Title: DASATINIB GLUCURONATE SALTS AND PROCESS FOR PREPARATION THEREOF

Abstract: The present invention relates to novel pharmaceutically acceptable glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof. (I) The present invention further relates to the processes for preparation of the said glucuronic acid addi-
tion salt of Dasatinib. The glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof may be useful as an anti-cancer
agent.
DASATINIB GLUCURONATE SALT & PROCESS FOR PREPARATION THEREOF

FIELD OF INVENTION

The present invention relates to novel pharmaceutically acceptable glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof.

\[ \text{(I)} \]

The present invention further relates to the processes for preparation of the said glucuronic acid addition salt of Dasatinib. The glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof may be useful as an anti-cancer agent.

BACKGROUND OF THE INVENTION

Dasatinib is chemically described as \( N\text{-}(2\text{-chloro-6-methylphenyl})\text{-}2\text{-}[6\text{-}[4\text{-}(2\text{-hydroxyethyl})\text{-}1\text{-piperazinyl}]\text{-}2\text{-methyl-4-pyrimidinyl}\text{amino}]\text{-}5\text{-thiazolecarboxamide} \) and is represented by Formula (Ia).

\[ \text{(Ia)} \]

The monohydrate form of Dasatinib is a kinase inhibitor and has been approved by USFDA as SPRYCEL\textsuperscript{TM} for the treatment of chronic phase Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukemia (CML), in newly diagnosed adult patients or patients having resistance or intolerance to prior therapy like Imatinib. SPRYCEL\textsuperscript{TM} is also indicated for the treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Das et al in US patent No. 6596746 B1 provided the first disclosure of the compound Dasatinib along with the process for preparation thereof. Further to this Lajeunesse et al. in
US 7491725 B2 provided the crystalline monohydrate, crystalline butanol solvate, crystalline ethanol solvate and neat forms of Dasatinib.

Chidambaram et al in WO2007035874 A1 disclosed various pharmaceutically acceptable salt forms of Dasatinib. The pharmaceutically acceptable salts disclosed in WO2007035874 A1 are for example, fumaric acid, hydrobromic acid, maleic acid, methanesulfonic acid, phosphoric acid, salicylic acid, sulfuric acid, tartaric acid, or p-toluene sulfonic acid.

Amongst other disclosures, Vraspir et al in WO2010062715 A2 disclosed isosorbide dimethyl ether solvate, N,N'-dimethylene urea solvate and N,N'-dimethyl-N,N'-propylene urea solvate of Dasatinib. Also, Parthasaradhi et al in WO 2010067374 A2 disclosed crystalline solvates of Dasatinib with DMF, DMSO, toluene, isopropyl acetate and processes for their preparation.

Exploring new forms of compound may be advantageous for dosage form development and enhancing bioavailability owing to the altered physiochemical properties. Some of the forms may turn out to be more efficacious than the other reported forms. It has generally been observed that different salts of the base compound have improved physical and chemical properties without affecting the pharmacological action of the drug and hence provide an opportunity to improve the drug performance characteristics of such product.

As per the available disclosures, still there appears to be a need for new salt forms of Dasatinib having further improved physical and/or chemical properties. Hence it was thought worthwhile by the inventors of the present application to explore novel pharmaceutically acceptable salts of Dasatinib, which may further improve the characteristics of drug Dasatinib.

Hence, inventors of the present application report glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof. The choice of glucuronic acid for salt formation with Dasatinib base has been based on the premise that this salt is sufficiently stable, pharmaceutically acceptable and may have acceptable safety profile.

Thus, present application provides novel pharmaceutically acceptable salt of glucuronic acid with Dasatinib or its hydrate or solvate thereof, and processes for its preparation. This new salt of Dasatinib as per present application is found to be stable and offers various advantages in terms of storage, shelf life, solubility, safety profile and improved physical and/or chemical properties.
SUMMARY OF THE INVENTION

Particular aspects of the present specification relate to the novel pharmaceutically acceptable glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof and processes for its preparation. Further, the invention of this application also relates to pharmaceutical compositions comprising of glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof, which may be useful in the treatment of various cancerous disorders.

