperature (20-25°C), during 15 minutes. After 5-minutes of stirring, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]-undecan-10-one (18.12 g, 0.1 mol), was added in one portion. The reaction mixture heated to 30-35°C, and the solid phase dissolved. The solution was stirred for 2 hours without external heating. The trifluoroacetic acid was removed by evaporation under reduced pressure until starting of crystallization. 10% of an aqueous solution of sodium carbonate (360 ml) was added, then toluene was removed by evaporation under reduced pressure. The precipitated Dolasetron base monohydrate was collected by filtration, washed with water (3×60 ml), and dried overnight at 40°C under reduced pressure. The dry product was weighed as 33.63 g (98% yield).

CLAIMS

1. A crystalline Dolasetron base characterized by a powder XRD pattern with peaks at about 12.9, 14.1, and 15.2 ± 0.2 degrees 2-theta.
2. The crystalline Dolasetron base of claim 1, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 7.6, 16.2, 16.5, 18.8, 21.2, 22.8, 26.9 ± 0.2 degrees 2-theta.
3. The crystalline Dolasetron base of claim 2, wherein the crystalline form is further characterized by the powder XRD pattern as depicted in figure 1.
4. The crystalline Dolasetron base of any one of the previous claims, wherein the crystalline form is further characterized by a weight loss of less than about 0.1% at temperatures up to about 100°C, as measured by TGA.
5. The crystalline Dolasetron base of any one of the previous claims, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at about 234°C.
6. The crystalline Dolasetron base of any one of the previous claims, wherein the crystalline form is an anhydrous form of the Dolasetron base.
7. The crystalline Dolasetron base of any one of the previous claims, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron base as measured by XRD.
8. The crystalline Dolasetron base of claim 7, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms B, C, D, E, and chemically pure crystalline form F of Dolasetron base.
9. A method for preparing crystalline form A of Dolasetron base comprising crystallizing Dolasetron base from iso-butyl acetate.
10. The method of claim 9, wherein the crystallization comprises providing a solution of Dolasetron base in iso-butyl acetate; and precipitating the said crystalline form of Dolasetron base.

11. The method of claim 10, wherein the solution of Dolasetron base in iso-butyl acetate is provided by combining the starting Dolasetron base and iso-butyl acetate, and heating the combination.
12. The method of claim 11, wherein the heating is to a temperature of about 40°C to about 120°C.
13. The method of any one of claims 10 and 11, wherein the precipitation is carried out by a process comprising concentrating the solution, and cooling the concentrated solution to obtain a suspension comprising of the said crystalline form of Dolasetron base.
14. The method of claim 13, wherein the cooling comprises first cooling to a temperature of about 15°C to about 35°C, and further cooling to a temperature of about 0°C to about 10°C.
15. A crystalline form of Dolasetron base characterized by a powder XRD pattern with peaks at about 13.6, 16.4, and 23.4. $\pm$ 0.2 degrees 2-theta.
16. The crystalline Dolasetron base of claim 15, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 9.4, 10.4, 14.9, 15.5, 17.9, 18.8, 28.4 $\pm$ 0.2 degrees 2-theta.
17. The crystalline Dolasetron base of claim 16, wherein the crystalline form is further characterized by the powder XRD pattern as depicted in figure 2.
18. The crystalline Dolasetron base of any one of claims 15 to 17, wherein the crystalline form is further characterized by a weight loss of about 5.5% at temperatures up to about 140°C, as measured by TGA.
19. The crystalline Dolasetron base of any one of claims 15 to 18, wherein the crystalline form is further characterized by a DSC thermogram having a first endothermic peak at about 140°C and a second at 226°C.
20. The crystalline Dolasetron base of any one of claims 15 to 19, wherein the crystalline form is a Dolasetron base monohydrate.

