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(54) Title: FORMS OF DOLASETRON MESYLATE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention provides crystalline polymorphic forms of Dolasetron mesylate. Also provided are methods of preparing the crystalline polymorphic forms of Dolasetron mesylate. Further, the crystalline Dolasetron mesylate forms may be used in pharmaceutical compositions.

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FORMS OF DOLASETRON MESYLATE AND PROCESSES FOR THEIR PREPARATION

CROSS REFERENCE TO RELATED APPLICATIONS

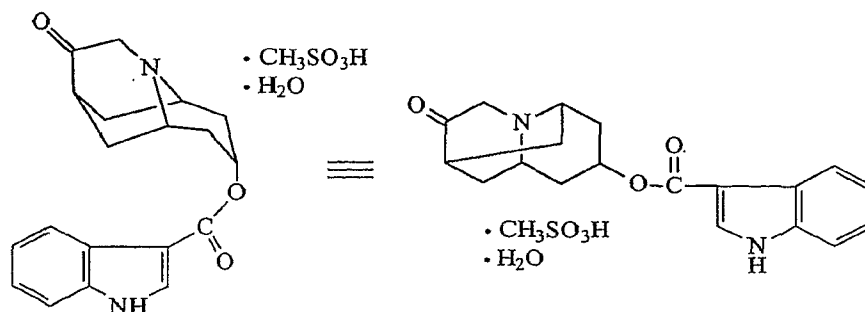
[0001] The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/756,690, filed January 5, 2006; 60/800,884, filed May 15, 2006; 60/838,758, filed August 17, 2006; 60/861,354, filed November 27, 2006; 60/802,842, filed May 22, 2006; 60/818,934, 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 encompasses the solid state chemistry of Dolasetron Mesylate.

BACKGROUND OF THE INVENTION

[0003] 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,



[0004] Dolasetron Mesylate monohydrate is a serotonin receptor (5-HT₃) antagonist used as an antiemetic and antinauseant agent in chemo- and radiotherapies.

[0005] 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®.

[0006] EP patent No. 0339669 describes the crystallization of DLS-MsOH·H₂O (monohydrate) from an aqueous isopropanol-ether mixture.

[0007] EP patent No. 0266730 describes the crystallization of DLS-MsOH.

[0008] The present invention relates to the solid state physical properties of Dolasetron mesylate. These properties can be influenced by controlling the conditions under which Dolasetron mesylate is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

[0009] Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

[0010] These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance that can be identified unequivocally by X-ray spectroscopy. The polymorphic form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by solid state ¹³C NMR spectrometry and infrared spectroscopy.

[0011] The present invention also relates to solvates of Dolasetron mesylate. When a substance crystallizes out of solution, it may trap molecules of solvent at regular intervals in the crystal lattice. Solvation also affects utilitarian physical properties of the solid state like flowability and dissolution rate.

[0012] One of the most important physical properties of a pharmaceutical compound, which can form polymorphs or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

[0013] The discovery of new polymorphic forms and solvates of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

SUMMARY OF THE INVENTION

[0014] In one embodiment, the present invention encompasses a crystalline form of Dolasetron Mesylate characterized by a powder XRD pattern with peaks at about 12.6, 18.2, and 19.6 ± 0.2 degrees two-theta.

[0015] In another embodiment the present invention encompasses an amorphous form of Dolasetron mesylate.

[0016] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 14.0, 14.8, 16.1, and 18.2 ± 0.2 degrees 2-theta.

[0017] In one embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 13.8, 16.5, 22.1, and 25.2 ± 0.2 degrees 2-theta.

[0018] In another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 13.0, 18.6 and 29.4 ± 0.2 degrees 2-theta.

[0019] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.9, 15.2, and 16.0 ± 0.2 degrees 2-theta.

[0020] In one embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 10.1, 16.3, and 22.6 ± 0.2 degrees 2-theta.

[0021] In another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.8, 18.3, and 27.9 ± 0.2 degrees 2-theta.

[0022] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.4, 17.7 and 27.1 ± 0.2 degrees 2-theta.

[0023] In one embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 14.1, 14.9, 16.2 and 18.2 ± 0.2 degrees 2-theta.

[0024] In another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 14.7, 17.6 and 18.2 ± 0.2 degrees 2-theta.

[0025] In yet another embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.1, 15.0 and 18.1 ± 0.2 degrees 2-theta.

[0026] In one embodiment the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 17.4, 17.9 and 22.1 ± 0.2 degrees 2-theta.

[0027] In another embodiment, the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 12.2, 14.1, 14.8, 16.3 and 22.2 ± 0.2 degrees 2-theta.

[0028] In yet another embodiment, the present invention encompasses a crystalline form of Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 12.1, 14.0, 14.8 15.1 and 22.1 ± 0.2 degrees 2-theta.

[0029] In one embodiment, the present invention also provides an alcoholate solvate of Dolasetron mesylate.

[0030] In another embodiment, the present invention provides an anhydrous Dolasetron mesylate.

[0031] In yet another embodiment, the present invention also provides a ketone solvate of Dolasetron mesylate.

[0032] In another embodiment, the present invention provides a carbonate solvate of Dolasetron mesylate.

[0033] In another embodiment, the present invention also provides an ether solvate of Dolasetron mesylate.

[0034] In another embodiment, the present invention provides an ester solvate of Dolasetron mesylate.

[0035] In another embodiment, the present invention also provides a nitromethane solvate of Dolasetron mesylate.

[0036] In another embodiment, the present invention also provides a hydrated Dolasetron mesylate.

[0037] In one embodiment, the present invention encompasses a process for preparing a crystalline form of Dolasetron mesylate, designated form II, comprising combining Dolasetron base, methanesulfonic acid, and a solvent mixture comprising acetone, and water.

[0038] In yet another embodiment, the present invention comprises a pharmaceutical composition comprising at least one of the above forms of Dolasetron Mesylate, and at least one pharmaceutically acceptable excipient.

[0039] In yet another embodiment, the present invention comprises a pharmaceutical composition comprising at least one of the above forms of Dolasetron Mesylate prepared according to the processes of the present invention, and at least one pharmaceutically acceptable excipient.

[0040] In one embodiment, the present invention further encompasses a process for preparing a pharmaceutical formulation comprising combining at least one of the above forms of Dolasetron Mesylate with at least one pharmaceutically acceptable excipient.

[0041] In another embodiment, the present invention comprises a process for preparing a pharmaceutical composition comprising at least one of the above forms of Dolasetron Mesylate, prepared according to the processes of the present invention, and at least one pharmaceutically acceptable excipient.

[0042] In yet another embodiment, the present invention further encompasses the use of at least one of the above forms of Dolasetron Mesylate, for the manufacture of a pharmaceutical composition.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a powder XRD pattern for crystalline form I of Dolasetron Mesylate.

Figure 2 shows a DSC thermogram for crystalline form I of Dolasetron Mesylate.

Figure 3 shows a TGA thermogram for crystalline form I of Dolasetron Mesylate.

Figure 4 shows a powder XRD pattern for dried Dolasetron mesylate prepared according to EP patent No. 0339669.

Figure 5 shows a powder XRD pattern of the amorphous form of Dolasetron mesylate.

Figure 6 shows a powder XRD pattern of crystalline form III of Dolasetron mesylate.

Figure 7 shows a powder XRD pattern of crystalline form IV of Dolasetron mesylate.

Figure 8 shows a powder XRD pattern of crystalline form V of Dolasetron mesylate.

Figure 9 shows a powder XRD pattern of crystalline form VI of Dolasetron mesylate.

Figure 10 shows a powder XRD pattern of crystalline form VIII of Dolasetron mesylate.

Figure 11 shows a powder XRD pattern of crystalline form IX of Dolasetron mesylate.

Figure 12 shows a powder XRD pattern of crystalline form X of Dolasetron mesylate.

Figure 13 shows a powder XRD pattern of crystalline form XI of Dolasetron mesylate.

Figure 14 shows a powder XRD pattern of crystalline form XII of Dolasetron mesylate.

Figure 15 shows a powder XRD pattern of crystalline form XIII of Dolasetron mesylate.

Figure 16 shows a powder XRD pattern of crystalline form XIV of Dolasetron mesylate.

Figure 17 shows a powder XRD pattern of crystalline form XV of Dolasetron mesylate.

Figure 18 shows a powder XRD pattern of crystalline form XVI of Dolasetron mesylate.

DETAILED DESCRIPTION

[0043] As used herein, the term “anhydrous” refers to a substance that contains no more than 1%, preferably no more than 0.6%, by weight of water or of any solvent.

[0044] As used herein the term "room temperature" refers to a temperature of about 20°C to about 30°C.

[0045] The EP 0339699 describes preparing a crystalline Dolasetron mesylate. This crystalline Dolasetron mesylate is designated herein as crystalline form II of Dolasetron mesylate. The crystalline form II of Dolasetron mesylate is characterized by a powder XRD pattern of with peaks at about 12.1, 12.9, 15.1, and 22.4 ± 0.2 degrees two-theta. The crystalline form II may be further characterized by a powder X-ray diffraction pattern with peaks at about 9.9, 17.0, 19.0, 19.7, 20.0, and 26.4 ± 0.2 degrees two-theta

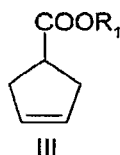
[0046] The present invention encompasses a crystalline form of Dolasetron Mesylate, designated form I, characterized by a powder XRD pattern with peaks at about 12.6, 18.2, and 19.6 ± 0.2 degrees two-theta. The crystalline form may be further characterized by a powder X-ray diffraction pattern with peaks at about 9.9, 13.8, 16.6, 21.1, 23.3, 27.9, and 29.6 ± 0.2 degrees two-theta. The crystalline form may also be substantially identified by the PXRD pattern as depicted in Figure 1. The above crystalline form may be further characterized by a DSC thermogram with endothermic peaks at about 160°C, and at 180°C, due to desolvation and a third peak at 209°C due to melting. Also, the crystalline form may be substantially identified by the DSC curve as depicted in Figure 2. In addition, the crystalline form may be further characterized by a weight loss of about 0.2%, at the temperature range of up to about 120°C, and of about 5.2% at the temperature range of about 131°C to about 208°C, as measured by TGA. The crystalline form may be substantially identified by the TGA curve as depicted in Figure 3. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR.

[0047] The above crystalline form is a solvated form of Dolasetron mesylate; preferably, an alcoholate, more preferably, ethanolate, most preferably, hemiethanolate.

[0048] The said crystalline form I of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form I of Dolasetron Mesylate comprises less than about 10%, preferably less than about 5%, more preferably less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD

[0049] The present invention further encompasses a process for preparing the crystalline form of Dolasetron Mesylate, designated form I, by a process comprising combining Dolasetron base, ethanol and methanesulfonic acid to obtain Dolasetron mesylate; and crystallizing it from a mixture of acetone and *tert*-butylmethyl ether.

[0050] Dolasetron base may be prepared, for example, according to the process disclosed in European Patent No. 0339699. Dolasetron base may also be prepared by a process comprising comprising the steps of a) combining a CCA-ester of formula III,



an oxidizing agent selected from the group consisting of: hydroperoxides, dialkyl peroxides, peroxyacids, peroxyesters, diacyl peroxides, persulphate, perborate and perphosphate, a catalyst and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form CCA-epoxide; b) admixing CCA-epoxide with an oxidizing agent, and a solvent selected from the group consisting of water and a water miscible organic solvent; c) raising the pH; d) admixing with a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising a carbonyl moiety selected from the group consisting of 1,3 acetonedicarboxylic acids, acetone and a C₁₋₄ ester thereof; e) admixing with a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof; f) admixing with a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an aprotic organic solvent to form a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compound (a SAN compound); g) admixing with a metal alkoxide, and a polar a-protic organic solvent to form a reaction mixture; h) heating the reaction mixture; i) quenching with a with a weak acid selected from the group consisting of acetic acid, formic acid, acetic acid, propionic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, and salicylic acid forming an *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (*trans*-hexahydro-4-alkoxycarbonyl-8-trialkylsilyloxy-2,6-methano-2H-quinolizin-3(4H)-one) compound (referred to as a SQO compound); j) admixing with a solvent

selected from a group consisting of: water, and water-immiscible organic solvent, and an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids; k) admixing with an anhydride, 3-indole carboxylic acid, a halogenated hydrocarbon, and a catalyst to obtain Dolasetron base. In this process the silylating reagents in step f) can be replaced by reagents comprising an ether protecting group forming a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-9-azabicyclo[3.3.1]nonane intermediate (referred to as a PAN intermediate) or with an acylating agent forming a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-acyloxy-9-azabicyclo[3.3.1]nonane intermediate (a PivAN intermediate). When a PivAN intermediate is prepared steps g), h), and i) are omitted.

[0051] Dolasetron mesylate is preferably provided by dissolving Dolasetron base in a C₁₋₄ alcohol, preferably ethanol followed by admixing the solution with methanesulfonic acid to obtain a second solution comprising Dolasetron mesylate. Preferably, the Dolasetron base is dissolved in the C₁₋₄ alcohol, preferably ethanol, at about room temperature, more preferably, at about 20°C to about 25°C.

[0052] Preferably, prior to the crystallization, the second solution is concentrated to obtain residue.

[0053] Preferably, the crystallization is done by a process comprising providing a solution of the residue of Dolasetron Mesylate in a mixture comprising acetone and *tert*-butylmethyl ether, and precipitating the crystalline form to obtain a suspension.

[0054] Preferably, precipitation is done by cooling the solution to a temperature of about -5°C to about 10°C, preferably to a temperature of about 0°C to about 10°C, more preferably, to a temperature of about 2°C to about 8°C. Preferably, the solution is cooled for at least about 12 hours, more preferably for at least 6 hours.

[0055] The process may further comprise recovering the said crystalline form. The recover may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, washing the filtered crystalline form, and drying it.

[0056] The present invention also encompasses an amorphous form of Dolasetron mesylate, designated Form VII. The amorphous form of Dolasetron mesylate may be substantially identified by the PXRD pattern as depicted in Figure 5. Form VII may also be characterized by a weight loss of about 1.9 %, up to a temperature of about 98°C, and a further weight loss of about 2.6%, up to a temperature of about 174°C, as measured by TGA. In addition, Form VII may be characterized by a DSC thermogram having 4 peaks, the first is a broad endothermic peak at a temperature of about 90°C, the second is a board endothermic peak at a temperature of about 128°C, due to solvation, the third is a glass transition peak at a temperature of about 172°C, and the fourth is an endothermic peak at a temperature of about 209°C, due to melting. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR.

[0057] The said amorphous form of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said amorphous form of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, with less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0058] The present invention encompasses a process for the preparation of the amorphous form of Dolasetron mesylate, designated form VII, comprising combining Dolasetron mesylate and methanol, and removing the methanol.

