

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

20 August 2020 (20.08.2020)



(10) International Publication Number

WO 2020/165807 A1

(51) International Patent Classification:

C07C 47/58 (2006.01) A61K 9/20 (2006.01)

A61K 31/33 (2006.01)

(21) International Application Number:

PCT/IB2020/051164

(22) International Filing Date:

13 February 2020 (13.02.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201941005900 14 February 2019 (14.02.2019) IN

201941011996 27 March 2019 (27.03.2019) IN

(71) Applicant: DR. REDDY'S LABORATORIES LIMIT-

ED [IN/IN]; 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Telangana, Hyderabad 500034 (IN).

(72) Inventors: GOPI, Shanmukha Prasad; House No.

36-92-301/1, Jaibharat Nagar, Kancharapalem, Visakhapatnam, Andhra Pradesh, Visakhapatnam 530008 (IN). YADAV, Jayprakash Amarpal; House No. 83/1, Badam Chawk, Near Post office, Heranj, District- Kheda, Gujarat 387510 (IN). THIRUNAHARI, Satyanarayana; House No.-Flat No. 104, Shashank Rosemount Apartments, Opp Volvo Service Centre, Bachupally, Hyderabad 500090 (IN).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(54) Title: SOLID FORMS OF DEUTETRABENAZINE AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention provides co-crystals of Deutetrabenazine and Vanillin, process for the preparation of co-crystals and pharmaceutical composition comprising said co-crystals of Deutetrabenazine. The co-crystals of Deutetrabenazine and Vanillin is non-hygroscopic, chemically and physically stable and suitable for pharmaceutical formulation and its use in the treatment of tardive dyskinesia and chorea associated with Huntington's disease.

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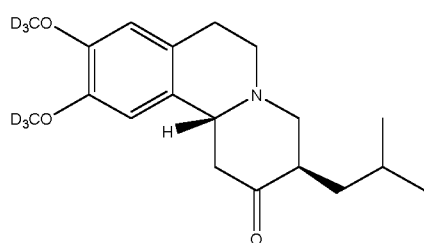
**SOLID FORMS OF DEUTETRABENAZINE AND PROCESS FOR THE  
PREPARATION THEREOF  
CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of Indian provisional patent application No. 201941005900 filed on 14 February 2019; Indian provisional patent application No. 201941011996 filed on 27 March 2019.

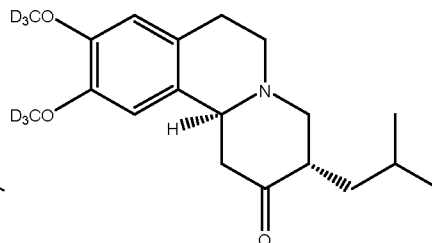
**INTRODUCTION**

Aspect of the present application provides co-crystals of Deutetrabenazine and Vanillin, process for the preparation of co-crystals and pharmaceutical composition comprising said co-crystals of Deutetrabenazine.

Deutetrabenazine or d<sub>6</sub>-tetrabenazine is a deuterated analog of tetrabenazine. The drug compound having the adopted name “Deutetrabenazine” has chemical name: (RR, SS)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d<sub>3</sub>)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one. Deutetrabenazine is a racemic mixture containing the following structures:



*RR*-Deutetrabenazine



*SS*-Deutetrabenazine

AUSTEDO™ (Deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor for oral administration. AUSTEDO™ was approved as oral tablets (6 mg, 9 mg, and 12 mg) by USFDA on 3 April 2017 for the treatment of chorea associated with Huntington’s disease. In August 2017 it was also approved for the treatment of tardive dyskinesia in adults.

US8524733B1 discloses Deutetrabenazine or a pharmaceutically acceptable salt thereof, method for the treatment of chronic hyperkinetic movement disorders and pharmaceutical composition thereof.

US9550780B2 discloses crystalline Form I and crystalline Form II of Deutetrabenazine.

WO2017221169A1 discloses premixes of deutetrabenazine with polyvinylpyrrolidone K-30, copovidone, talc and magnesium stearate.

WO2019166962 A1 discloses crystalline Form M1 of Deutetrabenazine. US 20190343815A1 disclose Deutetrabenazine Form APO-I, a co-crystal of Deutetrabenazine and quercetin, and Deutetrabenazine Form APO-II, a co-crystal of Deutetrabenazine and luteolin.

The occurrence of different crystal forms, i.e., polymorphism, is a property of some compounds. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties, such as PXRD patterns, IR absorption spectra, melting points (MP), TGA curves, DSC curves, and solubilities. Polymorphs are different solids having the same molecular structure, yet having distinct physical properties when compared to other polymorphs of the same structure.

The discovery of new polymorphs and solvates of a pharmaceutical active compound provides an opportunity to improve the performance of a drug product in terms of its bioavailability or release profile in vivo, or it may have improved stability or advantageous handling properties. Polymorphism is an unpredictable property of any given compound. This subject has been reviewed in recent articles, including A. Goho, "Tricky Business," Science News, August 21, 2004. In general, one cannot predict whether there will be more than one form for a compound, how many forms will eventually be discovered, or how to prepare any previously unidentified form.

There remains a need to provide the new polymorphic forms of Deutetrabenazine which can be used in the pharmaceutical composition.