21. The crystalline Dolasetron base of any one of claims 15 to 20, wherein the crystalline form has an amount of water of about 5.2% by weight as measured by KF.
22. The crystalline Dolasetron base of any one of claims 15 to 21, wherein the crystalline form is with less than about 10% of any other form of Dolasetron base as measured by XRD.
23. The crystalline Dolasetron base of claim 22, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms A, C, D, E, and chemically pure crystalline form F of Dolasetron base.
24. A method of preparing crystalline form B of Dolasetron base, comprising combining Indole-3-carboxylic acid, an anhydride, a C₁₋₂ halogenated hydrocarbon, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (referred to as HQO) and a catalyst to form a reaction mixture; quenching the reaction with an inorganic base; and removing the C₁₋₂ halogenated hydrocarbon from the reaction mixture to obtain a suspension comprising of the said crystalline form.
25. The method of claim 24, wherein the C₁₋₂ halogenated hydrocarbon is methylene chloride, the anhydride is trifluoroacetic anhydride, and the catalyst is 4-dimethylaminopyridine (DMAP).
26. The method of claim 25, wherein the Indole-3-carboxylic acid is added to a solution of trifluoroacetic anhydride in methylenechloride at a temperature of about 15°C to about 35°C, prior to the addition of HQO and DMAP.
27. The method of any one of claims 24 to 26, wherein the reaction mixture is maintained at a temperature of about 15°C to about 35°C, after the addition of HQO and catalyst, for a period of about 8 to about 24 hours.
28. The method of any one of claims 24 to 27, wherein the reaction is quenched with an aqueous solution of an inorganic base.

29. The method of claim 28, wherein the inorganic base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.
30. A crystalline Dolasetron base characterized by a powder XRD pattern with peaks at about 8.2, 11.7, 13.9 ± 0.2 degrees 2-theta.
31. The crystalline Dolasetron base of claim 30, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 12.8, 15.0, 16.4, 16.8, 17.1, 18.1, 25.3 ± 0.2 degrees 2-theta.
32. The crystalline Dolasetron base of claim 31, wherein the crystalline form is further characterized by the powder XRD pattern as depicted in figure 3.
33. The crystalline Dolasetron base of any one of claims 30 to 32, wherein the crystalline form is further characterized by a weight loss of less than about 0.1% at temperatures up to about 133°C, as measured by TGA.
34. The crystalline Dolasetron base of any one of claims 30 to 33, wherein the crystalline form is further characterized by a DSC thermogram having a first endothermic peak at about 220°C and a second at 234°C, and an exothermic peak at about 223°C.
35. The crystalline Dolasetron base of any one of claims 30 to 34, wherein the crystalline form is an anhydrous form of Dolasetron base.
36. The crystalline Dolasetron base of any one of claims 30 to 35, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron base as measured by XRD.
37. The crystalline Dolasetron base of claim 36, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms A, B, D, E, and chemically pure crystalline form F of Dolasetron base.
38. A method for preparing crystalline form C of Dolasetron base comprising crystallizing Dolasetron base from a solvent mixture comprising ethyl acetate and *n*-Hexane in a ratio of about 1:2 to about 1:8.

39. The method of claim 38, wherein the crystallization comprises providing a solution of Dolasetron base in a solvent mixture of ethylacetate and n-hexane in a ratio of about 1:2 to about 1:8; and precipitating the said crystalline form of Dolasetron base.
40. The method of claim 39, wherein the solution of Dolasetron base in the solvent mixture of ethylacetate and n-hexane is provided by combining the starting Dolasetron base and ethyl acetate; heating the mixture of the Dolasetron base and ethylacetate to obtain a first solution, and adding to the first solution n-hexane to obtain the said solution.
41. The method of claim 40, wherein heating is to a temperature of about room temperature to about 70°C.
42. The method of any one of claims 39 to 41, wherein the precipitation is done by cooling the said solution to obtain a suspension comprising of the said crystalline form of Dolasetron base.
43. The method of claim 42, wherein the solution is cooled to a temperature of about 15°C to about 35°C, providing the suspension..
44. A crystalline Dolasetron base characterized by a powder XRD pattern with peaks at about 14.3, 16.1, 16.5 and 18.5 ± 0.2 degrees 2-theta.
45. The crystalline Dolasetron base of claim 44, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 9.3, 17.5, 21.4, 24.6, 27.9, 28.5 ± 0.2 degrees 2-theta.
46. The crystalline Dolasetron base of claim 45, wherein the crystalline form is further characterized by a powder XRD pattern as depicted in figure 4.
47. The crystalline Dolasetron base of any one of claims 44 to 46, wherein the crystalline form is further characterized by a weight loss of about 5.3% at temperatures up to about 144°C, as measured by TGA.
48. The crystalline Dolasetron base of any one of claims 44 to 47, wherein the crystalline form is further characterized by a DSC thermogram having a first

endothermic peak at about 130°C, a second at 229°C, and a third endothermic peak at about 235°C, and an exothermic peak at about 232°C.