In one aspect of the present application, the present invention provides glucuronic acid addition salt of Dasatinib represented by Formula (I)

![Chemical Structure](image)

(I)

or its hydrate or solvate thereof.

In a further aspect of the present application, glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, contains Dasatinib base and glucuronic acid in about 1:1 proportion.

In another aspect of the present application, glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, exists in a crystalline form or as an amorphous solid. In a particular aspect of the present application, glucuronic acid addition salt of Dasatinib, or its hydrate or solvate thereof, is provided as an amorphous solid characterized by IR spectrum having at least 6 absorption peaks selected from 3255.9 cm\(^{-1}\), 2921.1 cm\(^{-1}\), 1610.1 cm\(^{-1}\), 1540.2 cm\(^{-1}\), 1318.5 cm\(^{-1}\), 1209.9 cm\(^{-1}\), 1146.8 cm\(^{-1}\), 1051.6 cm\(^{-1}\), 812.16 cm\(^{-1}\) and 776.9 cm\(^{-1}\), and DSC isotherm comprising at least one endothermic peak ranging between 135 to 145 °C.

In yet another aspect of the present application, it relates to a process for preparing glucuronic acid addition salt of Dasatinib comprising the steps of:
a) providing a solution of Dasatinib in an organic solvent;

b) addition of glucuronic acid of Formula (A) to the reaction mixture;

c) stirring the reaction mixture for time duration ranging from 10-60 mins;

d) heating the reaction mixture to a temperature ranging between 35 °C to reflux temperature of the solvent used;

e) lowering the temperature of reaction mixture to a temperature below 30 °C;

f) removing the solvent from the reaction mixture;

g) optionally treating the solid material obtained in step f) with organic solvent;

h) Isolating the glucuronic acid addition salt of Dasatinib.

In another aspect, the present invention also relates to a composition comprising glucuronic acid addition salt of Dasatinib or a hydrate or solvate thereof together with at least one or more pharmaceutically acceptable excipient. Further particular aspects of the present invention are detailed in the description of the invention, wherever appropriate.

15 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an example of X-ray powder diffraction ("XRPD") pattern of Dasatinib Glucuronate obtained as per process of Example 1.

Fig. 2 is an example of Differential Scanning Calorimetry ("DSC") curve of Dasatinib Glucuronate obtained as per process of Example 1.

Fig. 3 is an example of IR spectral pattern of Dasatinib Glucuronate obtained as per process of Example 1.
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<tr>
<td>DMF</td>
<td>DiMethylFormamide</td>
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<tr>
<td>DMSO</td>
<td>DiMethylSulfoXide</td>
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<tr>
<td>DMAc</td>
<td>DiMethylAcetamide</td>
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<tr>
<td>DSC</td>
<td>Differential Scanning Calorimetry</td>
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<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
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<tr>
<td>^1H NMR</td>
<td>Proton Nuclear Magnetic Resonance</td>
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<tr>
<td>KF</td>
<td>Karl Fischer Method</td>
</tr>
<tr>
<td>NMP</td>
<td>N-MethylPyrrolidone</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
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<tr>
<td>THF</td>
<td>TetraHydroFuran</td>
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<td>TGA</td>
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<td>XRPD</td>
<td>X-Ray Powder Diffraction</td>
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DETAILED DESCRIPTION

As set forth herein, embodiments of the present invention relate to novel glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof and processes for its preparation.

In one embodiment of the present application, it provides glucuronic acid addition salt of Dasatinib represented by Formula (I),

![Chemical Structure](image)

or its hydrate or solvate thereof.

In another embodiment of the present application, glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, contains Dasatinib base and glucuronic acid in a ratio of about 1:1. Ratio of about 1:1 means that the glucuronic acid addition salt of the present
application has Dasatinib base and glucuronic acid in stoichiometric ratio of 1:1. This composition may vary up to range of ± 5% (mole ratios) i.e. stoichiometric ratio may range from 1: 0.95 to 1: 1.05, without deviating from the spirit of the invention. Said compositions of about 1:1 stoichiometric ratio are found to retain their characteristic solid state parameters.

5 In a further embodiment of the present application, glucuronic acid addition salt of Dasatinib represented by Formula (I) or its hydrate or solvate thereof may be present in crystalline solid form or as an amorphous material.