[0059] The starting Dolasetron mesylate may be any form of Dolasetron mesylate, preferably, the Dolasetron mesylate monohydrate. Preferably, the starting Dolasetron mesylate is dissolved in methanol, at about 15°C to about 35°C, preferably about room temperature, more preferably, at about 20°C to about 25°C. Preferably, methanol, is removed by evaporation of the solution. Preferably, evaporation is done under reduced pressure. Preferably, the solvent is removed to dryness.

[0060] The present invention further provides an additional process for preparing the amorphous form by heating a Dolasetron mesylate polymorph selected from the group consisting of: crystalline form I of Dolasetron mesylate, crystalline form II of Dolasetron mesylate, crystalline form IV of Dolasetron mesylate, crystalline form VI of Dolasetron mesylate, crystalline form IX of Dolasetron mesylate, crystalline form X of Dolasetron mesylate, crystalline form XIII of Dolasetron mesylate, crystalline form XIV of Dolasetron mesylate, and mixtures

thereof to a temperature of at least 160°C, for at least 15 minutes, preferably at least 30 minutes.

[0061] Preferably, the starting Dolasetron mesylate forms are heated to a temperature of about 160°C to about 200°C, more preferably to a temperature of about 160°C to about 190°C. Preferably, the heating is done for about 30 to about 70 minutes, more preferably, for about 60 minutes.

[0062] The present invention further encompasses a crystalline form of Dolasetron mesylate, designated Form III, characterized by a powder XRD pattern with peaks at about 14.0, 14.8, 16.1, and 18.2 ± 0.2 degrees 2-theta. Form III may be further characterized by a powder XRD with peaks at about 9.2, 12.2, 20.9, 27.9, 29.0, and 29.6 ± 0.2 degrees 2-theta. Form III may also be substantially identified by the PXRD pattern as depicted in Figure 6. Form III may also be characterized by a weight loss of less than 0.1% up to a temperature of about 130°C, and by a decomposition temperature of about 200°C, as measured by TGA. In addition, Form III may be characterized by a DSC thermogram having a sharp endothermic peak at about 209°C, due to melting. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form III may also be an anhydrous form of Dolasetron mesylate.

[0063] The said crystalline form III of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form III of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0064] The present invention also encompasses a process for the preparation of Form III of Dolasetron mesylate comprising crystallizing Dolasetron mesylate from t-butanol.

[0065] The crystallization comprises providing a solution of Dolasetron mesylate in t-butanol and precipitating the said crystalline form to obtain a suspension.

[0066] The solution of Dolasetron mesylate is preferably provided by combining Dolasetron mesylate and t-butanol, and heating the mixture. Preferably, heating is to at a temperature of about 70°C to about 85°C, preferably about 80°C to about 85°C.

[0067] The Dolasetron mesylate starting material can be any form of Dolasetron mesylate, preferably, the Dolasetron mesylate monohydrate.

[0068] Preferably, precipitation of the crystalline form is carried out by cooling the solution to about 15°C to about 35°C, preferably to about room temperature, more preferably, to about 20°C to about 25°C.

[0069] Further, the cooled solution is preferably maintained at such temperature to increase the yield of the precipitated crystalline form. Preferably, the cooled solution is maintained at such temperature for a period of about 0.5 to about 5 days, more preferably for about 1 to 4 days, most preferably for 3 days.

[0070] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[0071] The present invention further provides an additional process for preparing the said Form III by heating a Dolasetron mesylate polymorph selected from the group consisting of: amorphous form of Dolasetron mesylate, crystalline Form I of Dolasetron mesylate, crystalline form XI of Dolasetron mesylate, and mixtures thereof, to a temperature of no more than 160°C, for no more than 60 minutes.

[0072] Preferably, the starting polymorph of Dolasetron mesylate is heated to a temperature of about 160°C. Preferably, the heating is done for about 30 minutes.

[0073] The present invention encompasses a crystalline form of Dolasetron mesylate, designated Form IV, characterized by a powder XRD pattern with peaks at about 13.8, 16.5, 22.1, and 25.2 ± 0.2 degrees 2-theta. Form IV may be further characterized by a powder XRD with peaks at about 9.7, 12.5, 18.0, 19.4, 20.7, and 27.5 ± 0.2 degrees 2-theta. Form IV may also be substantially identified by the PXRD pattern as depicted in Figure 7. Form IV may also be characterized by a weight loss of about 0.2 to about 0.6 % up to a temperature of about 100°C, and a further weight loss of about 4.3 to about 4.5 % up to a temperature of about 200°C, as measured by TGA. In addition, Form IV may be characterized by a DSC thermogram having an endothermic peak at a temperature of about 185°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form IV may also be a solvated form of Dolasetron mesylate, preferably, an alcoholate, more preferably, an ethanolate.

[0074] The said crystalline form IV of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other forms of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form IV of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0075] The present invention further encompasses a process for the preparation of Form IV of Dolasetron mesylate comprising combining Dolasetron mesylate and ethanol, preferably absolute ethanol, and removing the ethanol.

[0076] The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, Dolasetron mesylate monohydrate.

[0077] Preferably, the starting Dolasetron mesylate is dissolved in ethanol at about 15°C to about 35°C, preferably at about room temperature, more preferably at about 20°C to about 25°C. Preferably, ethanol is removed by concentration of the solution, preferably by evaporation of the solution. Preferably, evaporation is done under reduced pressure. Preferably, ethanol is removed to dryness.

[0078] The present invention also encompasses a crystalline form of Dolasetron mesylate, designated Form V, characterized by a powder XRD pattern with peaks at about 13.0, 18.6 and 29.4 ± 0.2 degrees 2-theta. Form V may be further characterized by a powder XRD with peaks at about 12.6, 17.3, 19.5, 20.1, 22.4, 24.0, and 28.2 ± 0.2 degrees 2-theta. Form V may also be substantially identified by the PXRD pattern as depicted in Figure 8. Form V may also be characterized by a weight loss of about 0.2 to about 2.3% up to a temperature of about 100°C, and a further weight loss of about 1.5 to about 4.2% up to a temperature of about 200°C, as measured by TGA. In addition, Form V may be characterized by a DSC thermogram having three peaks, the first is an endothermic peak at a temperature of about 163°C due to desolvation, the second is an exothermic peak at about 185°C due to recrystallization, and the third is endothermic peak at about 227°C due to melting of the recrystallized material. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form V may also be a solvated form of Dolasetron mesylate, preferably, a ketone solvate, more preferably, an acetate.

[0079] The said crystalline form V of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, measured by XRD.

Preferably, the said crystalline form V of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0080] The present invention encompasses a process for the preparation of Form V of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from acetone

[0081] The crystallization comprises providing a solution of Dolasetron mesylate in acetone and precipitating the crystalline form to obtain a suspension.

[0082] Preferably, the solution is provided by combining Dolasetron mesylate and acetone, and heating the mixture. The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, Dolasetron mesylate monohydrate. Preferably, heating the mixture is to a temperature of about 45°C to about 60°C, preferably at about 55°C to about 60°C.

[0083] Precipitation is preferably carried out by concentrating the solution to obtain a suspension. Further, the suspension is preferably cooled to increase the yield of the precipitated crystalline form. Preferably, cooling is to a temperature of about 0°C to about 10°C, more preferably of about 2°C to about 8°C.

[0084] Preferably, cooling to a temperature of about 0°C to about 10°C is carried out over a period of about 8 to about 24 hours, more preferably of about 10 to about 16 hours.

[0085] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[0086] The present invention further encompasses a crystalline form of Dolasetron mesylate, designated Form VI, characterized by a powder XRD pattern with peaks at about 9.9, 15.2, and 16.0 ± 0.2 degrees 2-theta. Form VI may be further characterized by a powder XRD with peaks at about 17.3, 18.1, 19.8, 20.6, 21.4, 24.3, and 28.2 ± 0.2 degrees 2-theta. Form VI may also be substantially identified by the PXRD pattern as depicted in Figure 9. Form VI may also be characterized by a weight loss of about 0.5%, up to a temperature of about 120°C, and a further weight loss of about about 6.1% up to a temperature of about 210°C, as measured by TGA. In addition, Form VI may be characterized by a DSC thermogram having an endothermic peak at a temperature of about 155°C. The crystalline form can be

characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form VI may also be a solvated form of Dolasetron mesylate, preferably, an alcoholate, more preferably, methanolate.

[0087] The said crystalline form VI of Dolasetron Mesylate may be with less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form VI of Dolasetron Mesylate may be with less than about 10%, preferably, with less than about 5% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0088] The present invention encompasses a process for the preparation of Form VI of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a mixture comprising methanol as a solvent and methyltertbutyl ether as an anti-solvent.

[0089] The crystallization comprises providing a solution of Dolasetron mesylate in methanol, and admixing the solution with methyltertbutyl ether to obtain a suspension comprising of the said crystalline form.

[0090] Preferably, the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and methanol, and heating the mixture. The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, Dolasetron mesylate monohydrate. Preferably, heating the mixture is to a temperature of about 60°C to about reflux, preferably to about 62°C to about 67°C.

[0091] Preferably, methyltertbutyl ether is added to the solution, to obtain a mixture containing of a sticky precipitate. Preferably, the mixture 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 to a temperature of about 0°C to about 10°C is carried out over a period of about 1 to about 5 days, more preferably of about 2 to about 4 days, most preferably of about 4 days.

[0092] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[0093] The present invention further encompasses a crystalline form of Dolasetron mesylate, designated Form VIII, characterized by a powder XRD pattern with peaks at about 10.1, 16.3, and 22.6 ± 0.2 degrees 2-theta. Form VIII may be further characterized by a powder XRD with peaks at about 12.5, 17.0, 20.1, 20.8,

25.9, 28.5, and 29.9 ± 0.2 degrees 2-theta. Form VIII may also be substantially identified by the PXRD pattern as depicted in Figure 10. Form VIII may also be characterized by a weight loss of about 0.1- 2.8% up to a temperature of about 134°C, and a further weight loss of about 1.5 to about 6.6%, up to a temperature of about 183°C, as measured by TGA. In addition, Form VIII may be characterized by a DSC thermogram having three peaks, the first is an endothermic peak at a temperature of about 160°C, the second is an exothermic peak at about 190°C, and the third is an endothermic melting peak of the recrystallized product, at a temperature of about 229°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form VIII may also be a solvated form of Dolasetron mesylate, preferably, a carbonated solvate, more preferably, methylcarbonate solvate.

[0094] The said crystalline form VIII of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, with less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form VIII of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[0095] The present invention also encompasses a process for the preparation of Form VIII of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a dimethylcarbonate.

[0096] Preferably, crystallization is done by a process comprising providing a solution of Dolasetron mesylate in dimethylcarbonate, and precipitating the said crystalline form to obtain a suspension.

[0097] Preferably, the solution is provided by combining Dolasetron mesylate and dimethylcarbonate, and heating the mixture. The starting Dolasetron mesylate maybe any form of Dolasetron mesylate, preferably, Dolasetron mesylate monohydrate. Preferably, heating mixture is to a temperature of about 85°C to about reflux, preferably of about 88°C to about 93°C. The dissolution may not be complete, thus a mixture may be obtained.

[0098] Preferably, precipitation is done by cooling the said solution. Preferably, cooling is to a temperature of about -10°C to about 10°C, preferably to about 5°C to about 10°C. Preferably, cooling is carried out over a period of about 8 to about 24 hours, more preferably of about 10 to about 16 hours.

[0099] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00100] The present invention encompasses a crystalline form of Dolasetron mesylate, designated Form IX, characterized by a powder XRD pattern with peaks at about 9.8, 18.3, and 27.9 ± 0.2 degrees 2-theta. Form IX may be further characterized by a powder XRD with peaks at about 12.7, 19.5, 20.3, 20.6, 22.1, 29.4, and 31.9 ± 0.2 degrees 2-theta. Form IX may also be substantially identified by the PXRD pattern as depicted in Figure 11. Form IX may also be characterized by a weight loss of about 2.7 to about 4.0% up to a temperature of about 140°C, and by another weight loss of about 2.6%, up to a temperature of about 200°C, as measured by TGA. In addition, Form IX may be characterized by a DSC thermogram having three peaks, the first is an endothermic peak at a temperature of about 153°C, the second is an exothermic peak at a temperature of about 170°C, and the third is an endothermic peak at a temperature of about 229°C due to desolvation and melting, respectively. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form IX may also be a solvated form of Dolasetron mesylate, preferably, a nitromethane solvate.

[00101] The said crystalline form IX of Dolasetron Mesylate comprises less than about 30% of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form IX of Dolasetron Mesylate comprises less than about 30% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00102] The present invention further encompasses a process for the preparation of Form IX of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a refluxed solution of Dolasetron mesylate in nitromethane; wherein the solution is refluxed at a about 98°C to about 102°C.

[00103] The crystallization is preferably done by a process comprising providing a solution of Dolasetron mesylate in nitromethane, at reflux temperature, and precipitating the said form to obtain a suspension.

[00104] The solution of Dolasetron mesylate in nitromethane is provided by combining Dolasetron mesylate and nitromethane and heating the mixture. The starting Dolasetron mesylate maybe any form of Dolasetron mesylate, preferably, the Dolasetron monohydrate.

[00105] Precipitation of the said form is preferably done by cooling the solution. Preferably, cooling is to a temperature of about 0°C to about 10°C, more preferably to about 2°C to about 8°C. Preferably, cooling is done over a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours.

[00106] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00107] The present invention also encompasses a crystalline form of Dolasetron mesylate, designated Form X, characterized by a powder XRD pattern with peaks at about 9.4, 17.7 and 27.1 ± 0.2 degrees 2-theta. Form X may be further characterized by a powder XRD with peaks at about 12.5, 16.5, 17.1, 18.8, 19.2, 20.4, and 21.2 ± 0.2 degrees 2-theta. Form X may also be substantially identified by the PXRD pattern as depicted in Figure 12. Form X may also be characterized by a weight loss of less than 0.1% up to a temperature of about 120°C, and a further weight loss of about 3.3%, up to a temperature of about 190°C, as measured by TGA. In addition, Form X may be characterized by a DSC thermogram having a first endothermic peak at a temperature of about 180°C, and a second endothermic peak at a temperature of about 197°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form X may also be a solvated form of Dolasetron mesylate, preferably, an ether solvate, more preferably a C₃₋₆ ether solvate, most preferably a dioxane solvate

[00108] The said crystalline form X of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form X of Dolasetron Mesylate comprises less than about 10%, preferably, with less than about 5%, more preferably, with less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00109] The present invention further encompasses a process for the preparation of Form X of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a C₃₋₆ ether, preferably 1,4-dioxane.

[00110] The crystallization is preferably done by a process comprising providing a solution of Dolasetron mesylate in 1,4-dioxane, precipitating the said form to obtain a suspension.

[00111] The solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and 1,4-dioxane, and heating the mixture. The starting Dolasetron mesylate maybe any form of Dolasetron mesylate, preferably, the starting Dolasetron mesylate monohydrate. Preferably, heating of the mixture is to a temperature of about 95°C to about reflux, preferably of about 98°C to about 102°C. Preferably, the 1,4-dioxane solvent contains about 1% to about 10% of water, more preferably, about 1% to about 5% of water, by weight.