49. The crystalline Dolasetron base of any one of claims 44 to 48, wherein the crystalline form is a Dolasetron base monohydrate.
50. The crystalline Dolasetron base of any one of claims 44 to 49, wherein the crystalline form has an amount of water of about 5.2% by weight as measured by KF.
51. The crystalline Dolasetron base of any one of claims 44 to 50, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron base as measured by XRD.
52. The crystalline Dolasetron base of claim 51, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms A, B, C, E, and chemically pure crystalline form F of Dolasetron base.
53. A method for preparing the crystalline form D of Dolasetron base comprising crystallizing Dolasetron base from a solution of a solvent selected from a solvent mixture of acetonitrile and water.
54. The method of claim 53, wherein the crystallization comprises providing a solution of Dolasetron base in a solvent mixture of acetonitrile and water; and precipitating the said crystalline form of Dolasetron base.
55. The method of claim 54, wherein the solution of Dolasetron base in a solvent mixture of acetonitrile and water is provided by combining the starting Dolasetron base and water; and heating the mixture.
56. The method of claim 55, wherein heating is to a temperature of about room temperature to about 85°C.
57. The method of any one of claims 54 to 56, wherein the precipitation is done by cooling the solution to obtain a suspension comprising of the said crystalline form of Dolasetron base.

58. The method of claim 57, wherein cooling is to a temperature of about 15°C to about 35°C, and further cooling to a temperature of about 0°C to about 10°C.
59. A method for preparing crystalline form D of Dolasetron base comprising suspending Dolasetron base Form A in a mixture comprising acetone and water.
60. The method of claim 59, wherein the suspension is provided at about 15°C to about 55°C.
61. A method of preparing a mixture of the crystalline forms B and D of Dolasetron base, comprising combining Indole-3-carboxylic acid, an anhydride, an organic solvent, HQO and a catalyst forming a reaction mixture; quenching the reaction with an inorganic base by addition of the inorganic base to the reaction mixture; and removing the organic solvent from the reaction mixture.
62. The method of claim 61, wherein the organic solvent is methylene chloride, the anhydride is trifluoroacetic anhydride, the catalysts is 4-dimethylaminopyridine (DMAP), and after adding HQO and DMAP an additional amount of trifluoroacetic anhydride is added prior to quenching the reaction mixture.
63. The method of claim 62, wherein Indole-3-carboxylic acid is added to a solution of trifluoroacetic anhydride in methylenechloride, prior to the addition of HQO and DMAP.
64. The method of claim 63, wherein the addition is done at a temperature of about 15°C to about 35°C.
65. The method of any one of claims 62 to 64, wherein the reaction mixture is maintained at a temperature of about 15°C to about 35°C, after the addition of HQO and DMAP, for a period of about 1 to about 4 hours.
66. The method of any one of claims 62 to 65, wherein trifluoroacetic anhydride is added in one portion, prior to quenching.
67. The method of claim 61, wherein the organic solvent is a mixture of toluene and trifluoroacetic acid, the anhydride is trifluoroacetic anhydride, and wherein the catalyst is not added to the reaction mixture.