In a preferred embodiment of the present invention glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, prepared according to the process of the present invention, is present in a substantially amorphous form and is characterized by:

a) X-ray powder diffraction pattern substantially according to Fig-1;

b) Differential Scanning Calorimetry ("DSC") curve substantially according to Fig-2; and

c) IR spectral pattern substantially according to Fig-3.

15 In a still further embodiment of the present application, it provides stable amorphous glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, characterized by IR spectrum having at least 6 absorption peaks selected from 3255.9 cm⁻¹, 2921.1 cm⁻¹, 1610.1 cm⁻¹, 1540.2 cm⁻¹, 1318.5 cm⁻¹, 1209.9 cm⁻¹, 1146.8 cm⁻¹, 1051.6 cm⁻¹, 812.16 cm⁻¹ and 776.9 cm⁻¹, and DSC isotherm comprising at least one endothermic peak ranging between 135 to 145 °C.

The XRPD pattern of Dasatinib glucuronate obtained by the process of the present invention shows no peaks thus demonstrating the amorphous nature of the solid with absence of any long range orderly pattern which is characteristic of crystalline materials.

Dasatinib glucuronate obtained by the process of the present invention is a substantially amorphous form. Term substantially amorphous means at least 80%, preferably 90%, more preferably 95%, and most preferably 99% by weight of the solid Dasatinib glucuronate obtained as final product is in the form of an amorphous solid. The remainder of the Dasatinib glucuronate in the final product, e.g., 20%, preferably 10%, more preferably 5%, and most preferably 1% or less of the total weight of Dasatinib glucuronate, may be in crystalline form. All percentages are based upon the total amount of the solid Dasatinib glucuronate obtained as the final product.
For the unknown mixture of crystalline and amorphous compounds, the intensities of the 100% peak(s) in the mixture, relative to an intensity of this peak in a calibration mixture, may be used to determine the percentage of the crystalline form in the mixture, with the remainder determined to be the amorphous material.

The glucuronic acid addition salt of Dasatinib (I) described herein may be characterized and analyzed by X-ray powder diffraction pattern (XRPD) on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu Ka radiation using the wavelength 1.5418 Å and lynx Eye detector. IR study was performed on Perkin Elmer Spectrum ES Version 10.03.03 instrument. DSC was done on a Perkin Elmer Pyris 7.0 instrument. Illustrative examples of analytical data for the Dasatinib glucuronate obtained in the examples are set forth in the Figs. 1-3.

The novel salt form of Dasatinib i.e. Dasatinib glucuronate as described by the present application has been found to be quite stable and easy to handle and store for longer time without any measurable changes in its morphology and physicochemical characteristics, while retaining its properties within the defined limits. This may offer advantages for large scale manufacturing in terms of handling, storage, shelf life and favorable impurity profile. Besides the physical/chemical properties, the novel salt form of the current application further provides advantage in terms of solubility of the drug and hence provides possibility of better bioavailability and pharmacological profile.

In another embodiment of the present application, it provides a process for preparing glucuronic acid addition salt of Dasatinib (I),

![Formula Image](image)

(I)

comprising the steps of:

a) providing a solution of Dasatinib with an organic solvent;

b) addition of glucuronic acid of Formula (A) to the reaction mixture;

![Formula Image](image)

(A)
c) stirring the reaction mixture for time duration ranging from 10-60 mins;
d) heating the reaction mixture to a temperature ranging between 35 °C to reflux temperature of the solvent used;
e) lowering the temperature of reaction mixture to a temperature below 30 °C;
f) removing the solvent from the reaction mixture;
g) optionally treating the solid material obtained in step f) with organic solvent;
h) isolating the glucuronic acid addition salt of Dasatinib.

The individual steps of the process according to the present invention for preparing glucuronic acid addition salt of Dasatinib (I) are detailed separately herein below.