## **SUMMARY OF THE INVENTION**

The present application provides co-crystal of Deutetrabenazine and Vanillin, process of preparing said co-crystal and pharmaceutical composition comprising said co-crystal and one or more pharmaceutically acceptable

excipients. Preferably, the pharmaceutical composition is in the form of a solid dosage form. Most preferably, the pharmaceutical composition is a tablet.

### **BRIEF DESCRIPTION OF THE DRAWING**

Figure 1 illustrates a characteristic PXRD pattern of co-crystal of Deutetrabenazine and Vanillin obtained from example 1.

Figure 2 illustrates a comparative PXRD pattern of co-crystal of Deutetrabenazine and Vanillin and simulated PXRD pattern obtained from single crystal data.

Figure 3 illustrates a single Crystal structure of co-crystal of Deutetrabenazine and Vanillin.

Figure 4 illustrates a characteristic DSC thermogram of co-crystal of Deutetrabenazine and Vanillin.

Figure 5 illustrates a characteristic TGA thermogram of co-crystal of Deutetrabenazine and Vanillin.

Figure 6 illustrates a characteristic PXRD pattern of co-crystal of Deutetrabenazine and Vanillin obtained from example 2.

### **DETAILED DESCRIPTION**

In an aspect, the co-crystal of Deutetrabenazine and Vanillin characterized by a PXRD pattern having X-ray powder diffraction peaks selected from the following at about  $8.34^{\circ}$ ,  $9.45^{\circ}$ ,  $14.08^{\circ}$  and  $15.85^{\circ} \pm 0.2^{\circ} 2\theta$  and it may be further characterized by X-ray powder diffraction peaks at about  $10.01^{\circ}$ ,  $16.94^{\circ}$  and  $23.78^{\circ} \pm 0.2^{\circ} 2\theta$ . In an aspect, the co-crystal of Deutetrabenazine and Vanillin characterized by a PXRD pattern having X-ray powder diffraction peaks selected from the following at about  $8.34^{\circ}$ ,  $9.45^{\circ}$ ,  $14.08^{\circ}$  and  $15.85^{\circ} \pm 0.2^{\circ} 2\theta$  is designated as Form DV1.

In another aspect, the application provides co-crystal of Deutetrabenazine and Vanillin, characterized by an X-ray powder diffraction pattern as illustrated in

Figure 1.

In another aspect, the present application provides process for the preparation of co-crystal of Deutetrabenazine and Vanillin by dissolving Deutetrabenazine and Vanillin in a suitable solvent and cooling the obtained solution.

In embodiments any suitable solvent can be used for preparing solution. The suitable solvents can be selected from ketones, alcohols, esters, nitriles, or their mixtures.

In embodiments the solution of Deutetrabenazine and Vanillin may be obtained by heating and stirring at suitable temperature. In embodiments the solution of Deutetrabenazine and Vanillin may be filtered to get particle free solution. In embodiments the seed of co-crystals of Deutetrabenazine and Vanillin may also be used for preparing product. The solution may be cooled to get precipitation at a temperature about -10 to 30°C, preferably about 0 to 25°C. The precipitated product may be isolated by filtration and dried at suitable temperature.

In another aspect, the present application provides process for the preparation of co-crystal of Deutetrabenazine and Vanillin, comprising the steps of; taking Deutetrabenazine and Vanillin into ball-milling capsule, adding acetonitrile in to it and grinding to obtain the Vanillin co-crystal of Deutetrabenazine.

In another aspect, the present application provides process for the preparation of co-crystal of Deutetrabenazine and Vanillin comprising;

- a) dissolving Deutetrabenazine and Vanillin in a solvent;
- b) adding the anti-solvent to the solution obtained in step (a); and
- c) isolating the co-crystal of Deutetrabenazine and Vanillin.

In embodiments any suitable solvent can be used for preparing solution. The suitable solvents can be selected from ketones, alcohols, esters, nitriles, or their mixtures.

In embodiment of step b), anti-solvent is added to solution obtained in step a). The anti-solvent can be a solvent in which Deutetrabenazine is

insoluble or having very poor solubility. In embodiments the anti-solvent can be selected from ethers, alkanes, cycloalkanes or mixtures thereof. In embodiments the anti-solvent can be a mixture of Methyl t-butyl ether and n-Heptane. In embodiments both anti-solvents can be added together or simultaneously. In embodiments Methyl t-butyl ether was added to the solution of step a) followed by addition of n-Heptane. In embodiments the ratio of solvent to anti-solvents can be in the range of 1:5 to 1:100 or preferably 1:5 to 1:50 or any suitable combination. In embodiments the ratio of anti-solvents Methyl t-butyl ether and n-Heptane can be in the range of 1:1 to 1:10 or any suitable combination.

In embodiments the seed of co-crystals of Deutetrabenazine and Vanillin may also be used for preparing product.

In embodiments, co-crystals of Deutetrabenazine and Vanillin according to the present application can be milled or micronized by any process known in the art, such as ball milling, jet milling, wet milling etc., to produce desired particle sizes and particle size distributions.

Single crystal X-ray structure of Deutetrabenazine and Vanillin reveals that the asymmetric unit consists of one molecule of Deutetrabenazine and one molecule of Vanillin. It is a 1:1 stoichiometric anhydrous co-crystal. The single crystal structure of co-crystal of Deutetrabenazine and Vanillin is illustrated in Figure-3.