68. The method of claim 67, wherein Indole-3-carboxylic acid is added to a solution of trifluoroacetic anhydride in a mixture of toluene and trifluoroacetic acid, prior to the addition of HQO.
69. The method of claim 68, wherein the addition is done at a temperature of about 15°C to about 35°C.
70. The method of any one of claims 67 to 69, wherein prior to quenching, the temperature is maintained at about 15°C to about 35°C.
71. The method of any one of claims 61 to 70, wherein the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.
72. A crystalline Dolasetron base, characterized by a powder XRD pattern with peaks at about 13.9, 16.9, and 21.8 ± 0.2 degrees 2-theta.
73. The crystalline Dolasetron base of claim 72, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 6.5, 8.0, 10.3, 10.8, 14.6, 19.4, 21.4 ± 0.2 degrees 2-theta.
74. The crystalline Dolasetron base of claim 73, wherein crystalline form is further characterized by the powder XRD pattern as depicted in figure 5.
75. The crystalline Dolasetron base of any one of claims 72 to 74, wherein the crystalline form is further characterized by a weight loss of about 6.4% at temperatures up to about 145°C, as measured by TGA.
76. The crystalline Dolasetron base of any one of claims 72 to 75, wherein the crystalline form is further characterized by a DSC thermogram having a first endothermic peak at about 94°C, a second at 225°C, and a third endothermic peak at about 235°C.
77. The crystalline Dolasetron base of any one of claims 72 to 76, wherein the crystalline Dolasetron base is a nitromethane solvate.

78. The crystalline Dolasetron base of claim 77, wherein the crystalline form has an amount of nitromethane of about 6.5% to about 8%, by weight as measured by TGA.
79. The crystalline Dolasetron base of any one of claims 72 to 78, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron base as measured by XRD.
80. The crystalline Dolasetron base of claim 79, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms A, B, C, D, and chemically pure crystalline form F of Dolasetron base.
81. A method for preparing crystalline form E of Dolasetron base comprising crystallization of Dolasetron base from nitromethane.
82. The method of claim 81, wherein the crystallization comprises providing a solution of Dolasetron base in nitromethane; and precipitating the said crystalline form of Dolasetron base.
83. The method of claim 82, wherein the solution of Dolasetron base in nitromethane is provided by combining Dolasetron base and nitromethane, at a temperature of about 15°C to about 35°C.
84. The method of any one of claims 82 and 83, wherein the precipitation is done by concentrating the solution to obtain a suspension.,
85. The method of claim 84, wherein the suspension is cooled to a temperature of about 0°C to about 10°C.
86. A crystalline Dolasetron base characterized by a powder XRD pattern with peaks at about 7.6, 12.1 and 13.7 ± 0.2 degrees 2-theta and without one or more of the peaks selected from the group consisting of: 11, 14.8, and 22.2 ± 0.2 degrees 2-theta, wherein the crystalline Dolasetron base is chemically pure.
87. The crystalline Dolasetron base of claim 86, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 11.3, 16.5,

18.2, 19.9, 21.3, 27.8, 28.5 ± 0.2 degrees 2-theta and without one or more of the peaks at about 9.4, 9.8, 10.4, 15.6, 16.1 and 35.8 ± 0.2 degrees 2-theta.

88. The crystalline Dolasetron base of any one of claims 86 and 87, wherein the crystalline form is further characterized by powder XRD pattern as depicted in figure 6.
89. The crystalline Dolasetron base of any one of claims 86 to 88, wherein the crystalline form of Dolasetron base is an anhydrous form.
90. The crystalline Dolasetron base of any one of claims 86 to 89, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron base as measured by XRD.
91. The crystalline Dolasetron base of claim 90, wherein the crystalline form comprises less than about 10% of any one of the crystalline forms A, B, C, D, and E of Dolasetron base.
92. A method for preparing chemically pure crystalline form F of Dolasetron base comprising crystallizing Dolasetron base from a mixture comprising tetrahydrofuran and water forming a crystalline material product; and drying the crystalline product.
93. The method of claim 92, wherein the crystallization comprises providing a solution of Dolasetron base in a mixture of tetrahydrofuran and water, and precipitating the said crystalline form of Dolasetron base.
94. The method of claim 93, wherein the solution of Dolasetron base in a mixture of tetrahydrofuran and water is provided by combining Dolasetron base and a mixture of tetrahydrofuran and water, and heating the resulting mixture.
95. The method of claim 94, wherein heating is to a temperature of about 40°C to about the reflux temperature.
96. The method of any one of claims 93 to 95, wherein the precipitation is done by cooling the obtained solution to obtain a suspension comprising of the said crystalline form.