Step a) comprises providing a solution of Dasatinib in an organic solvent;

Dasatinib from any source is added to an organic solvent, selected from C1-C4 alcohol, DMSO (dimethylsulfoxide), DMF (dimethylformamide), NMP (N-methylpyrrolidone), Acetonitrile, Dimethyl acetamide and THF (Tetrahydrofuran). In one of the preferred embodiment C1-C4 alcohol is used 2-20 times v/w (mL/g) w.r.t. weight of Dasatinib. C1-C4 alcohol used in this step may be selected from methanol, ethanol, n-propanol or iso-propanol. Dasatinib used as starting material for this reaction may be in the form of a hydrate or solvate or may be present as anhydrous/non-solvate form. Hydrate forms of Dasatinib may have variable moisture content, depending upon the source from which the Dasatinib starting material is procured.

Step b) comprises addition of glucuronic acid of Formula (A) to the reaction mixture;

![Glucuronic Acid](https://via.placeholder.com/150)

(A)

To the solution obtained from step a), glucuronic acid of Formula (A) is added in the mole ratio of 1.0 to 1.5 w.r.t. amount of Dasatinib. Addition of glucuronic acid to the reaction mixture is done at a temperature ranging between 20-80 °C. Glucuronic acid may optionally be added to the reaction mixture in the form of a solution in water or a suitable organic solvent. When glucuronic acid is added to the reaction mixture in solution form, addition is performed slowly over time duration of 10-20 mins.

Step c) comprises stirring the reaction mixture for time duration ranging from 10-60 mins;
The reaction mixture obtained in step b) is stirred for time duration ranging between 10-60 mins depending upon the dissolution of the reaction mixture.

Step d) comprises heating the reaction mixture to a temperature ranging between 35 °C to reflux temperature of the solvent used;

The reaction mixture obtained in step c) is heated to a temperature above 35 °C. Heating may be performed till the reflux temperature of the solvent used is achieved. The reaction mixture may be maintained at the raised temperature for the time duration ranging from 10 mins to 2 hrs depending upon the progress of the reaction and the batch size involved.

Step e) comprises lowering the temperature of reaction mixture to a temperature below 30 °C;

The reaction mixture obtained in step d) is allowed to cool down to a temperature below 30 °C. According to requirements and RT conditions, cooling may be performed in a controlled manner wherein cooling rate may be specified at not more than 1°C per min.

Step f) comprises removing the solvent from the reaction mixture;

From the reaction mixture obtained in step e) the solvent is recovered up to 90 to 95% of the amount of solvent present in original reaction mixture. Recovery of the solvent may be performed under reduced pressure conditions by techniques known to the person skilled in the art. In one of the preferred embodiment recovery of the solvent may be performed by distillation under vacuum at a raised temperature of 35-55 °C.

Step g) comprises optionally treating the solid material obtained in step f) with organic solvent;

The solid material obtained in step f) is optionally treated with other organic solvent selected from C3-C6 ketonic solvent like acetone and/or C2-C6 ether solvent like Diisopropyl ether, Tetrahydrofuran (THF) and MTBE or a mixture thereof. According to an embodiment of the present invention, other organic solvent may be utilized in a sequential manner wherein drying of the reaction mass may be performed between the treatment with two different solvents. The organic solvents used for this step may be utilized at a raised temperature of about 50-55 °C and in amount 5-35 times in volume (mL) w.r.t. the amount of Dasatinib (in
g) initially taken for the reaction. Organic solvent may be added to the reaction mixture in step-wise manner along with intermittent recovery of the solvents. The reaction mixture may finally be cooled to a temperature below 30 °C, wherein stirring may be performed for time duration of 1-4 hrs depending upon the isolation of the solid material. The solid material obtained may be filtered from the reaction mass by conventional methods well known in the prior art, and given a washing with the organic solvent used earlier.

**Step h)** comprises isolating the glucuronic acid addition salt of Dasatinib.

The solid material obtained in step g) is then dried at a temperature above 45 °C for a time duration ranging between 5-15 hrs, thus providing the pure glucuronic acid addition salt of Dasatinib as end product. Reduced pressure conditions may also be suitably utilized by person skilled in the art in order to isolate the glucuronic acid addition salt of Dasatinib. Drying may also be performed by any conventional process not limited to spray drying etc.

Process of isolating glucuronic acid addition salt of Dasatinib may also comprise other processes but not limited to conventional processes including scrapping, if required filtering from slurry and drying, which may be carried out at room temperature or a bit raised temperature for the suitable durations.