[00112] The precipitation of the said form is preferably done by cooling the said solution. Preferably, cooling is 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 1 to about 4 days, more preferably for about 2 to about 3 days, most preferably for about 3 days.

[00113] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00114] The present invention also encompasses a crystalline form of Dolasetron mesylate, designated Form XI, characterized by a powder XRD pattern with peaks at about 14.1, 14.9, 16.2 and 18.2 ± 0.2 degrees 2-theta. Form XI may be further characterized by a powder XRD with peaks at about 12.2, 12.9, 19.0, 20.9, 22.5, 23.6, 27.9, and 29.1 ± 0.2 degrees 2-theta. Form XI may also be also substantially identified by the PXRD pattern as depicted in Figure 13. Form XI may also be characterized by a weight loss of about 1.3 to about 1.5% up to a temperature of about 134°C, and a further weight loss of about 0.5 % up to a temperature of about 186°C, as measured by TGA. In addition, Form XI may be characterized by a DSC thermogram having an endothermic peak at a temperature of about 153°C, and two additional endothermic peaks at about 208°C and 228°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form XI may also be a solvated form of Dolasetron mesylate, preferably, an ester solvate, more preferably a C₂₋₆ ester, more preferably ethyl-lactate solvate.

[00115] The said crystalline form XI of Dolasetron Mesylate comprises less than about 30% of any other form of Dolasetron Mesylate, as measured by XRD.

Preferably, the said crystalline form XI of Dolasetron Mesylate comprises less than about 30% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00116] The present invention encompasses a process for the preparation of Form XI of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a mixture comprising a C₂₋₆ ester, preferably ethyl lactate as a solvent, and methyltertbutyl ether as an anti-solvent.

[00117] The crystallization is preferably done by a process comprising providing a solution of Dolasetron mesylate in ethyl lactate, and admixing the solution with methyltertbutyl ether to obtain a suspension comprising of the said crystalline form.

[00118] Preferably, the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and ethyl lactate, and heating the mixture. The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, Dolasetron mesylate monohydrate. Preferably, heating the mixture is to a temperature of about 40°C to about 60°C, more preferably of about 40°C to about 50°C.

[00119] Preferably, methyltertbutyl ether is added to the solution, to obtain a mixture comprising a sticky precipitate. Preferably, the mixture is cooled at a temperature of about 0°C to about 10°C, more preferably of about 2°C to about 8°C. Preferably, cooling is conducted for about 1 to about 5 days, more preferably for about 1 to about 4 days, most preferably for about 4 days, to obtain a solid.

[00120] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00121] The present invention further encompasses a crystalline form of Dolasetron mesylate, designated Form XII, characterized by a powder XRD pattern with peaks at about 14.7, 17.6 and 18.2 ± 0.2 degrees 2-theta. Form XII may be further characterized by a powder XRD with peaks at about 13.3, 14.0, 15.8, 20.5, 24.0, 24.9, and 27.1 ± 0.2 degrees 2-theta. Form XII may also be substantially identified by the PXRD pattern as depicted in Figure 14. Form XII may also be characterized by a weight loss of about about 0.2%, up to a temperature of about 150°C, as measured by TGA. In addition, Form XII may be characterized by a DSC thermogram having a sharp endothermic peak at a temperature of about 227°C due to melting. The crystalline form can be characterized by any other method known to a

skilled artisan, such as solid state NMR, and FTIR. The said crystalline form XII of Dolasetron Mesylate may be an anhydrous form of Dolasetron mesylate.

[00122] The said crystalline form XII of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form XII of Dolasetron Mesylate comprise less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00123] The present invention also encompasses a process for the preparation of Form XII of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a C₆₋₈ aromatic hydrocarbon, preferably toluene.

[00124] The crystallization is preferably done by a process comprising providing a solution of Dolasetron mesylate in toluene, and precipitating the said crystalline form to obtain a suspension.

[00125] The solution is provided by combining Dolasetron mesylate and toluene, and heating the mixture. The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, the starting Dolasetron mesylate is Dolasetron mesylate monohydrate. Preferably, heating is to a temperature of about 80°C to about reflux, preferably to about 108°C to about 112°C. Preferably, heating the mixture is done for about 0.5 to about 2 hours. Preferably, the heating is done while the process is conducted with removal of water, preferably by the use of a water trap.

[00126] Precipitation of Dolasetron mesylate is preferably done by cooling the said solution. Preferably, the solution is cooled to about 15°C to about 35°C, more preferably to about room temperature, most preferably, to a temperature of about 20°C to about 25°C. Preferably, cooling is conducted for about 8 to about 24 hours, more preferably for about 10 to about 16 hours.

[00127] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00128] The present invention further provides an additional process for preparing the said Form XII by heating a Dolasetron mesylate polymorph selected from the group consisting of: crystalline Form V of Dolasetron mesylate, crystalline form VIII of Dolasetron mesylate, and mixtures thereof.

[00129] Preferably, the starting Form of Dolasetron mesylate is heated to a temperature of about 150°C to about 220°C, more preferably, to about 160°C. Preferably, the heating is done for about 30 to about 70 minutes, more preferably, for about 60 minutes.

[00130] The present invention encompasses a crystalline form of Dolasetron mesylate, designated Form XIII, characterized by a powder XRD pattern with peaks at about 9.1, 15.0 and 18.1 ± 0.2 degrees 2-theta. Form XIII may be further characterized by a powder XRD with peaks at about 12.5, 16.8, 19.4, 21.0, 22.3, 23.2 and 27.2 ± 0.2 degrees 2-theta. Form XIII may also be substantially identified by the PXRD pattern as depicted in Figure 15. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR.

[00131] The said crystalline form XIII of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form XIII of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00132] The present invention also encompasses a process for the preparation of Form XIII of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from a solution of Dolasetron mesylate in nitromethane; wherein the solution is provided at about 15°C to about 35°C, more preferably to about room temperature.

[00133] The crystallization comprises providing a solution of Dolasetron mesylate in nitromethane at about room temperature, and precipitating the said form to obtain a suspension. The starting Dolasetron mesylate can be any form of Dolasetron mesylate, preferably, the Dolasetron mesylate monohydrate. Preferably, the dissolution is done at a temperature of about 20°C to about 25°C.

[00134] The precipitation is preferably done by cooling the solution. Preferably, the solution 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 over a period of about 8 to about 24 hours, more preferably for about 10 to about 16 hours.

[00135] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension.

[00136] The present invention encompasses a crystalline form of Dolasetron mesylate, designated Form XIV, characterized by a powder XRD pattern with peaks at about 17.4, 17.9 and 22.1 ± 0.2 degrees 2-theta. Form XIV may be further characterized by a powder XRD with peaks at about 12.6, 16.6, 19.3, 20.3, 20.7, 27.8 and 29.2 ± 0.2 degrees 2-theta. Form XIV may also be substantially identified by the PXRD pattern as depicted in Figure 16. Form XIV may also be characterized by a weight loss of about 3.9%, up to a temperature of about 154°C, as measured by TGA. In addition, Form XIV may be characterized by a DSC thermogram having three peaks, the first is an endothermic peak at a temperature of about 161°C, the second, is an exothermic peak at a temperature of about 174°C, and the third is an endothermic peak at a temperature of about 229°C. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form XIV may also be a hydrated form of Dolasetron mesylate, preferably, a monohydrate.

[00137] The said crystalline form XIV of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form XIV of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00138] The present invention further encompasses a process for the preparation of Form XIV of Dolasetron mesylate by drying form XIII.

[00139] Preferably, Form XIII is dried at a temperature of about 35°C to about 55°C, preferably of about 35°C to about 45°C. Preferably, the drying is conducted under reduced pressure. Preferably, drying is done for about 8 to about 24 hours, more preferably for about 10 to about 16 hours.

[00140] The present invention also encompasses a crystalline form of Dolasetron mesylate, designated Form XV, characterized by a powder XRD pattern with peaks at about 12.2, 14.1, 14.8, 16.3 and 22.2 ± 0.2 degrees 2-theta. Form XV may be further characterized by a powder XRD pattern with peaks at about 9.3, 18.6, 20.2, 20.6, 21.1, 22.2 and 28.2 ± 0.2 degrees 2-theta. Form XV may also be substantially identified by the PXRD pattern as depicted in Figure 17. Form XV may also be characterized by a weight loss of about 7.8%, up to a temperature of about 130°C, as measured by TGA. In addition, Form XV may be characterized by a DSC thermogram having 4 endothermic peaks, the first is at a temperature of about 60°C, the second is at about 100°C, the third is about 163°C, and the fourth at about 228°C

due to melting. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form XV may be a hydrated form of Dolasetron mesylate, preferably, a dihydrate form of Dolasetron mesylate.

[00141] The said crystalline form XV of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, less than about 1%, of any other form of Dolasetron Mesylate, as measured by XRD. Preferably, the said crystalline form XV of Dolasetron Mesylate comprises less than about 10%, preferably, less than about 5%, more preferably, with less than about 1%, of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00142] The present invention encompasses a process for preparing crystalline Form XV of Dolasetron mesylate by exposing crystalline Form III of Dolasetron mesylate to humidity.

[00143] Preferably, crystalline Form III is exposed to 100% relative humidity. Preferably, the exposure is done at a temperature of about 15°C to about 35°C, more preferably, at a temperature of about 22°C to about 25°C. Preferably, the exposure is done for about 2 to about 14 days, more preferably, for about 3 to about 10 days, most preferably, for about 3 days.

[00144] The present invention further encompasses a crystalline form of Dolasetron mesylate, designated Form XVI, characterized by a powder XRD pattern with peaks at about 12.1, 14.0, 14.8 15.1 and 22.1 ± 0.2 degrees 2-theta. Form XVI of Dolasetron mesylate may be further characterized by a powder XRD pattern with peaks at about 9.3, 19.6, 20.0, 20.5, 21.0, 22.1 and 28.7 ± 0.2 degrees 2-theta. Form XVI may also be substantially identified by the PXRD pattern as depicted in Figure 18. Form XVI may also be characterized by a weight loss of about 7.7%, up to a temperature of about 160°C, as measured by TGA. In addition, Form XVI may be characterized by a DSC thermogram having 5 peaks, the first is an endothermic peak at a temperature of about 55°C, the second is an endothermic peak at a temperature of about 85°C, the third is an endothermic peak at about 163°C, the fourth is an exothermic peak at about 175°C, due to recrystallization, and the and an the fifth is an endothermic peak at about 228°C, due to melting. The crystalline form can be characterized by any other method known to a skilled artisan, such as solid state NMR, and FTIR. The said Form XVI is an hydrated form of Dolasetron mesylate, preferably, a dihydrate form of Dolasetron mesylate.

[00145] The said crystalline form XVI of Dolasetron Mesylate comprises less than about 10% any other form of Dolasetron Mesylate, as measured by XRD.

Preferably, the said crystalline form XVI of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

[00146] The present invention also encompasses a process for preparing crystalline Form XVI of Dolasetron mesylate by exposing crystalline Form XII of Dolasetron mesylate to humidity.

[00147] Preferably, crystalline Form XII is exposed to 100% relative humidity. Preferably, the exposure is done at a temperature of about 20°C to about 30°C, more preferably, at a temperature of about 22°C to about 25°C. Preferably, the exposure is done for about 2 to about 14 days, more preferably, for about 3 to about 10 days, most preferably, for about 3 days.

[00148] The present invention also encompasses a process for preparing crystalline form of Dolasetron mesylate, designated form II, comprising combining Dolasetron base, methanesulfonic acid, and a solvent mixture of acetone and water to obtain Dolasetron mesylate; and crystallizing it from the said solvent mixture. Preferably, the Dolasetron mesylate is provided, at about room temperature, more preferably, at about 20°C to about 25°C.

[00149] Preferably, the ratio of acetone and water in the solvent mixture is of about 99:1 to about 80:20, respectively, more preferably, of about 99:5 to about 99:1, respectively. Preferably, the addition of methane sulfonic acid transforms the suspension into a solution.

[00150] The crystallization is done by obtaining a suspension comprising the said crystalline form. Preferably, the suspension is formed after a few minutes after the addition of methane sulfonic acid. Further, the suspension is preferably cooled to increase the yield of the crystallized product. 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 about 8 to about 24 hours, more preferably for about 10 to about 16 hours.

[00151] The process may further comprise recovering the said crystalline form. The recovery may be done by any method known to a skilled artisan. The recovering of the precipitate may be done by filtering the suspension, and drying the filtered crystalline form.

[00152] The present invention also provides preparing crystalline form II of Dolasetron mesylate by heating amorphous Dolasetron mesylate Form VII at about 90°C for about 15 minutes to 30 minutes.

[00153] The present invention also provides an alcoholate solvate of Dolasetron mesylate. Preferably, the alcoholate solvate is an ethanol solvate or methanol solvate of Dolasetron mesylate.

[00154] The present invention provides an anhydrous Dolasetron mesylate.

[00155] The present invention also provides a ketone solvate of Dolasetron mesylate. Preferably, the ketone solvate is an acetone solvate of Dolasetron mesylate.

[00156] The present invention provides a carbonate solvate of Dolasetron mesylate. Preferably the carbonate solvate is a methyl carbonate solvate of Dolasetron mesylate.

[00157] The present invention also provides an ether solvate of Dolasetron mesylate. Preferably, the ether solvate is a 1,4 dioxane solvate of Dolasetron mesylate.

[00158] The present invention provides an ester solvate of Dolasetron mesylate. Preferably, the ester solvate is an ethyl lactate solvate of Dolasetron mesylate.

[00159] The present invention also provides a nitromethane solvate of Dolasetron mesylate.

[00160] The present invention also provides a hydrated Dolasetron mesylate. Preferably, the hydrated Dolasetron mesylate is a monohydrate or dihydrate of Dolasetron mesylate.

[00161] The present invention comprises a pharmaceutical composition comprising any one of the designated forms of Dolasetron Mesylate, Forms I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, and at least one pharmaceutically acceptable excipient.

[00162] The present invention further comprises a pharmaceutical composition comprising any one of the designated forms of Dolasetron Mesylate, Forms I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, prepared according to the processes of the present invention, and at least one pharmaceutically acceptable excipient.

[00163] The present invention also encompasses a process for preparing a pharmaceutical formulation comprising combining any one of the designated forms of

Dolasetron Mesylate, Forms I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, with at least one pharmaceutically acceptable excipient.

[00164] The present invention also encompasses a process for preparing a pharmaceutical formulation comprising combining any one of the designated forms of Dolasetron Mesylate, Forms I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, prepared according to the processes of the present invention, with at least one pharmaceutically acceptable excipient.

[00165] The present invention also encompasses the use of any one of the designated forms of Dolasetron Mesylate, Forms I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, for the manufacture of a pharmaceutical composition.