97. The method of claim 96, wherein cooling comprises first cooling to a temperature of about 15°C to about 35°C, and further cooling to a temperature of about 0°C to about 10°C.
98. The method of any one of claims 92 to 97, wherein drying the crystal product is at a temperature of about 20°C to about 80°C.
99. A method for preparing chemically pure crystalline form F of Dolasetron base comprising heating a Dolasetron base selected from the group consisting of the crystalline Dolasetron base Form D, crystalline Dolasetron base form B and mixtures thereof, to a temperature of about 60°C to about 130°C.
100. The method of claim 99, wherein heating is to a temperature of about 80°C to about 120°C.
101. An anhydrous crystalline Dolasetron base.
102. A crystalline Dolasetron base monohydrate.
103. A crystalline Dolasetron base nitromethane solvate.
104. A method for preparing a Dolasetron salt, comprising preparing one or more of the crystalline Forms A, B, C, D, E, or chemically pure crystalline form F of Dolasetron base, and mixtures thereof, and converting the crystalline Dolasetron base to a Dolasetron salt.
105. The method of claim 104, wherein converting the crystalline Dolasetron base to a Dolasetron salt comprises combining crystalline Dolasetron base with methanesulfonic acid.
106. The method of any one of claims 104 and 105, wherein the Dolasetron salt is Dolasetron mesylate monohydrate.