In a preferred embodiment, the moisture content of the final API obtained by the process of the present invention ranges from 2.5 to 4%. Without deviating from the scope of the invention, the Dasatinib glucuronate salt obtained as end product may be in the form of a hydrate or a solvate thereof. Moisture content may be measured by any recognized technology, for example by using Karl Fischer method (KF) and an appropriate instrument (goniometer) such as a Mettler DL-35, a Scintag PAD V, a Brukker D5000, or by TGA analysis using moisture analysis instruments such as the Mettler DSC20, TG50, and TC10A.

In another preferred embodiment the Dasatinib glucuronate obtained by the process of the present invention is obtained as an amorphous material but by suitable modifications of the process using methods well known in the prior art, the end product may be obtained as a crystalline solid also.

The merit of the process according to the present invention resides in that - product isolated after drying is adequately stable to handle and store for longer time (alateast up to more than 6 months) without any significant or measurable change in its morphology and physicochemical characteristics. Dasatinib glucuronate obtained according to the process of the present invention results in the final API purity by HPLC of more than 99 % w/w.
Dasatinib glucuronate salt as per the invention of present application additionally offers advantage in terms of good solubility in water as compared to any other known form of Dasatinib.

It is worth mentioning that glucuronic acid used in the present invention is found to occur naturally and may be obtainable by synthetic processes as well. Glucuronic acid is a naturally occurring carboxylic acid and is reported to be present in food articles like Kombucha, which is an effervescent fermentation of sweetened tea that is used as a functional food. Otherwise, glucuronic acid is commonly found in carbohydrate chains of proteoglycans and is part of mucous animal secretions (such as saliva), cell glycocalyx and intercellular matrix. In the animal body, glucuronic acid is involved in the xenobiotic metabolism of substances such as bilirubin, androgens, estrogens, mineralocorticoids, glucocorticoids, fatty acid derivatives, retinoids, and bile acids.

The formation of glucuronic acid takes place in the liver of animals, including humans and other primates, and is derived from glucose. In most of the plants and mammals glucuronic acid is also a precursor of ascorbic acid, which is also known as Vitamin C. Moreover, glucuronic acid is part of the natural detoxification process in the body. Hence it has also been looked at as a treatment for certain diseases, most notably prostate cancer. In addition to removing harmful toxins in the body it also appears to regulate testosterone levels, which can help with this type of cancer.

In a further embodiment according to this patent’s specification, the invention also relates to a composition containing glucuronic acid addition salt of Dasatinib (I) or a hydrate or solvate thereof.

The glucuronic acid addition salt of Dasatinib (I) or a hydrate or solvate thereof obtained by the process of the present application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product is mixed with one or more pharmaceutically acceptable excipients. The drug substance can be formulated as liquid compositions for oral administration including solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerin, propylene glycol or liquid paraffin.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several
ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients used in the compositions comprising glucuronic acid addition salt of Dasatinib (I) or a hydrate or solvate thereof, of the present application include, but are not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, pre-gelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, Croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Pharmaceutically acceptable excipients used in the compositions of glucuronic acid addition salt of Dasatinib or a hydrate or solvate thereof of the present application may also comprise to include the pharmaceutically acceptable carriers used for the preparation of solid dispersion, wherever utilized in the desired dosage form preparation.

EXAMPLE

Example-01: PROCESS FOR PREPARATION OF DASATINIB GLUCURONATE

20 mL methanol was charged into a 100 mL round bottomed flask at 25-30°C and 2.0 g Dasatinib monohydrate and 0.80 g Glucuronic acid was added to it. The reaction mixture was stirred for 15 mins, followed by heating to a temperature of ~ 65 °C. Further stirring of the reaction mixture was performed for 30 mins maintaining the temperature of ~ 65 °C. Then the reaction mixture was allowed to cool down to a temperature of ~ 25 °C.

The reaction mixture was subjected to distillation under vacuum at a temperature of ~ 55° C, till approximately 1/10 of initial volume of reaction mixture was left. Then 10.0 mL acetone was added to the reaction mixture. Again the reaction mixture was subjected to
distillation under vacuum at temperature of ~ 55°C, till approximately 1/10 of initial volume of reaction mixture was left. At the same raised temperature of ~ 55°C, 20.0 mL of acetone was added to the reaction mixture and the reaction mixture was allowed to cool to ~ 25 °C. The obtained reaction mixture was stirred for about 1 h at this temperature. The solid obtained was filtered and washed with 4.0 mL chilled acetone.