[00166] The pharmaceutical composition of the present invention can be administered in various preparations depending on the age, sex, and symptoms of the patient. The pharmaceutical compositions can be administered, for example, as tablets, pills, powders, liquids such as suspensions and emulsions, granules, capsules, suppositories, injection preparations (suspensions), and the like.

[00167] Pharmaceutical compositions of the present invention can optionally be mixed with other forms of Dolasetron Mesylate and/or other active ingredients. In addition, pharmaceutical compositions of the present invention can contain inactive ingredients such as diluents, carriers, fillers, bulking agents, binders, disintegrants, disintegration inhibitors, absorption accelerators, wetting agents, lubricants, glidants, surface active agents, flavoring agents, and the like.

[00168] Diluents increase the bulk of a solid pharmaceutical composition and can make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g., Avicel[®]), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g., Eudragit[®]), potassium chloride, powdered cellulose, sodium chloride, sorbitol, or talc.

[00169] Carriers for use in the pharmaceutical compositions may include, but are not limited to, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, or silicic acid.

[00170] Binders help bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include for example acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel[®]), hydroxypropyl methyl cellulose (e.g. Methocel[®]), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon[®], Plasdone[®]), pregelatinized starch, sodium alginate, or starch.

[00171] Disintegrants can increase dissolution. Disintegrants include, for example, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol[®], Primellose[®]), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon[®], Polyplasdone[®]), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab[®]) and starch.

[00172] Disintegration inhibitors may include, but are not limited to, white sugar, stearin, coconut butter, hydrogenated oils, and the like.

[00173] Absorption accelerators may include, but are not limited to, quaternary ammonium base, sodium laurylsulfate, and the like.

[00174] Wetting agents may include, but are not limited to, glycerin, starch, and the like. Adsorbing agents used include, but are not limited to, starch, lactose, kaolin, bentonite, colloidal silicic acid, and the like.

[00175] A lubricant can be added to the composition to reduce adhesion and ease release of the product from a punch or dye during tableting. Lubricants include for example magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

[00176] Glidants can be added to improve the flowability of non-compacted solid composition and improve the accuracy of dosing. Excipients that can function as glidants include for example colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

[00177] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for

pharmaceutical products that can be included in the composition of the present invention include for example maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[00178] Tablets can be further coated with commonly known coating materials such as sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coatings, tablets coated with films, double layered tablets, and multi-layered tablets. Capsules can be coated with shell made, for example, from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[00179] Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[00180] In liquid pharmaceutical compositions of the present invention, the Dolasetron Mesylate of the present invention is suspended, while maintaining its crystalline characteristics, and any other solid ingredients are dissolved or suspended in a liquid carrier, such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

[00181] Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

[00182] Liquid pharmaceutical compositions of the present invention can also contain viscosity enhancing agents to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include for example acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

[00183] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar can be added to improve the taste.

[00184] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid can be added at safe levels to improve storage stability.

[00185] A liquid composition according to the present invention can also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate.

[00186] Selection of excipients and the amounts to use can be readily determined by an experienced formulation scientist in view of standard procedures and reference works known in the art.

[00187] A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, which causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate can then be tableted or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

[00188] A tableting composition can be prepared conventionally by dry blending. For instance, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can be compressed subsequently into a tablet.

[00189] As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well-suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[00190] A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

[00191] When shaping the pharmaceutical composition into pill form, any commonly known excipient used in the art can be used. For example, carriers include, but are not limited to, lactose, starch, coconut butter, hardened vegetable oils,

kaolin, talc, and the like. Binders used include, but are not limited to, gum arabic powder, tragacanth gum powder, gelatin, ethanol, and the like. Disintegrating agents used include, but are not limited to, agar, laminaria, and the like.

[00192] For the purpose of shaping the pharmaceutical composition in the form of suppositories, any commonly known excipient used in the art can be used. For example, excipients include, but are not limited to, polyethylene glycols, coconut butter, higher alcohols, esters of higher alcohols, gelatin, semisynthesized glycerides, and the like.

[00193] When preparing injectable pharmaceutical compositions, suspensions are sterilized and are preferably made isotonic to blood. Injection preparations may use carriers commonly known in the art. For example, carriers for injectable preparations include, but are not limited to, water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and fatty acid esters of polyoxyethylene sorbitan. One of ordinary skill in the art can easily determine with little or no experimentation the amount of sodium chloride, glucose, or glycerin necessary to make the injectable preparation isotonic. Additional ingredients, such as dissolving agents, buffer agents, and analgesic agents may be added. If necessary, coloring agents, preservatives, perfumes, seasoning agents, sweetening agents, and other medicines may also be added to the desired preparations during the treatment of schizophrenia.

[00194] The amount of Dolasetron Mesylate of the present invention contained in a pharmaceutical composition according to the present invention is not specifically restricted; however, the dose should be sufficient to treat, ameliorate, or reduce the condition.

[00195] The present invention also provides a method of treating a patient comprising administering a therapeutically effective amount of any one of crystalline Dolasetron mesylate forms I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, or mixtures thereof, to a patient in need thereof. The patient may be a patient in need of an antiemetic or antinauseant agent while undergoing chemo- and/or radiotherapy.

[00196] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the process and compositions of the

invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

Instruments

XRD

[00197] XRD diffraction was performed on X-Ray powder diffractometer, ARL, θ - θ goniometer, Cu-tube, solid state detector with Peltier cooling. Sample holder: A round standard aluminum sample holder with round zero background was used.

Scanning parameters: Range: 2-40 deg.2 θ , Continuous Scan, Rate: 3deg./min.

Thermal analysis

[00198] DSC thermogram was performed on DSC822^c, Mettler Toledo

Sample weight: 3-5mg

Heating rate: 10°C/min

Number of holes in the crucible: 3

Nitrogen flow rate: 40 ml/min.

TGA

[00199] TGA thermogram was performed on Mettler TGA/SDTA 851 using standard Alumina pan.

Sample weight: 7-15 mg,

Heating rate: 10°C/min

Nitrogen flow rate: 50 ml/min.

Example 1: Preparation of crystalline form I of Dolasetron Mesylate

[00200] DLS base (1.70 g, 5.24 mmol) was dissolved in 96 % of ethanol (100 ml) at room temperature. Methanesulfonic acid (0.34 ml, 1 equiv.) was added and the solution was evaporated to 22 g. Acetone (100ml), then *tert*-butylmethyl ether (100 ml) were added to the residue. The solution was put into the fridge overnight. The formed crystals were filtered off, washed with acetone, dried at room temperature on air and obtained 1.80 g (82 %). The dry substance obtained was crystalline.

Comparative Example 2: Preparation of Dolasetron Mesylate monohydrate, Form II, according to EP 0339669

[00201] To a solution of DLS base (2.87 g, 8.85 mmol) in acetone (30 ml) was added dropwise methanesulfonic acid (0.62 ml) during about 5 minutes at 20-25°C. After a few minutes, DLS-MsOH began to separate and solidify. The mixture was stirred at 0-5°C for 2 hours and filtered. The solid material was washed with acetone (2×5 ml) and dried in vacuo at 35-40°C overnight to obtain 3.38 g (91%) of Dolasetron mesylate.

[00202] The dried DLS-MsOH (2.7 g, 6.42 mmol) was recrystallized by dissolving in hot 5% aqueous isopropanol (41 ml) and adding ether (7 ml) to the cloud point at about 30°C. The stirring was continued at 20-25°C for 6 hours, then the precipitated material was filtered, washed with ether (2×5 ml) and dried at 20-25°C to obtain 2.0 g (71%) of Dolasetron mesylate monohydrate characterized by a powder XRD pattern with peaks at 9.9, 12.1, 12.9, 15.1, 17.1, 19.0, 19.7, 20.0 and 22.4± 0.2 degrees two-theta.

Example 3: Preparation of Dolasetron mesylate Form II.

[00203] Methanesulfonic acid (2.85 ml, 1 equiv) was added to a stirred suspension of Dolasetron base (14.24 g, 43.9 mmol) in a mixture of acetone-water 95:5 (100 ml). The solid dissolved immediately, and 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 the same solvent mixture (2×15 ml), dried overnight in an air-ventilated oven at 40 °C. The yield was 15.63 g (81 %).

Example 4: Preparation of Amorphous Dolasetron mesylate Form VII.

[00204] Dolasetron mesylate monohydrate (0.50 g) was dissolved in methanol (80 ml) at room temperature. The solution was evaporated to dryness under reduced pressure.

Example 5: Preparation of Dolasetron mesylate Form III

[00205] Dolasetron mesylate monohydrate (0.50 g) was dissolved in tert-butanol (90 ml) under reflux. The solution was allowed to stand at room temperature for 3 days. The precipitated crystals are filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form III.

Example 6: Preparation of Dolasetron mesylate Form IV

[00206] Dolasetron mesylate monohydrate (0.50 g) was dissolved in abs. ethanol (400 ml) at room temperature. The solution was evaporated to dryness under reduced pressure.

Example 7: Preparation of Dolasetron mesylate Form V

[00207] Dolasetron mesylate monohydrate (0.50 g) was dissolved in acetone (200 ml) under reflux. The solution was evaporated to small volume until starting of crystallization (6 g) under reduced pressure. The mixture was put into fridge overnight. The precipitated crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form V.

Example 8: Preparation of Dolasetron mesylate Form VI

[00208] Dolasetron mesylate monohydrate (0.50 g) was dissolved in methanol (5 ml) under reflux. Methyl tert-butyl ether (20 ml) was added to the solution, the material precipitated in sticky form. The mixture was put into fridge for 4 days. The sticky material solidified, the crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form VI.

Example 9: Preparation of Dolasetron mesylate Form VIII

[00209] Dolasetron mesylate monohydrate (0.50 g) was dissolved in dimethyl carbonate (200 ml) under reflux. The solid did not dissolve totally. The mixture was put into the fridge overnight. The precipitated crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form VIII.

Example 10: Preparation of Dolasetron mesylate Form IX

[00210] Dolasetron mesylate monohydrate (0.50 g) was dissolved in nitromethane (5 ml) under reflux. The solution was put into fridge overnight. The precipitated crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form IX.

Example 11: Preparation of Dolasetron mesylate Form X

[00211] Dolasetron mesylate monohydrate (0.50 g) was dissolved in a mixture of 1,4-dioxane and water 95:5 (60 ml) under reflux. The solution was allowed to stand at room temperature for 3 days. The precipitated crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form X.

Example 12: Preparation of Dolasetron mesylate Form XI

[00212] Dolasetron mesylate monohydrate (0.50 g) was dissolved in ethyl lactate (5 ml) at 40-50°C. Methyl tert-butyl ether (12 ml) was added to the solution, the material precipitated in sticky form. The mixture was put into fridge for 4 days. The sticky material solidified, the crystals were filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form XI.

Example 13: Preparation of Dolasetron mesylate Form XII

[00213] Dolasetron mesylate monohydrate (0.50 g) was refluxed in toluene (120 ml) with water trap for 1 hour. The mixture was allowed to stand at room temperature overnight. The precipitated crystals are filtered off, dried overnight at 40°C under reduced pressure. Wet and dry samples were form XII.

Example 14: Preparation of Dolasetron mesylate Form XIII

[00214] Dolasetron mesylate monohydrate (0.50 g) was dissolved in nitromethane (20 ml) at room temperature. The solution was put into fridge overnight. The precipitated crystals were filtered off, leading to form XIII.

Example 15: Preparation of Dolasetron mesylate Form XIV

[00215] Form XIII obtained in example 14 was dried overnight at 40°C under reduced pressure to give form XIV.

Example 16: Preparation of Dolasetron mesylate Form XV

[00216] 200 mg of Form III of Dolasetron mesylate was exposed of in a glass bottle to 100 % relative humidity for three days, at 25°C.

Example 17: Preparation of Dolasetron mesylate Form XVI

[00217] 200 mg of Dolasetron mesylate form XII was exposed in a glass bottle to 100% relative humidity for three days at 25°C.

Example 18: Heat transformations

FORM	HEAT TRANSFORMATION					
	TEMP. (°C)	TIME	RESULT	TEMP.	TIME	RESULT
II	100	30 min.	II			
	80	1 hour	II			
	80	2 hours	II			
	80	3 hours	II			
	100	1 hour	II			
	120	1 hour	II			
I	190	30 min.	Amorphous> III			

VII amorpho us	160	60 min.	III			
VIII	160	60 min.	XII			
VIII	160	30	XII			
IX	160	60 min.	VII	90 °C	15 min	II
XI	160	60 min.	III			
XIII	160	60 min.	VII	90 °C	15 min	VII
XIV	160	60 min.	VII	90 °C	15 min	II
I	160	30min	III	160	30 min	III
II	160	30 min	VII	160	30 min	VII >III
IV	160	60 min	VII +IV			
V	160	60 min	XII			
VI	160	60 min	VII			
X	160	30 min	VII	160	30 min	VII

Claims

1. A crystalline Dolasetron Mesylate characterized by a powder XRD pattern with peaks at about 12.6, 18.2, and 19.6 ± 0.2 degrees two-theta.
2. The crystalline Dolasetron mesylate of claim 1, wherein the crystalline form is further characterized by an X-ray powder diffraction pattern with peaks at about 9.9, 13.8, 16.6, 21.1, 23.3, 27.9, and 29.6 ± 0.2 degrees two-theta.
3. The crystalline Dolasetron mesylate of claim 2, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 1.
4. The crystalline Dolasetron mesylate of any one of claims 1 to 3, wherein the crystalline form is further characterized by a DSC thermogram with endothermic peaks at about 160°C, 180°C, and 209°C.
5. The crystalline Dolasetron mesylate of claim 4, wherein the crystalline form is further characterized by the DSC thermogram is as depicted in Figure 2.
6. The crystalline Dolasetron mesylate of any one of claims 1 to 5, wherein the crystalline form I is further characterized by a weight loss of about 0.2% at the temperature range of up to about 120°C, and of about 5.2% at the temperature range of about 131°C to about 208°C as measured by TGA.
7. The crystalline Dolasetron mesylate of claim 6, wherein the crystalline form is further characterized by the TGA curve as depicted in Figure 3.
8. The crystalline Dolasetron mesylate of any one of claims 1 to 7, wherein the crystalline form of Dolasetron mesylate is an alcoholate solvate.
9. The crystalline Dolasetron mesylate of claim 8, wherein the crystalline form is hemiethanolate.
10. The crystalline Dolasetron mesylate of any one of claims 1 to 9, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.