FIGURES

Fig.1. XRD pattern of Dolasetron base form A

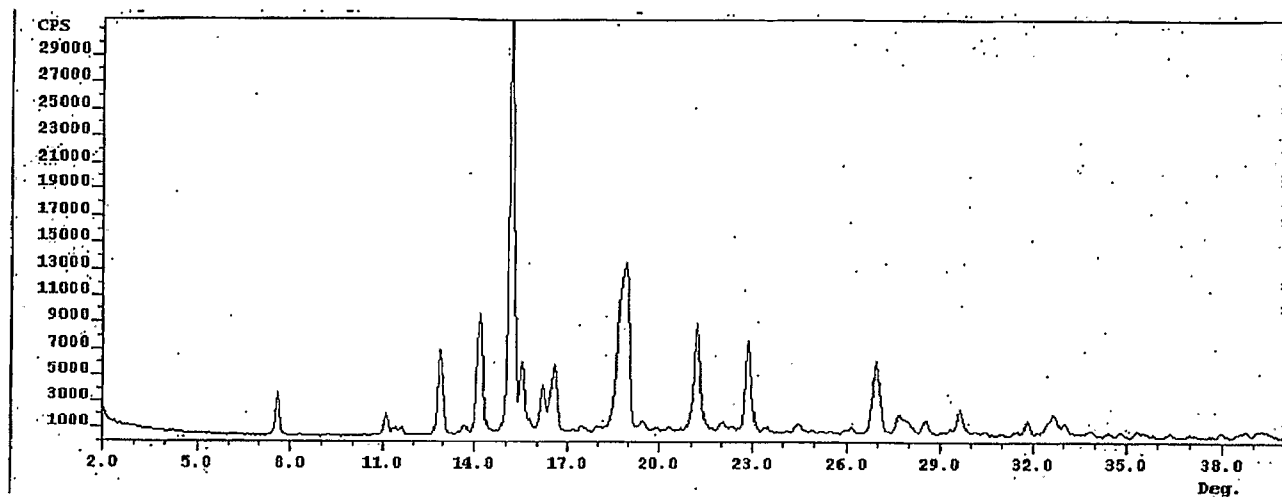


Fig.2. XRD pattern of Dolasetron base form B

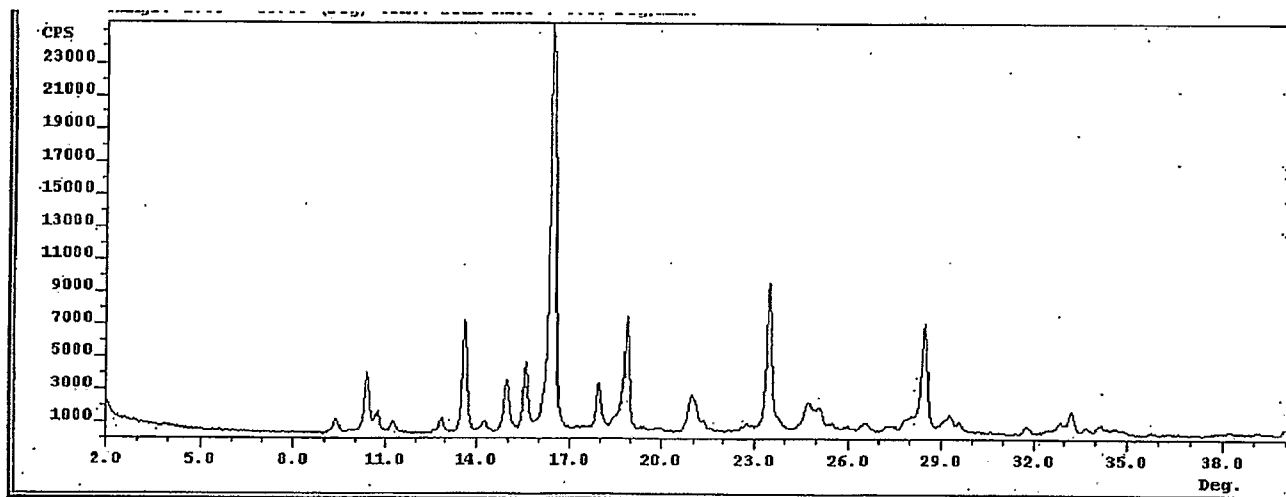


Fig.3. XRD pattern of Dolasetron base form C