The reaction mass was then suck dried and the wet material obtained was unloaded. The wet material was further dried under vacuum at a temperature of ~ 65 °C for 8 hrs, to obtain 2.60 g Dasatinib glucuronate having XRPD pattern according to Fig-1, DSC pattern according to Fig-2 and IR spectrum according to Fig-3.

Yield: 94.2 %  Moisture Content (By KF method): 3.43 %

\[ ^1H \text{ NMR (400 MHz, DMSO-d}_6) \delta 11.45 \text{ (s, 1H), 9.8 (s, 1H), 8.22 (s, 1H), 7.4 (m, 2H), 7.28 (dd, 2H), 6.4 (br-s, 1H), 6.05 (s, 1H), 4.9 (s, 1H), 4.45 (t, 1H), 4.3 (d, 1H), 3.9 (d, 1H), 3.5 (m, 6H), 3.5 (m, 2H), 3.4 (m, 1H), 3.1 (m, 1H), 2.9 (t, 1H), 2.48 (m, 3H), 2.44 (m, 3H), 2.41 (s, 3H), 2.24 (s, 3H) \]

**Example-02: PROCESS FOR PREPARATION OF DASATINIB GLUCURONATE**

20 mL methanol was charged into a 100 mL round bottomed flask at 25-30°C and 2.0 g Dasatinib (Moisture Content: 1.4%) and 0.83 g Glucuronic acid was added to it. The reaction mixture was stirred for 20 mins, followed by heating to a temperature of ~ 65 °C. Further stirring of the reaction mixture was performed for 30 mins maintaining the temperature of ~ 65 °C. Then the reaction mixture was allowed to cool down to a temperature upto ~ 25 °C.

The reaction mixture was subjected to distillation under vacuum at a temperature of ~ 50°C, till approximately 1/10 of initial volume of reaction mixture was left. Then 10.0 mL acetone was added to the reaction mixture. Again the reaction mixture was subjected to distillation under vacuum at temperature of ~ 50°C, till approximately 1/10 of initial volume of reaction mixture was left. At the same raised temperature of ~ 50°C, 20.0 mL of acetone was added to the reaction mixture and the reaction mixture was allowed to cool to ~ 25 °C. The obtained reaction mixture was stirred for about 1.0 h at this temperature. The solid obtained was filtered and washed with 4.0 mL chilled acetone.
The reaction mass was then sucked dried and the wet material obtained was unloaded. The wet material was further dried under vacuum at a temperature of ~ 60 °C for 10 hrs, to obtain 2.66 g Dasatinib glucuronate having XRPD pattern similar to Fig-1, DSC pattern similar to Fig-2 and IR spectrum similar to Fig-3.

Yield: 95.6 %

Moisture Content (By KF method): 3.36 %

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.45 (s, 1H), 9.8 (s, 1H), 8.22 (s, 1H), 7.4 (m, 2H), 7.28 (dd, 2H), 6.4 (br-s, 1H), 6.05 (s, 1H), 4.9 (s, 1H), 4.45 (t, 1H), 4.3 (d, 1H), 3.9 (d, 1H), 3.5 (m, 6H), 3.5 (m, 2H), 3.4 (m, 1H), 3.1 (m, 1H), 2.9 (t, 1H), 2.48 (m, 3H), 2.44 (m, 3H), 2.41 (s, 3H), 2.24 (s, 3H)

Example-03: PROCESS FOR PREPARATION OF DASATINIB GLUCURONATE

20 mL methanol was charged into a 100 mL round bottomed flask at 25-30°C and 2.0 g Dasatinib (Moisture Content: 1.4%) and 0.83 g Glucuronic acid was added to it. The reaction mixture was stirred for 20 mins, followed by heating to a temperature of ~ 65 °C. Further stirring of the reaction mixture was performed for 30 mins maintaining the temperature of ~ 65 °C. Then the reaction mixture was allowed to cool down to a temperature upto ~ 25 °C.