11. The crystalline Dolasetron mesylate of claim 10, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
12. A method for preparing crystalline form I of Dolasetron Mesylate, by a process comprising combining Dolasetron base, a C₁₋₄ alcohol and methanesulfonic acid to obtain Dolasetron mesylate; and crystallizing it from a mixture of acetone and *tert*-butylmethyl ether.
13. The method of claim 12, wherein the C₁₋₄ alcohol is ethanol.
14. The method of any one of claims 12 and 13, wherein the Dolasetron mesylate is provided by dissolving Dolasetron base in ethanol, followed by admixing the solution with methanesulfonic acid to obtain a second solution comprising of Dolasetron mesylate.
15. The method of claim 14, wherein prior to the crystallization, the second solution is concentrated to obtain residue.
16. The method of any one of claims 12 to 15, wherein the crystallization is done by a process comprising providing a solution of the residue of Dolasetron Mesylate in a mixture comprising acetone and *tert*-butylmethyl ether, and precipitating the crystalline form to obtain a suspension.
17. The method of claim 16, wherein the precipitation is done by cooling the solution to a temperature of about -5°C to about 10°C.
18. An amorphous Dolasetron mesylate, designated Form VII.
19. The amorphous form of Dolasetron mesylate of claim 18, further characterized by the PXRD pattern as depicted in Figure 5.
20. The amorphous Dolasetron mesylate of any one of claims 18 and 19, wherein the amorphous form is further characterized by a weight loss of about 1.9% up to a temperature of about 98°C, and a further weight loss of about 2.5% to about 3% up to a temperature of about 174°C, as measured by TGA.

21. The amorphous Dolasteron mesylate of any one of claims 18 to 20, wherein the amorphous form is characterized by a DSC thermogram having an endothermic peak at a temperature of about 90°C, at a temperature of about 128°C, at a temperature of about 209°C, and a glass transition peak at a temperature of about 172°C.
22. The amorphous Dolasetron mesylate of any one of claims 18 to 21, wherein the amorphous form comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
23. The amorphous Dolasetron mesylate of claim 22, wherein the amorphous form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
24. A method for the preparation of an amorphous Dolasetron mesylate, designated form VII, comprising combining Dolasetron mesylate and methanol, and removing the methanol.
25. The method of claim 24, wherein the starting Dolasetron mesylate is dissolved in methanol, at about 15°C to about 35°C.
26. A method for preparing an amorphous Dolasetron mesylate comprising heating a Dolasetron mesylate polymorph selected from the group consisting of: crystalline form I of Dolasetron mesylate, crystalline form II of Dolasetron mesylate, crystalline form IV of Dolasetron mesylate, crystalline form VI of Dolasetron mesylate, crystalline form IX of Dolasetron mesylate, crystalline form X of Dolasetron mesylate, crystalline form XIII of Dolasetron mesylate, crystalline form XIV of Dolasetron mesylate, and mixtures thereof to a temperature of at least 160°C, for a period of at least 15 minutes.
27. The method of claim 26, wherein the starting Dolasetron mesylate forms are heated to a temperature of about 160°C to about 200°C.
28. The method of any one of claims 26 and 27, wherein the heating is done for about 30 to about 70 minutes.
29. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 14.0, 14.8, 16.1, and 18.2 ± 0.2 degrees 2-theta.

30. The crystalline Dolasetron mesylate of claim 29, wherein the crystalline form is further characterized by a powder XRD with peaks at about 9.2, 12.2, 20.9, 27.9, 29.0, and 29.6 ± 0.2 degrees 2-theta.
31. The crystalline Dolasetron mesylate of claim 30, wherein the crystalline form is further characterized by the PXRD pattern depicted in Figure 6.
32. The crystalline Dolasetron mesylate of any one of claims 29 to 31, wherein the crystalline form is further characterized by a weight loss of less than 0.1% up to a temperature of about 130°C, and by a decomposition temperature of about 200°C, as measured by TGA.
33. The crystalline Dolasetron mesylate of any one of claims 29 to 32, wherein the crystalline is further characterized by a DSC thermogram having an endothermic peak at about 209°C.
34. The crystalline Dolasetron mesylate of any one of claims 29 to 33, wherein the crystalline Form is an anhydrous form of Dolasetron mesylate.
35. A method for the preparation of crystalline Dolasetron mesylate form III comprising crystallizing Dolasetron mesylate from tert-butanol.
36. The method of claim 35, wherein the crystallization comprises providing a solution of Dolasetron mesylate in t-butanol and precipitating the said crystalline form to obtain a suspension.
37. The method of claim 36, wherein the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and t-butanol, and heating the mixture.
38. The method of claim 37, wherein the heating is to a temperature of about 70°C to about 85°C.
39. The method of any one of claims 36 and 37, wherein the precipitation of the said crystalline form is done by cooling the solution to about 15°C to about 35°C.

40. A method for preparing crystalline Dolasetron mesylate form III comprising heating a Dolasetron mesylate polymorph selected from the group consisting of: amorphous Dolasetron mesylate, crystalline Form I of Dolasetron mesylate, crystalline form XI of Dolasetron mesylate, and mixtures thereof, to a temperature of no more than 160°C, for a period of no more than 60 minutes.
41. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 13.8, 16.5, 22.1, and 25.2 ± 0.2 degrees 2-theta.
42. The crystalline Dolasetron mesylate of claim 41, wherein the crystalline form is further characterized by a powder XRD with peaks at about 9.7, 12.5, 18.0, 19.4, 20.7, and 27.5 ± 0.2 degrees 2-theta.
43. The crystalline Dolasetron mesylate of claim 42, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 7.
44. The crystalline Dolasetron mesylate of any one of claims 41 to 43, wherein the crystalline form is further characterized by a weight loss of about 0.2 to about 0.6 % up to a temperature of about 100°C, and a further weight loss of about 4.3 to about 4.5 % up to a temperature of about 200°C, as measured by TGA.
45. The crystalline Dolasetron mesylate of any one of claims 41 to 44, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 185°C.
46. The crystalline Dolasetron mesylate of any one of claims 41 to 45, wherein the crystalline form is an alcoholate solvate of Dolasetron mesylate.
47. The crystalline Dolasetron mesylate of claim 46, wherein the alcoholate is an ethanolate.
48. The crystalline Dolasetron mesylate of any one of claims 41 to 47, wherein the crystalline form comprises less than about 10 of any other forms of Dolasetron Mesylate, as measured by XRD.
49. The crystalline Dolasetron mesylate of claim 48, wherein the crystalline comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.

50. A method for the preparation of the crystalline form of Dolasetron mesylate form IV comprising combining Dolasetron mesylate and ethanol, and removing the ethanol.
51. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 13.0, 18.6 and 29.4 ± 0.2 degrees 2-theta.
52. The crystalline Dolasetron mesylate of claim 51, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.6, 17.3, 19.5, 20.1, 22.4, 24.0, and 28.2 ± 0.2 degrees 2-theta.
53. The crystalline Dolasetron mesylate of claim 52, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 8.
54. The crystalline Dolasetron mesylate of any one of claims 51 to 53, wherein the crystalline form is further characterized by a weight loss of about 0.2 to about 2.3% up to a temperature of about 100°C, and a further weight loss of about 1.5 to about 4.2 % up to a temperature of about 200°C, as measured by TGA.
55. The crystalline Dolasetron mesylate of any one of claims 51 to 54, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak, at a temperature of about 163°C, and at about 227°C, and an exothermic peak at about 185°C.
56. The crystalline Dolasetron mesylate of any one of claims 51 to 55, wherein the crystalline form is a ketone solvated Dolasetron mesylate.
57. The crystalline Dolasetron mesylate of claim 56, wherein the crystalline form is acetone solvate.
58. The crystalline Dolasetron mesylate of any one of claims 51 to 57, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron Mesylate, measured by XRD.
59. The crystalline Dolasetron mesylate of claim 58, wherein the crystalline form comprises less than about 10%, preferably, with less than about 5% of crystalline form II of Dolasetron Mesylate, as measured by XRD

60. A method for the preparation Dolasetron mesylate form V by a process comprising crystallizing Dolasetron mesylate from acetone.
61. The method of claim 60, wherein the crystallization comprises providing a solution of Dolasetron mesylate in acetone and precipitating the said crystalline form to obtain a suspension.
62. The method of claim 61, wherein the solution is provided by combining Dolasetron mesylate and acetone, and heating the mixture.
63. The method of any one of claims 61 and 62, wherein the heating is to a temperature of about 45°C to about 60°C.
64. The method of any one of claims 61 to 63, wherein the precipitation is done by concentrating the solution to obtain a suspension.
65. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.9, 15.2, and 16.0 ± 0.2 degrees 2-theta.
66. The crystalline Dolasetron mesylate of claim 65, wherein the crystalline form is further characterized by a powder XRD with peaks at about 17.3, 18.1, 19.8, 20.6, 21.4, 24.3, and 28.2 ± 0.2 degrees 2-theta.
67. The crystalline Dolasetron mesylate of claim 66, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 9.
68. The crystalline Dolasetron mesylate of any one of claims 65 to 67, wherein the crystalline form is further characterized by a weight loss of about 0.5% up to a temperature of about 120°C, and a further weight loss of about 6.1% up to a temperature of about 210°C, as measured by TGA.
69. The crystalline Dolasetron mesylate of any one of claims 65 to 68, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 155°C.
70. The crystalline Dolasetron mesylate of any one of claims 65 to 69, wherein the crystalline form is an alcoholate solvate of Dolasetron mesylate.

71. The crystalline Dolasetron mesylate of any one of claims 65 to 70, wherein the crystalline form is methanolate solvate.
72. The crystalline Dolasetron mesylate of any one of claims 65 to 71, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
73. The crystalline Dolasetron mesylate of claim 72, wherein the crystalline form comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
74. A method for the preparation of the crystalline Dolasetron mesylate form VI comprising crystallizing Dolasetron mesylate from a mixture comprising methanol as a solvent and methyltertbutyl ether as an anti-solvent.
75. The method of claim 74, wherein the crystallization comprises providing a solution of Dolasetron mesylate in methanol, and admixing the solution with methyltertbutyl ether to obtain a suspension comprising of the said crystalline form.
76. The method of claim 75, wherein the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and methanol, and heating the mixture.
77. The method of any one of claims 75 and 76, wherein the heating is to a temperature of about 60°C to about reflux.
78. The method of any one of claims 75 to 77, wherein the methyltertbutyl ether is added to the solution, to obtain a mixture containing of a sticky precipitate.
79. The method of claim 78, wherein the mixture is cooled to a temperature of about 0°C to about 10°C.
80. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 10.1, 16.3, and 22.6 ± 0.2 degrees 2-theta.

81. The crystalline Dolasetron mesylate of claim 80, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.5, 17.0, 20.1, 20.8, 25.9, 28.5, and 29.9 ± 0.2 degrees 2-theta.
82. The crystalline Dolasetron mesylate of claim 81, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 10.
83. The crystalline Dolasetron mesylate of any one of claims 80 to 82, wherein the crystalline form is further characterized by a weight loss of about 0.1- 2.8% up to a temperature of about 134°C, and a further weight loss of about 1.5 to about 6.6 %, up to a temperature of about 183°C, as measured by TGA.
84. The crystalline Dolasetron mesylate of any one of claims 80 to 83, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at about 160°C, at about 190°C, and at about 229°C.
85. The crystalline Dolasetron mesylate of any one of claims 80 to 84, wherein the crystalline Dolasetron mesylate is a carbonated solvate.
86. The crystalline Dolasetron mesylate of claim 85, wherein the crystalline Dolasetron mesylate is methylcarbonate solvate.
87. The crystalline Dolasetron mesylate of any one of claims 80 to 86, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
88. The crystalline Dolasetron mesylate of claim 87, wherein the crystalline form comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
89. A method for the preparation of crystalline Dolasetron mesylate form VIII by a process comprising crystallizing Dolasetron mesylate from a dimethylcarbonate.
90. The method of claim 89, wherein the crystallization is done by a process comprising providing a solution of Dolasetron mesylate in dimethylcarbonate, and precipitating the said crystalline form to obtain a suspension.

91. The method of claim 90, wherein the solution is provided by combining Dolasetron mesylate and dimethylcarbonate, and heating the mixture.
92. The method of claim 91, wherein the heating is to a temperature of about 85°C to about reflux.
93. The method of any one of claims 90 to 92, wherein the precipitation is done by cooling the solution to a temperature of about -10°C to about 10° C.
94. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.8, 18.3, and 27.9 ± 0.2 degrees 2-theta.
95. The crystalline Dolasetron mesylate of claim 94, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.7, 19.5, 20.3, 20.6, 22.1, 29.4, and 31.9 ± 0.2 degrees 2-theta.
96. The crystalline Dolasetron mesylate of claim 95, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 11.
97. The crystalline Dolasetron mesylate of any one of claims 94 to 96, wherein the crystalline form is further characterized by a weight loss of about 2.7 to about 4.0% up to a temperature of about 140°C, and by another weight loss of about 2.5% to about 3% up to a temperature of about 200°C, as measured by TGA.
98. The crystalline Dolasetron mesylate of any one of claims 94 to 97, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 153°C, and at about 229°C, and an exothermic peak at about 229°C.
99. The crystalline Dolasetron mesylate of any one of claims 94 to 98, wherein the crystalline Dolasetron mesylate is a nitromethane solvated form of Dolasetron mesylate.
100. The crystalline Dolasetron mesylate of any one of claims 94 to 99, wherein the crystalline form of Dolasetron Mesylate comprises less than about 30% of any other form of Dolasetron Mesylate, as measured by XRD.

101. The crystalline Dolasetron mesylate of claim 100, wherein the crystalline form of Dolasetron Mesylate comprises less than about 30% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
102. A method for the preparation of crystalline Dolasetron mesylate form IX by a process comprising crystallizing Dolasetron mesylate from a refluxed solution of Dolasetron mesylate in nitromethane; wherein the solution is refluxed at a about 98°C to about 102°C.
103. The method of claim 102, wherein the crystallization is done by a process comprising providing a solution of Dolasetron mesylate in nitromethane, at reflux temperature, and precipitating the said form to obtain a suspension.
104. The method of claim 103, wherein the solution of Dolasetron mesylate in nitromethane is provided by combining Dolasetron mesylate and nitromethane and heating the mixture.
105. The method of any one of claims 103 and 104, wherein the precipitation of the said form is done by cooling the said solution to a temperature of about 0°C to about 10°C.
106. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.4, 17.7 and 27.1 ± 0.2 degrees 2-theta.
107. The crystalline Dolasetron mesylate of claim 106, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.5, 16.5, 17.1, 18.8, 19.2, 20.4, and 21.2 ± 0.2 degrees 2-theta.
108. The crystalline Dolasetron mesylate of claim 107, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 12.
109. The crystalline Dolasetron mesylate of any one of claims 106 to 108, wherein the crystalline form is further characterized by a weight loss of less than 0.1% up to a temperature of about 120°C, and a further weight loss of about 3.3% up to a temperature of about 190°C, as measured by TGA.