Crystal data and structure refinement of Deutetrabenazine and Vanillin 1:1 co-crystal.

|                      |                                                                                                 |
|----------------------|-------------------------------------------------------------------------------------------------|
| Empirical formula    | C <sub>19</sub> H <sub>27</sub> N O <sub>3</sub> , C <sub>8</sub> H <sub>8</sub> O <sub>3</sub> |
| Formula weight       | 469.56                                                                                          |
| Temperature          | 293 K                                                                                           |
| Wavelength           | 0.71073 Å                                                                                       |
| Crystal system       | Monoclinic                                                                                      |
| Space group          | P2 <sub>1</sub> /n                                                                              |
| Unit cell dimensions | a=12.3194(3)Å, α=90°                                                                            |

|                                      |                                              |
|--------------------------------------|----------------------------------------------|
|                                      | $b=12.4434(3)\text{\AA}$ , $\beta=97.396(2)$ |
|                                      | $c=16.2941(5)\text{\AA}$ , $\gamma=90^\circ$ |
| Volume                               | $2477.03(11)\text{\AA}^3$                    |
| Z                                    | 4                                            |
| Density                              | $1.259\text{ g cm}^3$                        |
| Absorption coefficient               | $0.088\text{ mm}^{-1}$                       |
| F(000)                               | 1008.0                                       |
| Theta range for data collection      | $3.5370$ to $30.1880^\circ$                  |
| Reflections collected                | 48318                                        |
| Unique reflections                   | 5857                                         |
| Completeness to $\theta=25.97^\circ$ | 99.75%                                       |
| Refinement method                    | Full matrix least-squares on $F^2$           |
| Goodness of fit on $F^2$             | 1.0036                                       |
| Final R indices [ $I>2\sigma(I)$ ]   | $R1=0.0411$ , $wR2=0.1147$                   |
| Measurement                          | Xta LAB Pro: Kappa dual home/near            |

The co-crystals of Deutetrabenazine and Vanillin has a differential scanning calorimetric thermogram (DSC) substantially as shown in Figure. 4, which exhibits an endothermic peak at about  $101.16^\circ\text{C}$ .

The co-crystals of Deutetrabenazine and Vanillin has a thermal gravimetric analysis thermogram substantially as shown in Figure. 5.

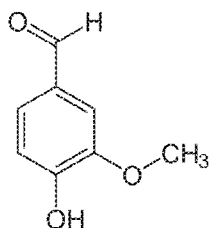
The co-crystals of Deutetrabenazine and Vanillin is non-hygroscopic, chemically and physically stable and suitable for pharmaceutical formulation. The following table provides the stability data of co-crystals of Deutetrabenazine and Vanillin.

**Table-1 Stability data of co-crystals of Deutetrabenazine and Vanillin**

| Storage condition                                           | Time Period | Description             | %Water content | %Total Impurities | PXRD        |
|-------------------------------------------------------------|-------------|-------------------------|----------------|-------------------|-------------|
| $40^\circ\text{C}\pm 2^\circ\text{C}$<br>$75\%\text{RH}\pm$ | Initial     | Off-White colored solid | 0.4            | 0.33              | Crystalline |

|                         |          |                         |     |      |                      |
|-------------------------|----------|-------------------------|-----|------|----------------------|
| 5RH                     | 1 Month  | Off-White colored solid | 0.3 | 0.31 | Matches with Initial |
|                         | 3 Months | Off-White colored solid | 0.1 | 0.40 | Matches with Initial |
|                         |          |                         |     |      |                      |
| 25°C±2°C<br>60%RH ± 5RH | Initial  | White colored solid     | 0.4 | 0.33 | Crystalline          |
|                         | 1 Month  | White colored solid     | 0.2 | 0.34 | Matches with Initial |
|                         | 3 Months | White colored solid     | 0.1 | 0.31 | Matches with Initial |

Vanillin used in the present application is an organic compound with the molecular formula  $C_8H_8O_3$  and represented by the chemical structure;



Any physical form of Deutetrabenazine may be utilized for preparing the co-crystal of the present application. For example Deutetrabenazine may be prepared by the processes described in US8524733B1, US9550780B2, WO2015084622A1, WO2011153157A2 and WO2017182916A1.

In another aspect, the present application provides a pharmaceutical composition comprising the co-crystals of Deutetrabenazine and Vanillin as described in the present application together with at least one pharmaceutically acceptable excipient. Preferably, the pharmaceutical composition is a solid dosage form suitable for oral administration, such as a capsule, tablet, pill, powder or granulate. Most preferably, the pharmaceutical composition is a tablet. Preferably, the pharmaceutical composition provides a dose of Deutetrabenazine that is equivalent to the 6 mg, 9 mg or 12 mg of Deutetrabenazine found in AUSTEDO®

drug products.