The reaction mixture was subjected to distillation under vacuum at a temperature of ~ 50°C, till approximately 1/10 of initial volume of reaction mixture was left. Then 2x10.0 mL acetone was added to the reaction mixture. Again the reaction mixture was subjected to distillation under vacuum at temperature of ~ 50°C, till approximately 1/10 of initial volume of reaction mixture was left. At the same raised temperature of ~ 50°C, 20.0 mL of acetone was added to the reaction mixture and the reaction mixture was allowed to cool to ~ 25 °C. The obtained reaction mixture was stirred for about 2-3 h at this temperature. The solid obtained was filtered and washed with 4.0 mL chilled acetone.

The obtained material was dried at ~60 °C for ~8 h under vacuum. The dried material was added to 40 mL Methyl t-Butyl Ether (MTBE) and heated for ~2h at temperature of ~55 °C. The solid material obtained was filtered and given washing with 4 mL MTBE.

The reaction mass was then sucked dried and the wet material obtained was unloaded.

The wet material was further dried under vacuum at a temperature of ~ 60 °C for 10 hrs, to obtain 2.0 g Dasatinib Glucuronate.
While the foregoing provides a detailed description of the preferred embodiments of the invention, it is to be understood that the descriptions are illustrative only of the principles of the invention and not limiting. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.
We Claim:

1. Glucuronic acid addition salt of Dasatinib represented by Formula (I)

   ![Chemical Structure](image)

   (I)

   or its hydrate or solvate thereof.

2. Glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, according to claim 1, wherein the said acid addition salt form is in a crystalline form or in an amorphous form.

3. Glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, according to claim 1, wherein the said acid addition salt form contains Dasatinib base and glucuronic acid in about 1:1 proportion.

4. Amorphous glucuronic acid addition salt of Dasatinib or its hydrate or solvate thereof, characterized by IR spectrum having at least 6 absorption peaks selected from 3255.9 cm\(^{-1}\), 2921.1 cm\(^{-1}\), 1610.1 cm\(^{-1}\), 1540.2 cm\(^{-1}\), 1318.5 cm\(^{-1}\), 1209.9 cm\(^{-1}\), 1146.8 cm\(^{-1}\), 1051.6 cm\(^{-1}\), 812.16 cm\(^{-1}\) and 776.9 cm\(^{-1}\).

5. Glucuronic acid addition salt of Dasatinib according to claim 4, wherein the said salt is further characterized by DSC isotherm comprising at least one endothermic peak ranging between 135 to 145 °C.

6. A process for preparing glucuronic acid addition salt of Dasatinib, comprising the steps of:
   
   a) providing a solution of Dasatinib with an organic solvent;
   
   b) addition of glucuronic acid of Formula (A) to the reaction mixture;

   ![Chemical Structure](image)

   (A)

   c) stirring the reaction mixture for time duration ranging from 10-60 mins;

   d) heating the reaction mixture to a temperature ranging between 35 °C to reflux temperature of the solvent used;

   e) lowering the temperature of reaction mixture to a temperature below 30 °C;
f) removing the solvent from the reaction mixture;

h) Isolating the glucuronic acid addition salt of Dasatinib.

7. A process for preparing glucuronic acid addition salt of Dasatinib according to claim 6, wherein the organic solvent used in step a) is selected from C₁-C₄ alcohol, DMSO, DMF, NMP, THF, Acetonitrile or Dimethyl acetamide.

8. A process for preparing glucuronic acid addition salt of Dasatinib according to claim 6, wherein organic solvent used in step g) is selected from a C₃-C₆ ketonic solvent and/or C₂-C₆ ether solvent.

9. A pharmaceutical composition comprising glucuronic acid addition salt of Dasatinib (I) or its hydrate or solvate thereof, according to claim-1, together with at least one or more pharmaceutically acceptable excipients.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/506,C07D417/12,C07H7/033,A61K31/426,A61P35/00 Version=2014.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC Version=2014.01 : A61K, C07D, C07H, A61P

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

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

Questel Orbit, IPO-internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search 21-10-2014

Date of mailing of the international search report 21-10-2014

Name and mailing address of the ISA/Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer Rohit Rathore
Telephone No. +91-1125300200

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