110. The crystalline Dolasetron mesylate of any one of claims 106 to 109, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 180°C, and at about 197°C.
111. The crystalline Dolasetron mesylate of any one of claims 106 to 110, wherein the crystalline Dolasetron mesylate is an ether solvate.
112. The crystalline Dolasetron mesylate of claim 111, wherein the crystalline Dolasetron mesylate is a dioxane solvate.
113. The crystalline form of Dolasetron Mesylate of any one of claims 106 to 112, wherein the crystalline form comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
114. The crystalline form of Dolasetron Mesylate of claim 113, wherein the crystalline form comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
115. A method for the preparation of crystalline Form X of Dolasetron mesylate by a process comprising crystallizing Dolasetron mesylate from 1,4-dioxane.
116. The method of claim 115, wherein the crystallization is done by a process comprising providing a solution of Dolasetron mesylate in 1,4-dioxane, precipitating the said form to obtain a suspension.
117. The method of claim 116, wherein the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and 1,4-dioxane, and heating the mixture.
118. The method of claim 117, wherein the heating is to a temperature of about 95°C to about reflux.
119. The method of any one of claims 116 to 117, wherein the precipitation of the said form is done by cooling the said solution to a temperature of about 0°C to about 10°C.
120. A crystalline Dolasetron mesylate, designated Form XI, characterized by a powder XRD pattern with peaks at about 14.1, 14.9, 16.2 and 18.2 ± 0.2 degrees 2-theta.

121. The crystalline Dolasetron mesylate of claim 120, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.2, 12.9, 19.0, 20.9, 22.5, 23.6, 27.9, and 29.1 ± 0.2 degrees 2-theta.
122. The crystalline Dolasetron mesylate of claim 121, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 13.
123. The crystalline Dolasetron mesylate of any one of claims 120 to 122, wherein the crystalline form is further characterized by a weight loss of about 1.3 to about 1.5% up to a temperature of about 134°C, and a further weight loss of about 0.5% up to a temperature of about 186°C, as measured by TGA.
124. The crystalline Dolasetron mesylate of any one of claims 120 to 123, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 153°C, at about 208°C, and at about 228°C.
125. The crystalline Dolasetron mesylate of any one of claims 120 to 124, wherein the crystalline Dolasetron mesylate is an ester solvate.
126. The crystalline Dolasetron mesylate of claim 125, wherein the crystalline Dolasetron mesylate is an ethyl-lactate solvate.
127. The crystalline Dolasetron mesylate of any one of claims 120 to 126, wherein the crystalline form comprises less than about 30% of any other form of Dolasetron Mesylate, as measured by XRD.
128. The crystalline Dolasetron mesylate of claim 127, wherein the crystalline form XI of Dolasetron Mesylate comprises less than about 30% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
129. A method for the preparation of Dolasetron mesylate form XI by a process comprising crystallizing Dolasetron mesylate from a mixture comprising a ethyllactate as a solvent, and methyltertbutyl ether as an anti-solvent.
130. The method of claim 129, wherein the crystallization is done by a process comprising providing a solution of Dolasetron mesylate in ethyllactate, and

admixing the solution with methyltertbutyl ether to obtain a suspension comprising of the said crystalline form.

131. The method of claim 130, wherein the solution of Dolasetron mesylate is provided by combining Dolasetron mesylate and ethyllactate, and heating the mixture.
132. The method of claim 131, wherein the heating is to a temperature of about 40°C to about 60°C.
133. The method of any one of claims 130 to 132, wherein the methyltertbutyl ether is added to the solution, to obtain a mixture comprising a sticky precipitate.
134. The method of claim 133, wherein the mixture is cooled at a temperature of about 0°C to about 10°C.
135. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 14.7, 17.6 and 18.2 ± 0.2 degrees 2-theta.
136. The crystalline Dolasetron mesylate of claim 135, wherein the crystalline form is further characterized by a powder XRD with peaks at about 13.3, 14.0, 15.8, 20.5, 24.0, 24.9, and 27.1 ± 0.2 degrees 2-theta.
137. The crystalline Dolasetron mesylate of claim 136, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 14.
138. The crystalline Dolasetron mesylate of any one of claims 136 and 137, wherein the crystalline form is an anhydrous form of Dolasetron mesylate.
139. The crystalline Dolasetron mesylate of any one of claims 136 to 138, wherein the crystalline form is further characterized by a weight loss of about 0.2 % up to a temperature of about 150°C, as measured by TGA.
140. The crystalline Dolasetron mesylate of any one of claims 136 to 139, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 227°C.

141. The crystalline Dolasetron mesylate of any one of claims 136 to 140, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
142. The crystalline Dolasetron mesylate of claim 141, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
143. A method for the preparation of crystalline Dolasetron mesylate form XII by a process comprising crystallizing Dolasetron mesylate from toluene.
144. The method of claim 143, wherein the crystallization is done by a process comprising providing a solution of Dolasetron mesylate in toluene, and precipitating the said crystalline form to obtain a suspension.
145. The method of claim 144, wherein the solution is provided by combining Dolasetron mesylate and toluene, and heating the mixture.
146. The method of claim 145, wherein the heating is to a temperature of about 80°C to about reflux.
147. The method of any one of claims 144 to 146, wherein the precipitation of Dolasetron mesylate is done by cooling the said solution to about 15°C to about 35°C.
148. A method for preparing crystalline Dolasetron mesylate Form XI by heating a Dolasetron mesylate polymorph selected from the group consisting of: crystalline Form V of Dolasetron mesylate, crystalline form VIII of Dolasetron mesylate, and mixtures thereof.
149. The method of claim 148, wherein the starting Form of Dolasetron mesylate is heated to a temperature of about 150°C to about 220°C.
150. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 9.1, 15.0 and 18.1 ± 0.2 degrees 2-theta.
151. The crystalline Dolasetron mesylate of claim 150, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.5, 16.8, 19.4, 21.0, 22.3, 23.2 and 27.2 ± 0.2 degrees 2-theta.

152. The crystalline Dolasetron mesylate of claim 151, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 15.
153. The crystalline Dolasetron mesylate of any one of claims 150 to 152, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
154. The crystalline Dolasetron mesylate of claim 153, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
155. A method for the preparation of the crystalline Dolasetron mesylate of form XIII by a process comprising crystallizing Dolasetron mesylate from a solution of Dolasetron mesylate in nitromethane; wherein the solution is provided at about 15°C to about 35°C.
156. The method of claim 155, wherein the crystallization comprises providing a solution of Dolasetron mesylate in nitromethane at room temperature, and precipitating the said form to obtain a suspension.
157. The method of claim 156, wherein the precipitation is done by cooling the solution to a temperature of about 0°C to about 10°C.
158. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 17.4, 17.9 and 22.1 ± 0.2 degrees 2-theta.
159. The crystalline Dolasetron mesylate of claim 158, wherein the crystalline form is further characterized by a powder XRD with peaks at about 12.6, 16.6, 19.3, 20.3, 20.7, 27.8 and 29.2 ± 0.2 degrees 2-theta.
160. The crystalline Dolasetron mesylate of claim 159, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 16.
161. The crystalline Dolasetron mesylate of any one of claims 158 to 160, wherein the crystalline form is further characterized by a weight loss of about 3.9% up to a temperature of about 154°C, measured by TGA.

162. The crystalline Dolasetron mesylate of any one of claims 158 to 161, wherein the crystalline form is further characterized by a DSC thermogram having an endothermic peak at a temperature of about 161°C, and at about 229°C, and an exothermic peak at about 174°C.
163. The crystalline Dolasetron mesylate of any one of claims 158 to 162, wherein the crystalline form is a Dolasetron mesylate monohydrate.
164. The crystalline Dolasetron mesylate of any one of claims 158 to 163, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
165. The crystalline Dolasetron mesylate of claim 164, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
166. A method for the preparation of crystalline Form XIV of Dolasetron mesylate by drying the crystalline form form XIII.
167. The method of claim 166, wherein the drying is at a temperature of about 35°C to about 55°C.
168. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 12.2, 14.1, 14.8, 16.3 and 22.2 ± 0.2 degrees 2-theta.
169. The crystalline Dolasetron mesylate of claim 168, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 9.3, 18.6, 20.2, 20.6, 21.1, 22.2 and 28.2 ± 0.2 degrees 2-theta.
170. The crystalline Dolasetron mesylate of claim 169, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 17.
171. The crystalline Dolasetron mesylate of any one of claims 168 to 170, wherein the crystalline form is further characterized by a weight loss of about 7.8% up to a temperature of about 130°C, as measured by TGA.
172. The crystalline Dolasetron mesylate of any one of claims 168 to 171, wherein the crystalline form is further characterized by a DSC thermogram having an

endothermic peak at a temperature of about 60°C, at about 100°C, at about 163°C, and at about 228°C.

173. The crystalline Dolasetron mesylate of any one of claims 168 to 172, wherein the crystalline form is a Dolasetron mesylate dihydrate.
174. The crystalline Dolasetron mesylate of any one of claims 168 to 173, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of any other form of Dolasetron Mesylate, as measured by XRD.
175. The crystalline Dolasetron mesylate of claim 174, wherein the crystalline form of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
176. A method for preparing crystalline Dolasetron mesylate Form XV by exposing the crystalline Form III of Dolasetron mesylate to humidity.
177. The method of claim 176, wherein the starting crystalline Form is exposed to relative humidity of 100% at a temperature of about 20°C to about 30°C for a period of about 2 to about 14 days.
178. A crystalline Dolasetron mesylate characterized by a powder XRD pattern with peaks at about 12.1, 14.0, 14.8 15.1 and 22.1 ± 0.2 degrees 2-theta.
179. The crystalline Dolasetron mesylate of claim 178, wherein the crystalline form is further characterized by a powder XRD pattern with peaks at about 9.3, 19.6, 20.0, 20.5, 21.0, 22.1 and 28.7 ± 0.2 degrees 2-theta.
180. The crystalline Dolasetron mesylate of claim 179, wherein the crystalline form is further characterized by the PXRD pattern as depicted in Figure 18.
181. The crystalline Dolasetron mesylate of any one of claims 178 to 180, wherein the crystalline form is further characterized by a weight loss of about 7.7% up to a temperature of about 160°C, as measured by TGA.
182. The crystalline Dolasetron mesylate of any one of claims 178 to 181, wherein the crystalline form is further characterized by a DSC thermogram having an

- endothermic peak at a temperature of about 55°C, at about 85°C, at about 163°C, and at about 228°C, and an exothermic peak at about 175°C.
183. The crystalline Dolasetron mesylate of any one of claims 178 to 182, wherein the crystalline Dolasetron mesylate is an hydrated form of Dolasetron mesylate.
184. The crystalline Dolasetron mesylate of any one of claims 178 to 183, wherein the crystalline form comprises less than about 10% any other form of Dolasetron Mesylate, as measured by XRD.
185. The crystalline Dolasetron mesylate of claim 184, wherein the said crystalline form XVI of Dolasetron Mesylate comprises less than about 10% of crystalline form II of Dolasetron Mesylate, as measured by XRD.
186. A method for preparing crystalline Dolasetron mesylate Form XVI by exposing the crystalline Form XII of Dolasetron mesylate to humidity.
187. The method of claim 186, wherein the starting Dolasetron mesylate is exposed to a relative humidity of 100% at a temperature of about 15°C to about 35°C for a period of about 2 to about 14 days.
188. A method for preparing crystalline Dolasetron mesylate, designated form II, comprising combining Dolasetron base, methanesulfonic acid, and a solvent mixture comprising acetone, and water to obtain Dolasetron mesylate; and crystallizing it from the said solvent mixture.
189. The method of claim 188, wherein Dolasetron mesylate is provided by combining Dolasetron base in a solvent mixture comprising acetone and water to obtain a suspension, and admixing the suspension with methanesulfonic acid to obtain a solution comprising of Dolasetron mesylate.
190. The method of claim 189, wherein the crystallization is done by obtaining a suspension comprising the said crystalline form.
191. The method of claim 190, wherein the suspension is formed after a few minutes after the addition of methane sulfonic acid.
192. A crystalline anhydrous Dolasetron mesylate.

193. A crystalline ketone solvate of Dolasetron mesylate.
194. The crystalline ketone solvate of claim 193, wherein the ketone solvate is an acetone solvate of Dolasetron mesylate.
195. A crystalline carbonate solvate of Dolasetron mesylate.
196. The crystalline carbonate solvate of claim 195, wherein the carbonate solvate is a methyl carbonate solvate of Dolasetron mesylate.
197. A crystalline ether solvate of Dolasetron mesylate.
198. The crystalline ether solvate of claim 197, wherein the ether solvate is a 1,4 dioxane solvate of Dolasetron mesylate.
199. A crystalline ester solvate of Dolasetron mesylate.
200. The crystalline ester solvate of claim 199, wherein the ester solvate is an ethyl lactate solvate of Dolasetron mesylate.
201. A crystalline nitromethane solvate of Dolasetron mesylate.
202. A crystalline hydrated Dolasetron mesylate.
203. The crystalline hydrated Dolasetron mesylate of claim 202, wherein the hydrated Dolasetron mesylate is a monohydrate or dihydrate of Dolasetron mesylate.
204. A pharmaceutical composition comprising a crystalline Dolasetron mesylate polymorph selected from the group consisting of: form I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, and at least one pharmaceutically acceptable excipient.
205. A method for preparing a pharmaceutical formulation comprising combining a crystalline Dolasetron Mesylate polymorph selected from the group consisting of: Form I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, with at least one pharmaceutically acceptable excipient.

206. A method for preparing a pharmaceutical formulation comprising combining a crystalline Dolasetron Mesylate polymorph selected from the group consisting of: Form I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI prepared according to the processes of the present invention, with at least one pharmaceutically acceptable excipient.
207. A method of treating a patient comprising administering a therapeutically effective amount of any one of crystalline Dolasetron mesylate forms I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, or mixtures thereof, to a patient in need thereof.
208. Use of any one of crystalline Dolasetron mesylate forms I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, and XVI, or mixtures thereof for the manufacture of a pharmaceutical composition.

FIGURES

Fig.1: powder XRD pattern for Dolasetron Mesylate crystalline form of the present invention.

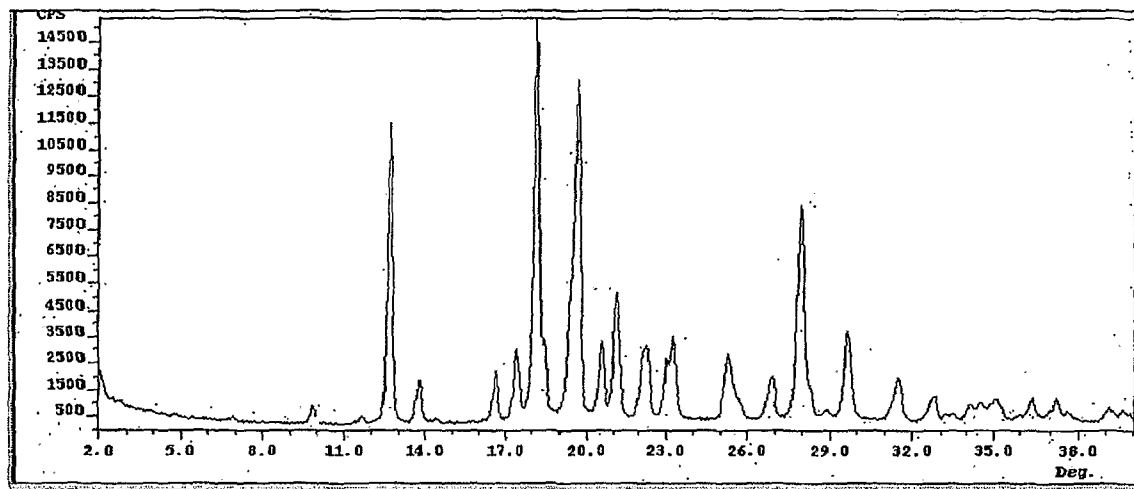


Fig.2. DSC thermogram for Dolasetron Mesylate crystalline form of the present invention.