Suitable pharmaceutically acceptable excipients are preferably inert with respect to the co-crystal of Deutetrabenazine and Vanillin of the present invention, and may include, for example, one or more excipients selected from binders such as lactose, starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, gelatine, polyvinylpyrrolidone (PVP) and sodium alginate; fillers or diluents such as lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g., microcrystalline cellulose, cellulose), calcium sulphate, xylitol and lactitol; disintegrants such as croscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycolate, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose; lubricants such as magnesium stearate, magnesium lauryl stearate, sodium stearyl fumarate, stearic acid, calcium stearate, zinc stearate, potassium benzoate, sodium benzoate, myristic acid, palmitic acid, mineral oil, hydrogenated castor oil, medium-chain triglycerides, poloxamer, polyethylene glycol and talc; and dispersants or solubility enhancing agents, such cyclodextrins, glyceryl monostearate, hypromellose, meglumine, Poloxamer, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, polyoxylglycerides, povidone, and stearic acid. Other excipients including preservatives, stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants may be added as required. Other suitable excipients and the preparation of solid oral dosage forms is well known to person of skill in the art, and is described generally, for example, in *Remington The Science and Practice of Pharmacy 21st Edition* (Lippincott Williams & Wilkins: Philadelphia; 2006; Chapter 45).

Optionally, when the pharmaceutical compositions are solid dosage forms, the solid dosage forms may be prepared with coatings, such as enteric coatings and extended release coatings, using standard pharmaceutical coatings. Such coatings, and their application, are well known to persons skilled in the art, and

are described, for example, in *Remington The Science and Practice of Pharmacy 21st Edition* (Lippincott Williams & Wilkins: Philadelphia; 2006; Chapter 47).

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

The term "about" when used in the present application preceding a number and referring to it, is meant to designate any value which lies within the range of  $\pm 10\%$ , preferably within a range of  $\pm 5\%$ , more preferably within a range of  $\pm 2\%$ , still more preferably within a range of  $\pm 1\%$  of its value. For example "about 10" should be construed as meaning within the range of 9 to 11, preferably within the range of 9.5 to 10.5, more preferably within the range of 9.8 to 10.2, and still more preferably within the range of 9.9 to 10.1.

### General description of the PXRD equipment

All PXRD data reported herein are obtained using a PANalytical X-ray Diffractometer, with copper K $\alpha$  radiation.

Instrumental parameters.

| Model & Detector   |                                     |
|--------------------|-------------------------------------|
| Model              | PANalytical & X'Pert PRO            |
| Detector           | X'Celerator                         |
| Instrument Setting |                                     |
| Goniometer         | Theta/Theta                         |
| Mode of Collection | Reflection                          |
| Measuring circle   | 240 mm                              |
| Radiation          | Cu K-alpha (Wave length = 1.5406 Å) |
| Scan Parameters    |                                     |

|                                  |                 |
|----------------------------------|-----------------|
| Voltage (kV) and Current (mA)    | 45 kV and 40 mA |
| Scan range ( $^{\circ}2\theta$ ) | 3-40            |
| Step size ( $^{\circ}2\theta$ )  | 0.017           |
| Scan Step Time (s)               | 64.77           |
| Run Time (min)                   | 20 min          |
| Scan mode                        | Continuous      |
| Divergent slit ( $^{\circ}$ )    | 0.5             |
| Anti-scattering slit (mm)        | 5.5 mm          |
| Rotation/min                     | On              |

### Differential Scanning Calorimetry (DSC)

Analytical Instrument: TA Instruments Discovery (DSC)

Heating rate: 10 $^{\circ}$  C per minute.

Purge gas: nitrogen

### Thermal Gravimetric Analysis (TGA)

Analytical Instrument: TA Instruments Q500 (TGA)

Heating rate: 10 $^{\circ}$  C. per minute.

Purge gas: nitrogen.

## EXAMPLES

### Example-1: Preparation of co-crystal of Deutetrabenazine and Vanillin

Deutetrabenazine (1.616 g), Vanillin (0.760) and ethylformate (8 mL) were taken into EasyMax reactor and stirred at 50 $^{\circ}$ C to get clear solution. The clear solution was cooled to 35 $^{\circ}$ C and seed material (100 mg) was added. The obtained suspension was stirred for 2 h at 25 $^{\circ}$ C. The precipitated product was filtered to obtain the co-crystal of Deutetrabenazine and Vanillin.

Yield: 1.9 g

The PXRD pattern of the isolated material is represented as Figure-1.

**Example-2: Preparation of co-crystal of Deutetrabenazine and Vanillin**

Deutetrabenazine (300 mg) and Vanillin (141 mg) were taken into ball-milling capsule and added 1 ml of Acetonitrile and kept for grinding with 25 RPM for 1 h to obtain the co-crystal of Deutetrabenazine and Vanillin.

The PXRD pattern of the isolated material is represented as Figure-6.

**Example-3: Preparation of co-crystal of Deutetrabenazine and Vanillin**

Deutetrabenazine (970 mg), Vanillin (456 mg) and acetonitrile (6 mL) were taken into EasyMax reactor and stirred for 1 h at 50°C to clear get solution. The temperature was reduced to 40°C and seed material was added to the solution. The solution was gradually cooled to 25°C. The precipitated product was filtered to obtain the co-crystal of Deutetrabenazine and Vanillin.