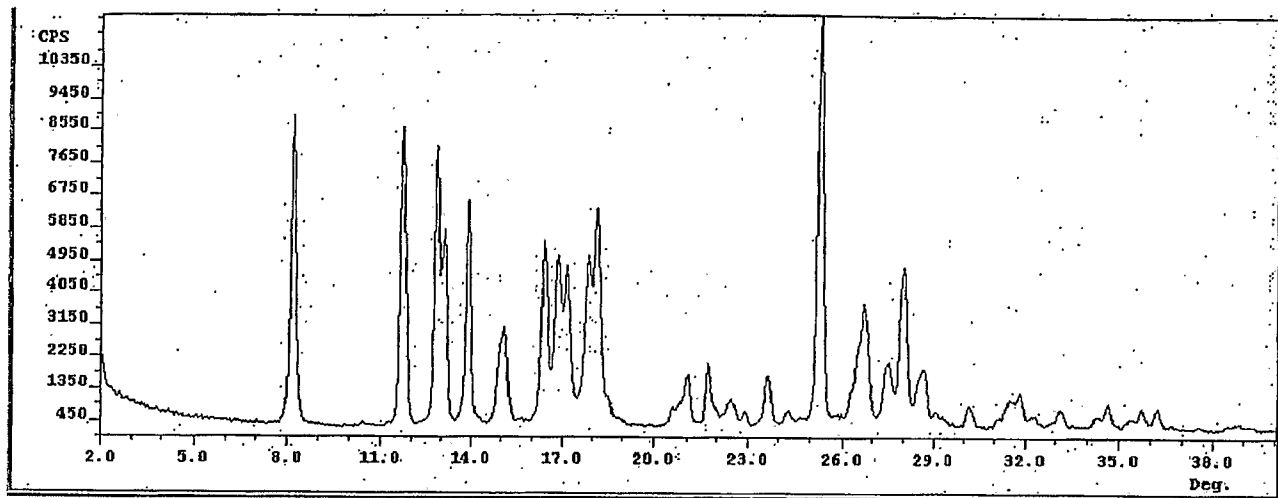


Fig.4. XRD pattern of Dolasetron base form D

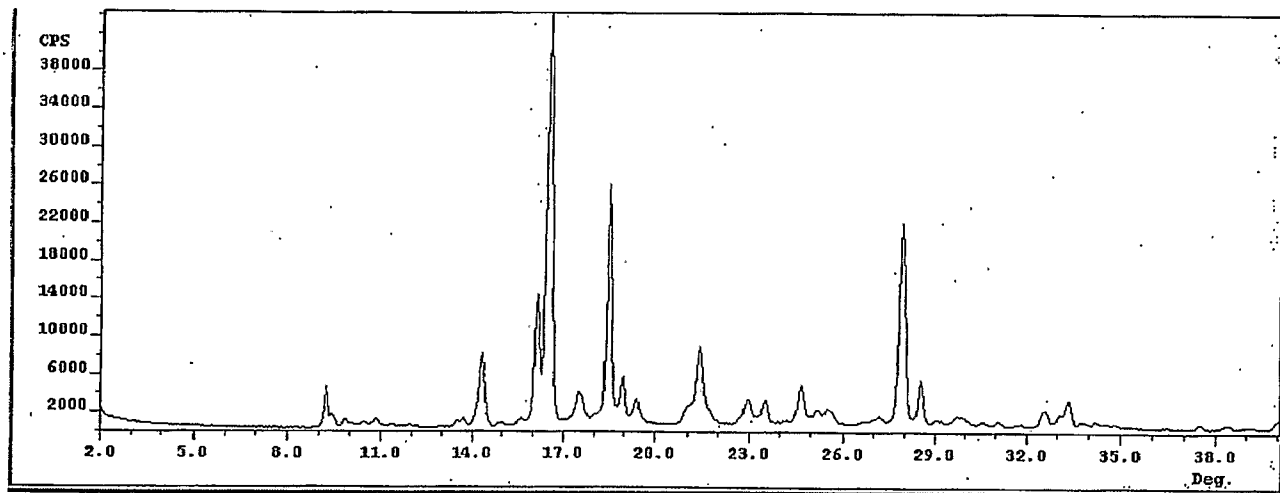


Fig.5. XRD pattern of Dolasetron base form E

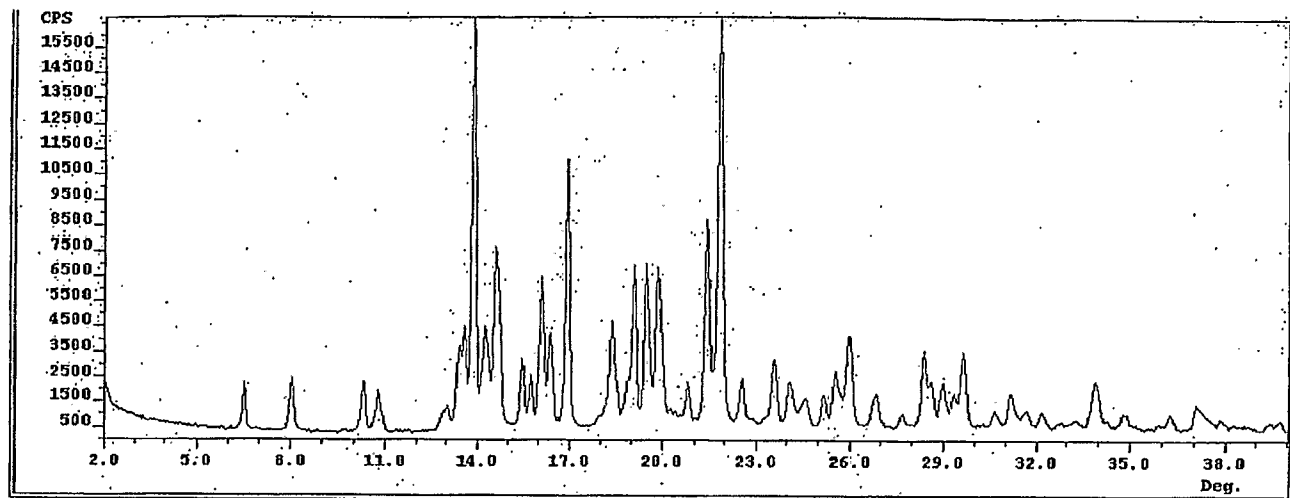


Fig.6. XRD pattern of Dolasetron base form F