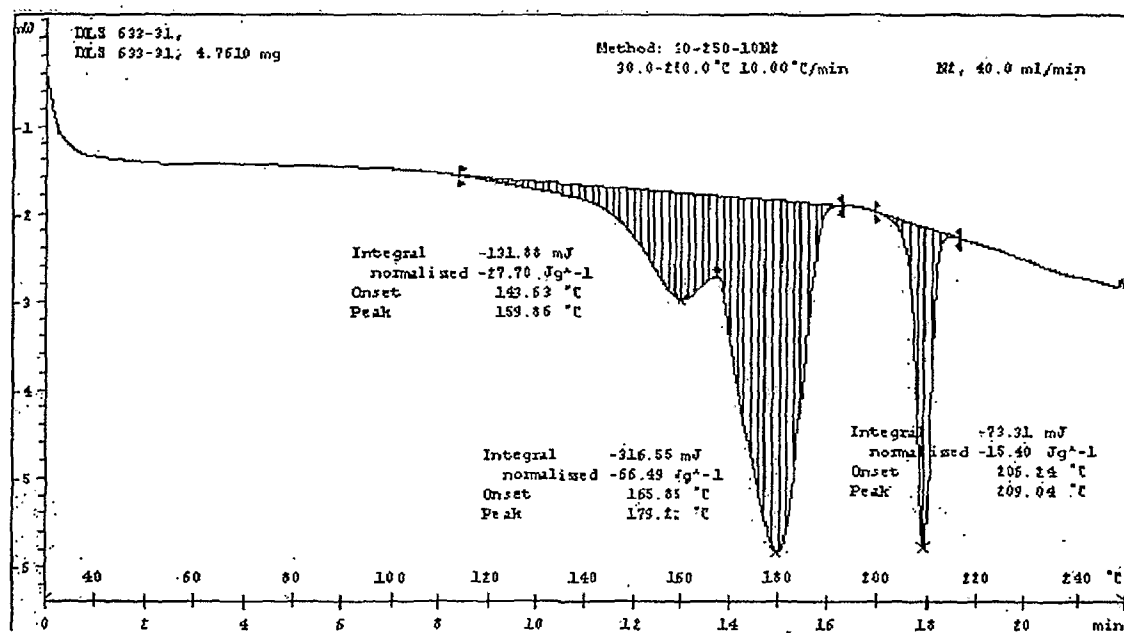


Fig.3. TGA thermogram for Dolasetron Mesylate crystalline form of the present invention.

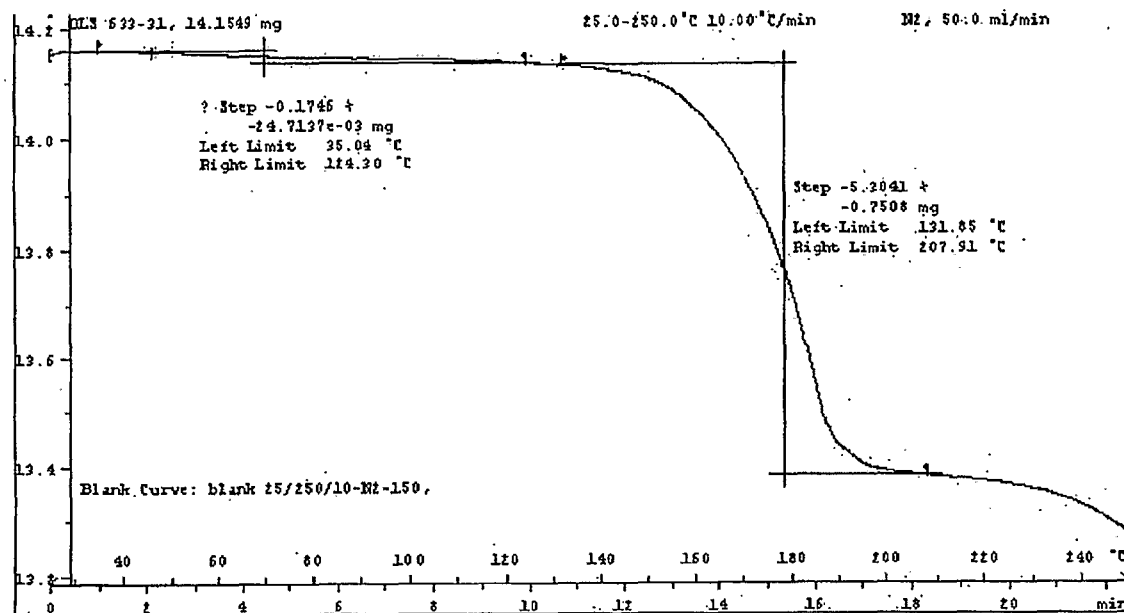


Fig. 4. powder XRD pattern for dried Dolasetron mesylate prepared according to EP patent No. 0339669.

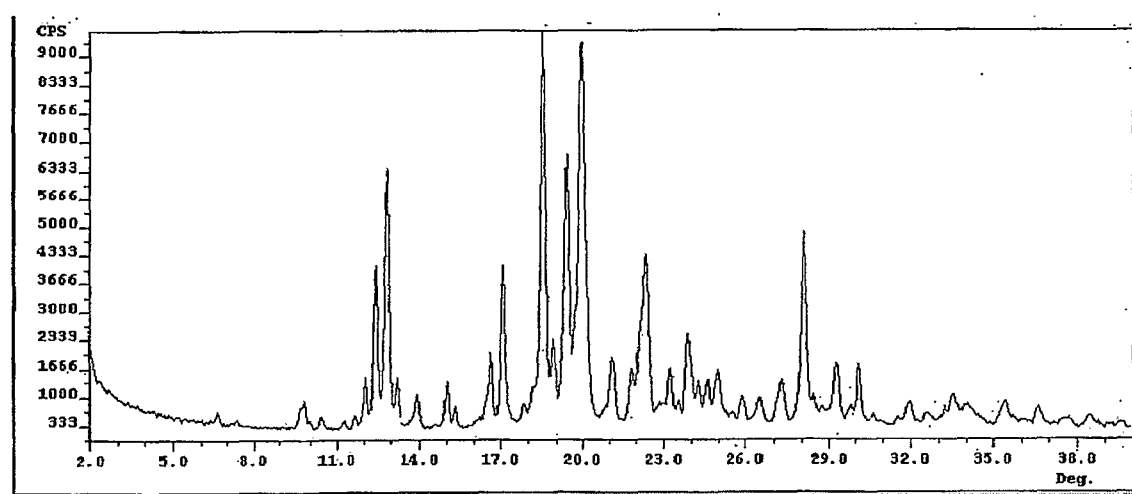


Figure 5: powder XRD pattern of the amorphous form of Dolasetron mesylate.

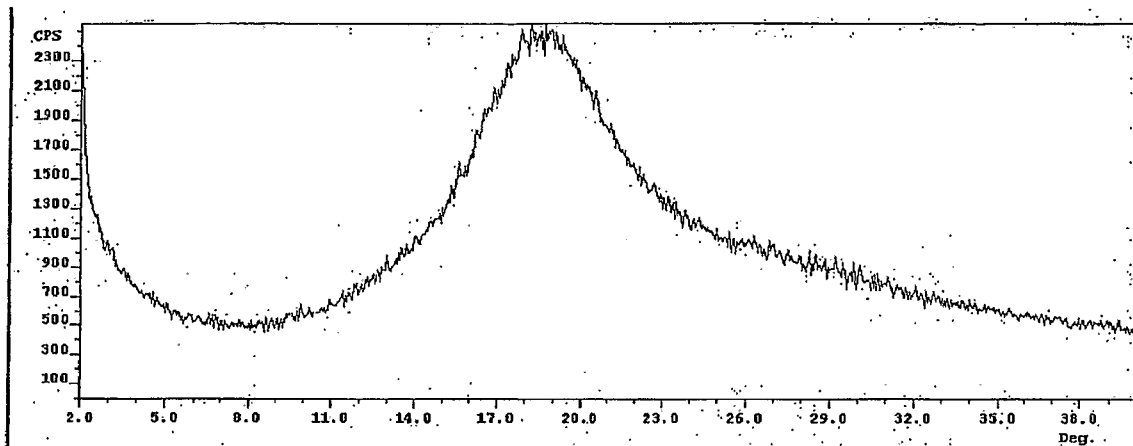


Figure 6: powder XRD pattern of Dolasetron mesylate Form III.

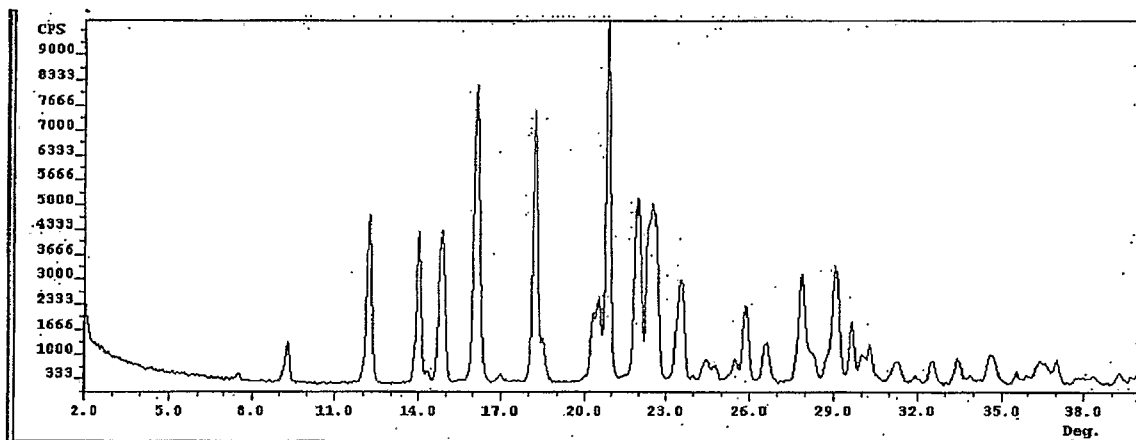


Figure 7: powder XRD pattern of Dolasetron mesylate Form IV.

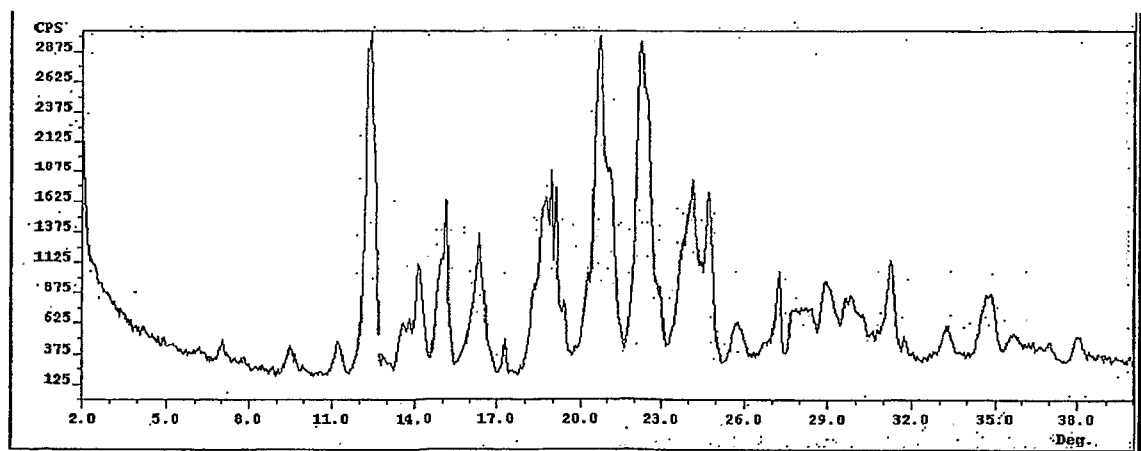


Figure 8: powder XRD pattern of Dolasetron mesylate Form V.

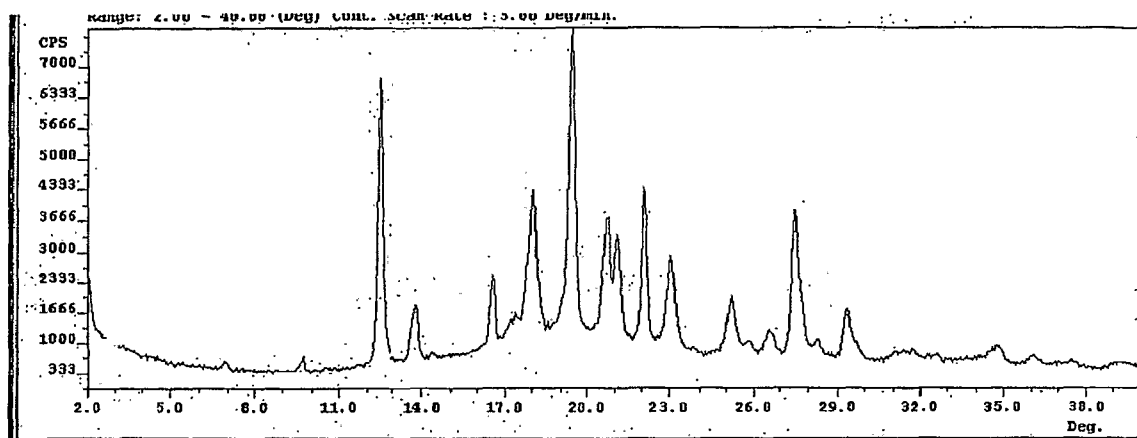


Figure 9: powder XRD pattern of Dolasetron mesylate Form VI.