**Example-4: Preparation of co-crystal of Deutetrabenazine and Vanillin**

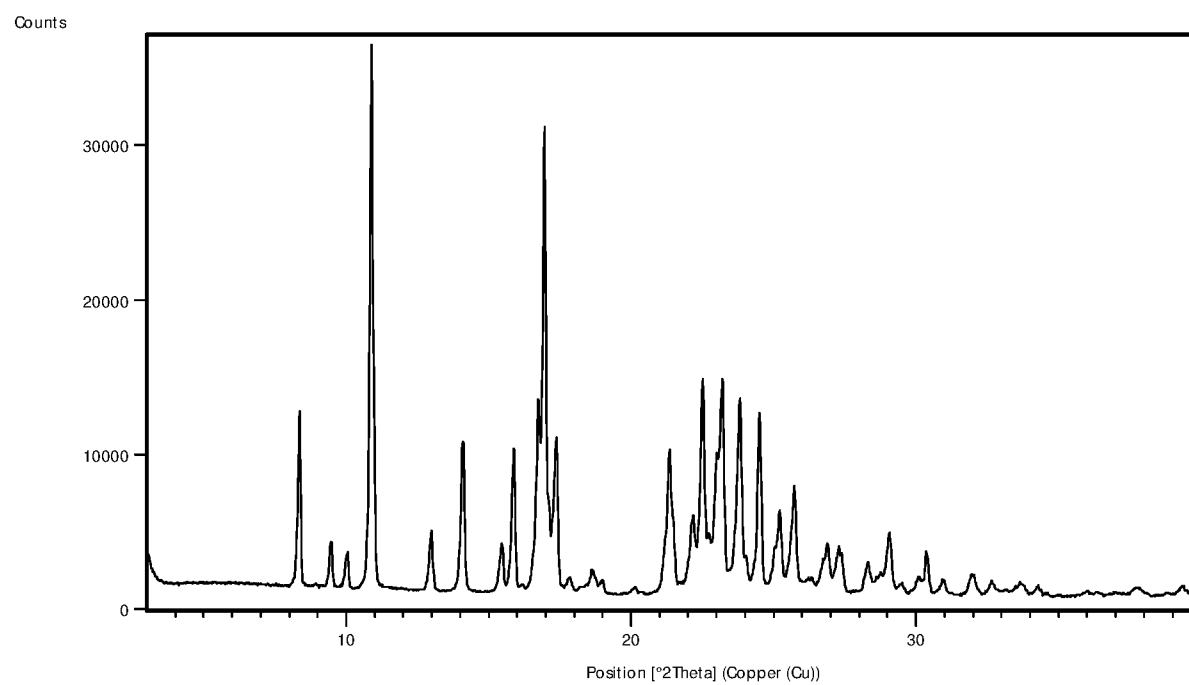
Deutetrabenazine (323 mg), Vanillin (152 mg) and acetonitrile (3 mL) were taken into EasyMax reactor and stirred for 20 min at 45°C to get clear solution. The solution was filtered to get particle free solution. Methyl t-butyl ether (10 mL) and n-Heptane (15 mL) were added to the clear solution under stirring. The solution was kept overnight for evaporation of solvent. The title product was obtained by filtration.

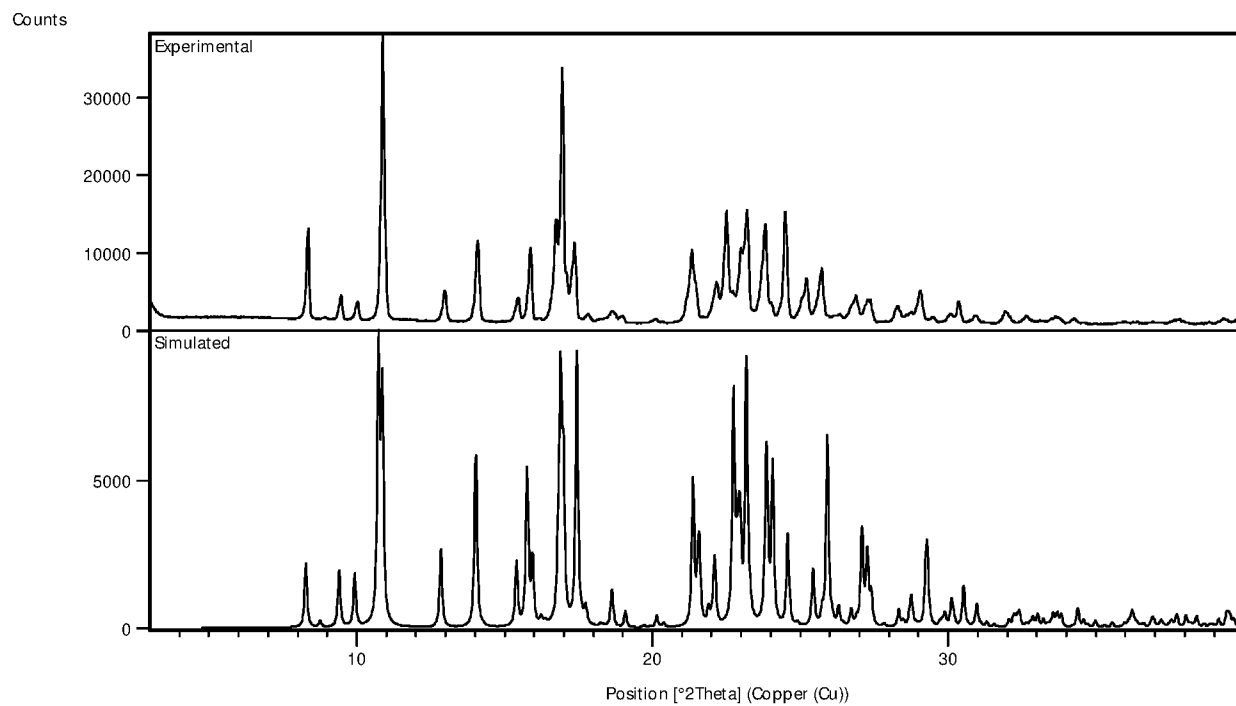
## Claims:

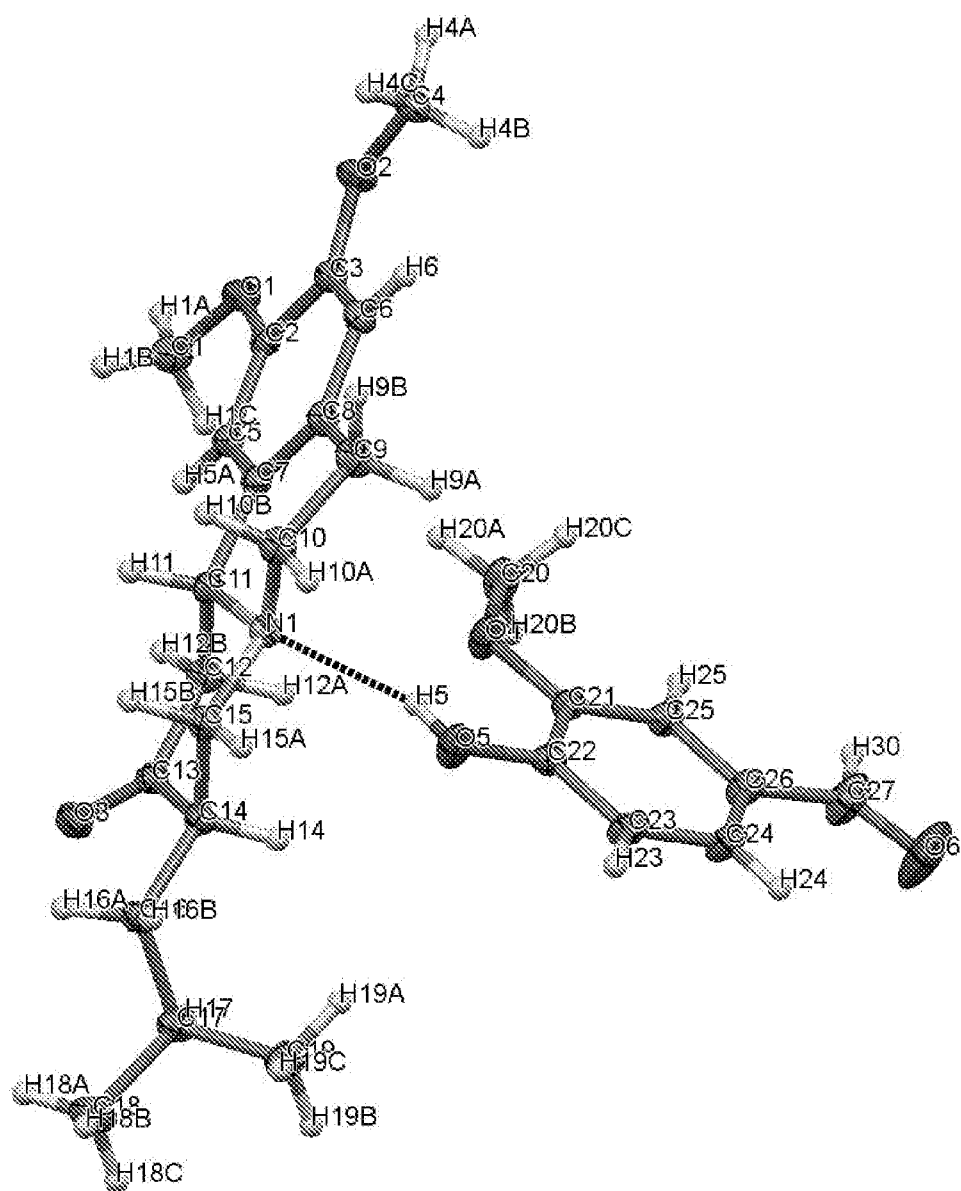
1. A co-crystal of Deutetrabenazine and Vanillin.
2. The co-crystal of claim 1, wherein the molar ratio of Deutetrabenazine to Vanillin is 1:1.
3. The co-crystal of claim 1, characterized by a PXRD diffractogram comprising peaks, at  $8.34^\circ$ ,  $9.45^\circ$ ,  $14.08^\circ$  and  $15.85^\circ \pm 0.2^\circ 2\theta$ .
4. The co-crystal of claim 1, further comprising peaks at  $10.01^\circ$ ,  $16.94^\circ$  and  $23.78^\circ \pm 0.2^\circ 2\theta$ .
5. The co-crystal of claim 1, providing a PXRD diffractogram substantially the same as the PXRD diffractogram provided in Figure 1.
6. A process for the preparation of co-crystal of Deutetrabenazine and Vanillin comprising; dissolving Deutetrabenazine and Vanillin in a suitable solvent and cooling the solution.
7. The process of claim 6, wherein the solvent can be selected from ketones, alcohols, esters, nitriles, or their mixtures.
8. A process for the preparation of co-crystal of Deutetrabenazine and Vanillin comprising the steps of; taking Deutetrabenazine and Vanillin into ball-milling capsule, adding acetonitrile in to it and grinding.
9. A process for the preparation of co-crystal of Deutetrabenazine and Vanillin comprising:
  - a) dissolving Deutetrabenazine and Vanillin in a solvent;
  - b) adding the anti-solvent to the solution obtained in step (a); and
  - c) isolating the co-crystal of Deutetrabenazine and Vanillin.
10. The process of claim 9, wherein the solvent in step a) can be selected from ketones, alcohols, esters, nitriles, or their mixtures.
11. The process of claim 9, wherein the anti-solvent in step b) can be selected from ethers, alkanes, cycloalkanes or mixtures thereof.
12. The process of claim 9, wherein the anti-solvent is Methyl t-butyl ether and n-heptane.
13. A pharmaceutical composition comprising a co-crystal of Deutetrabenazine and Vanillin and one or more pharmaceutically

acceptable excipients.

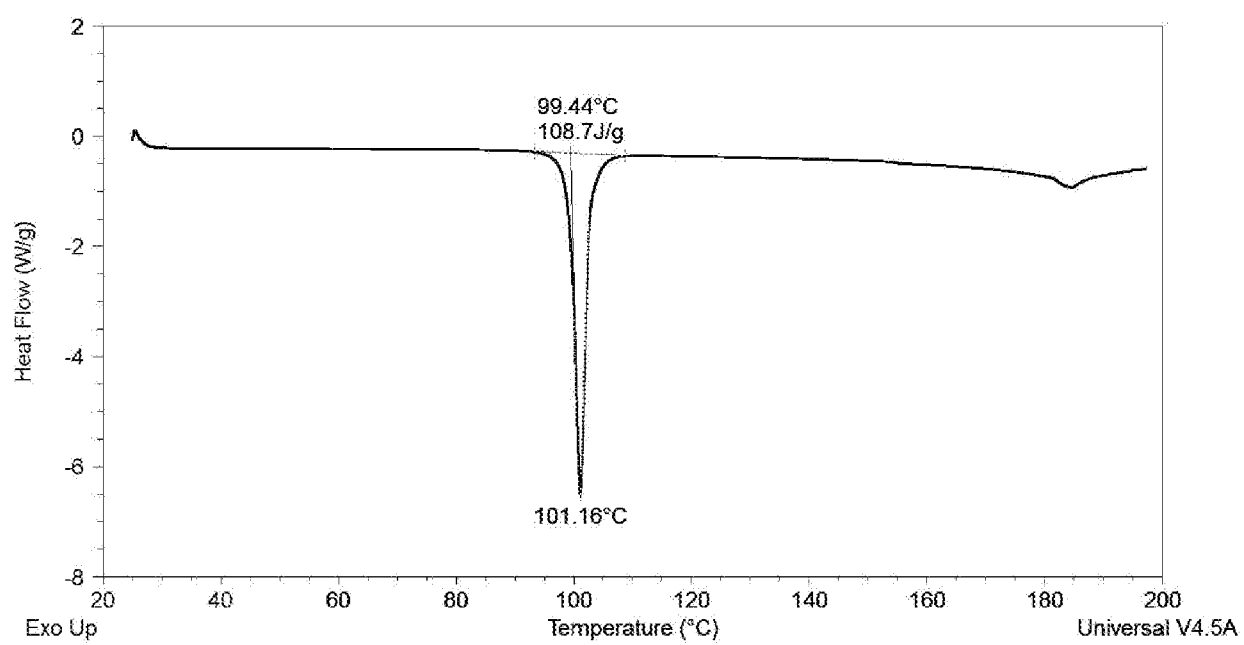
14. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition is a tablet.