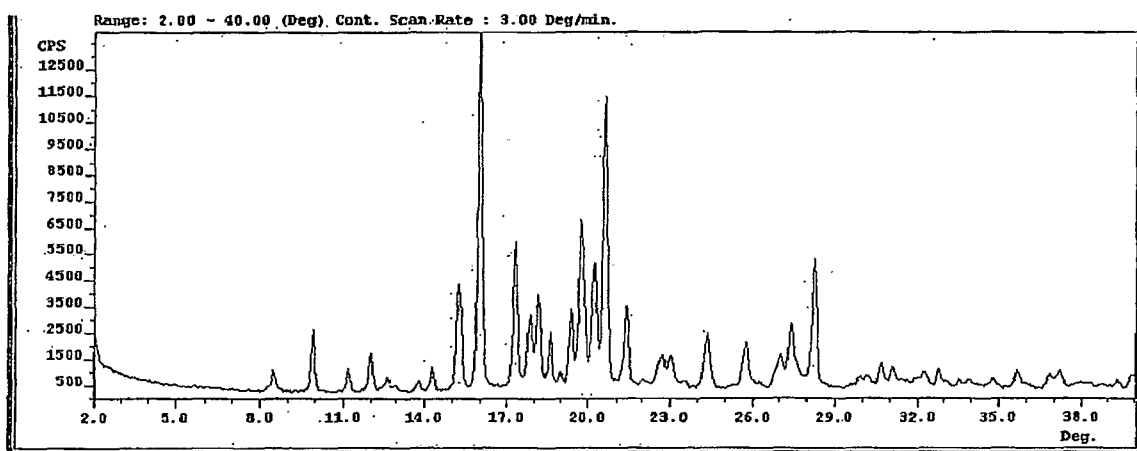


Figure 10: powder XRD pattern of Dolasetron mesylate Form VIII.

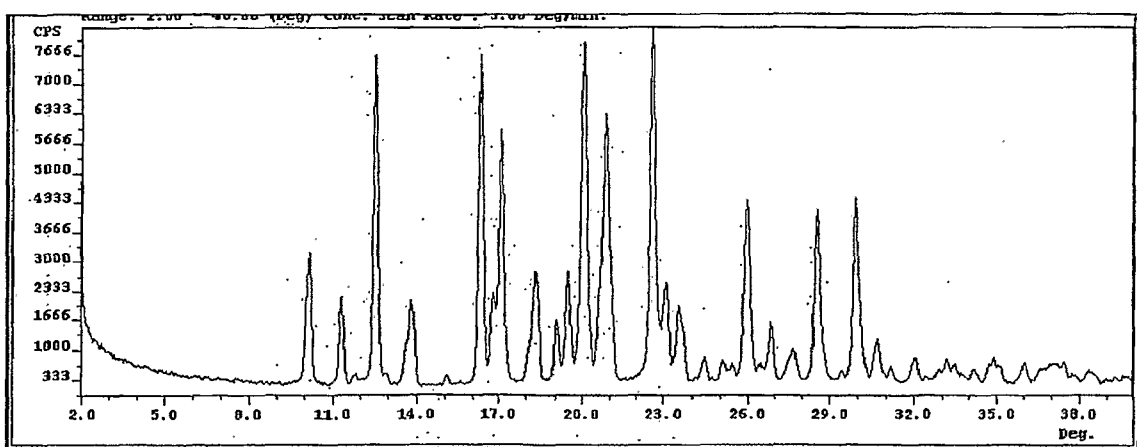


Figure 11: powder XRD pattern of Dolasetron mesylate Form IX.

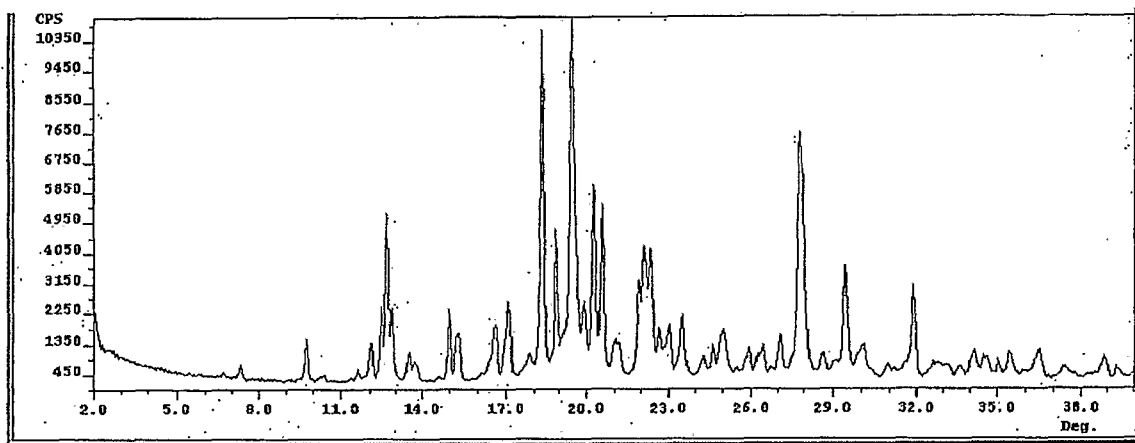


Figure 12: powder XRD pattern of Dolasetron mesylate Form X.

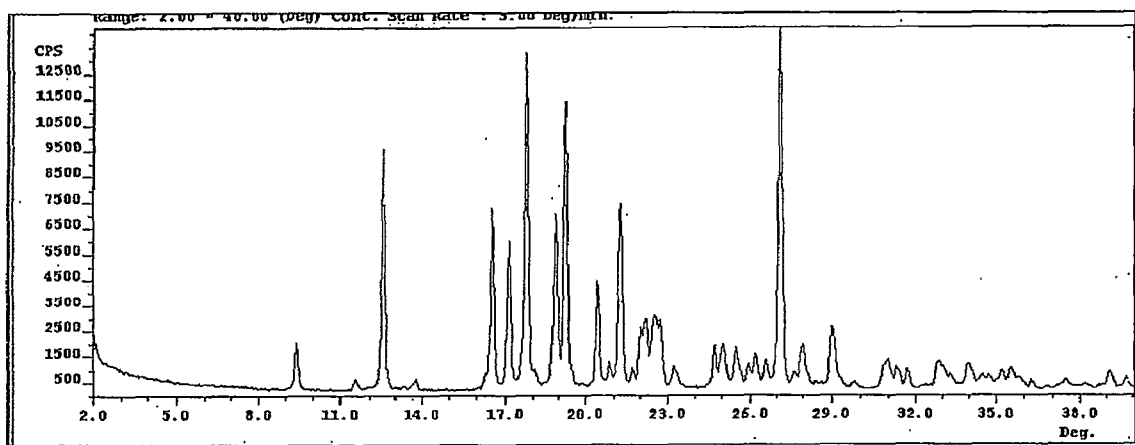


Figure 13: powder XRD pattern of Dolasetron mesylate Form XI.

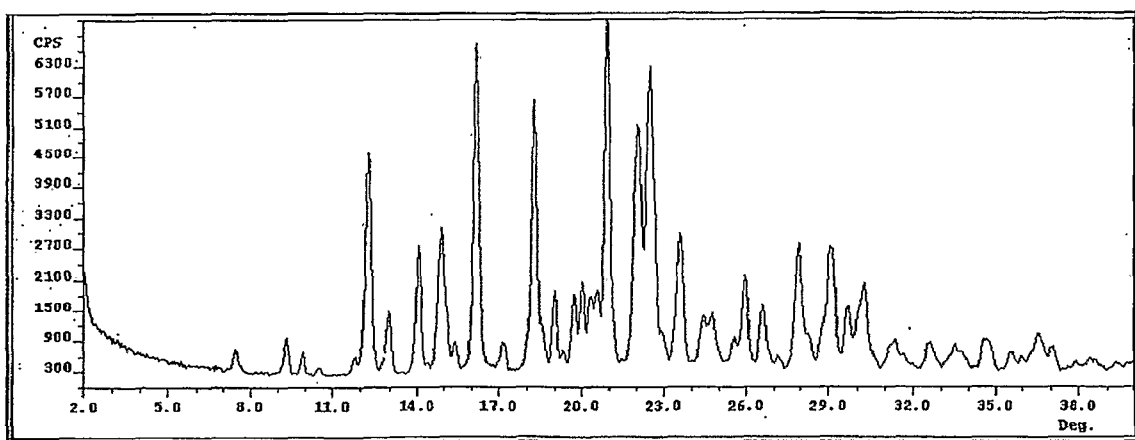


Figure 14: powder XRD pattern of Dolasetron mesylate Form XII.

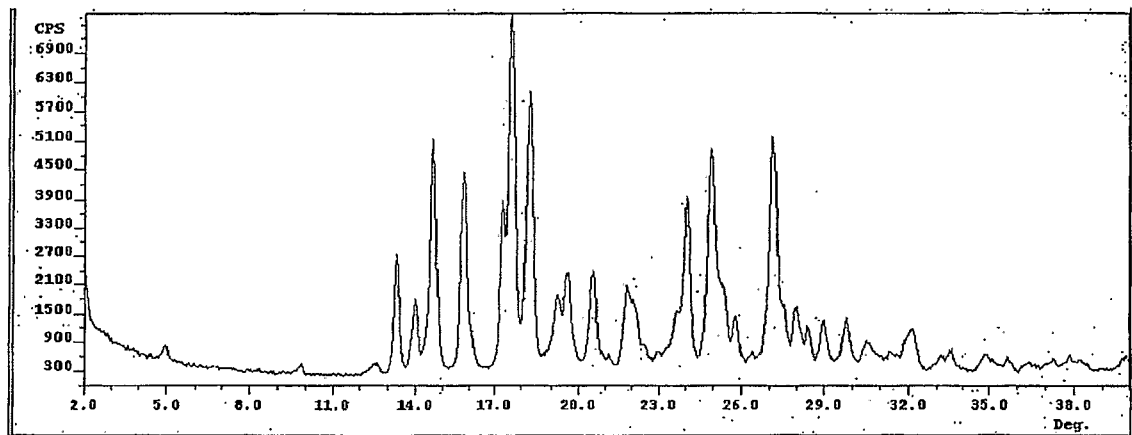


Figure 15: powder XRD pattern of Dolasetron mesylate Form XIII.

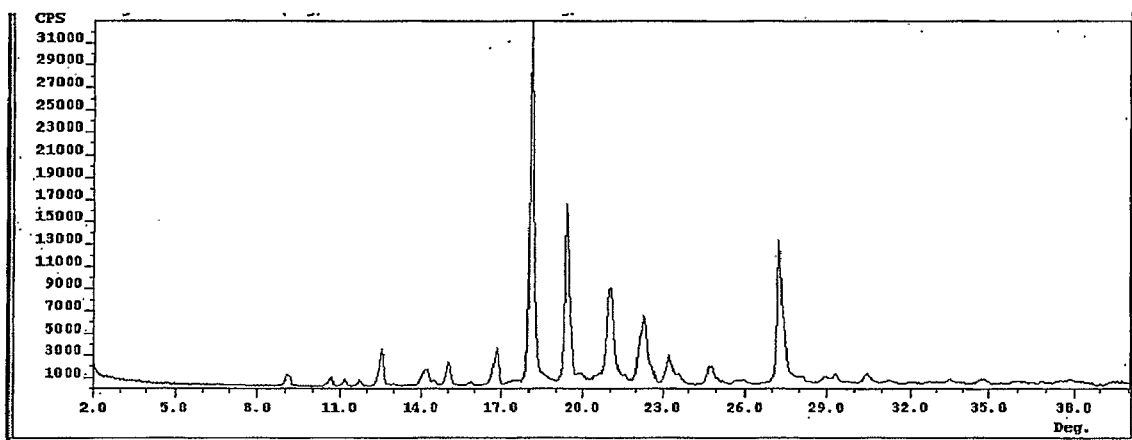


Figure 16: powder XRD pattern of Dolasetron mesylate Form XIV.

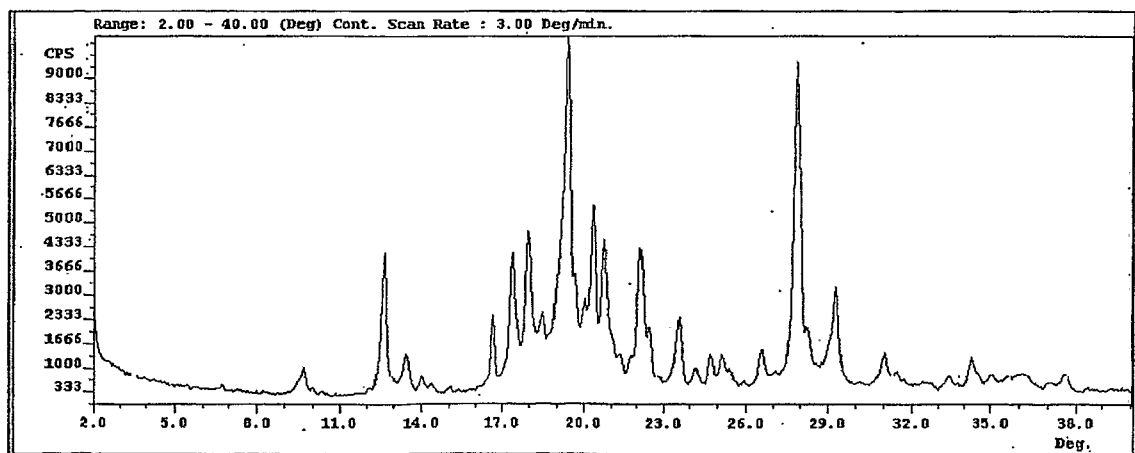


Figure 17: powder XRD pattern of Dolasetron mesylate Form XV

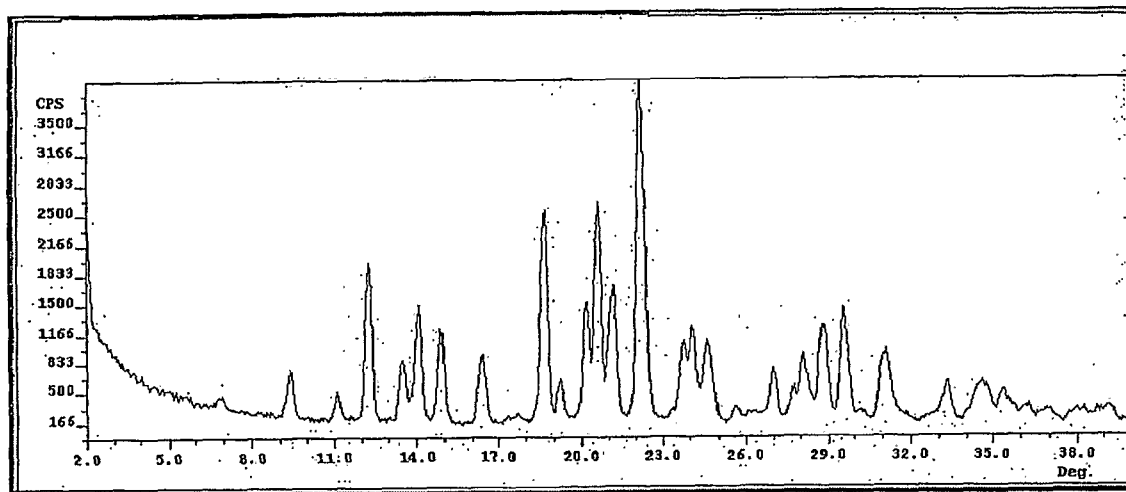


Figure 18: powder XRD pattern of Dolasetron mesylate Form XVI