**Figure 1**

**Figure 2**



### Figure 3

**Figure 4**

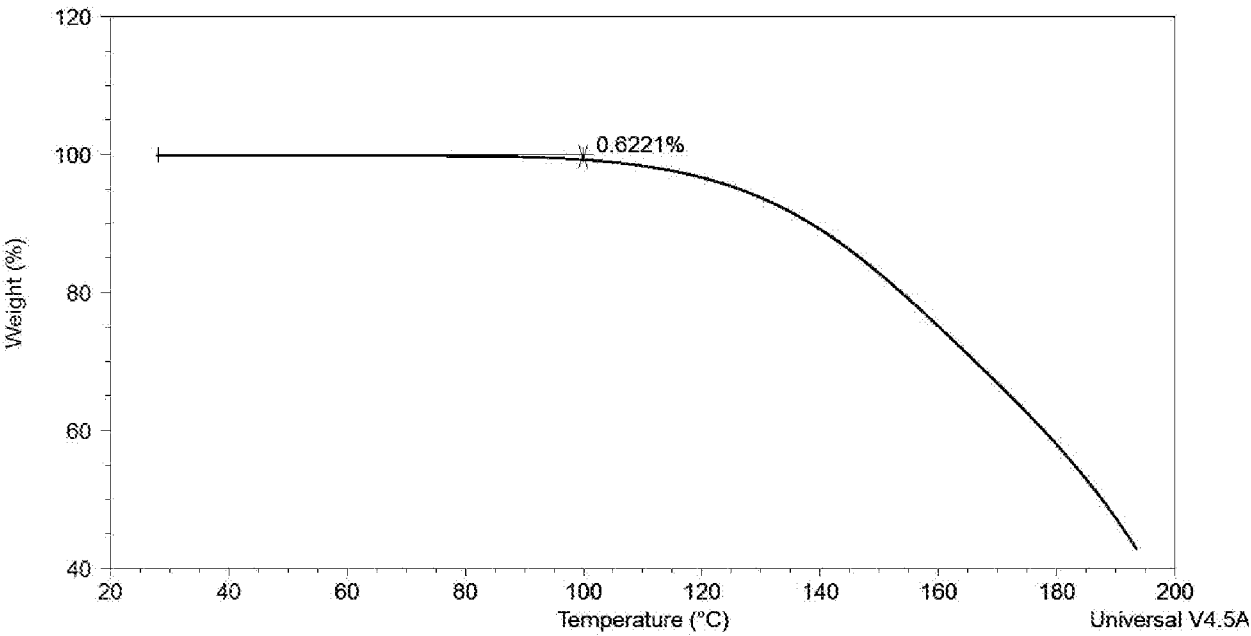
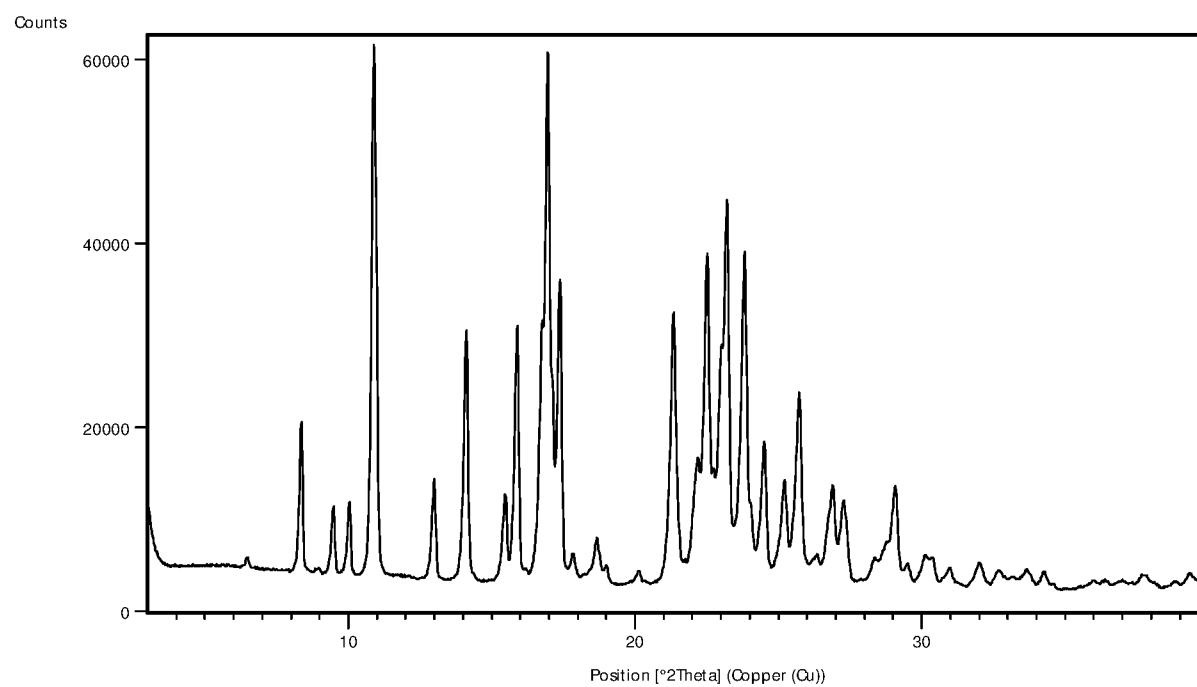


Figure 5

**Figure 6**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2020/051164

## A. CLASSIFICATION OF SUBJECT MATTER

C07C47/58, A61K31/33, A61K9/20 Version=2020.01

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)

C07C, A61K

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

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

TotalPatent One, IPO Internal Database

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                            | Relevant to claim No. |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Y         | US 2018263972 A1 (AUSPEX PHARMACEUTICALS INC[US])<br>20 September 2018 (20-09-2018)<br>abstract, paras-0051, 0130, examples, claims-1,<br>8-9                 | 1-14                  |
| Y         | Co-crystals and salts of vanillic acid and<br>vanillin with amines, Francoise M. Amombo Noa et<br>al. 8 January 2018 (08-01-2018) whole document              | 1-14                  |
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☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Plot No.32, Sector 14, Dwarka, New Delhi-110075  
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Debasish Ghosh

Telephone No. +91-1125300200

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PCT/IB2020/051164

| Citation         | Pub.Date   | Family           | Pub.Date   |
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