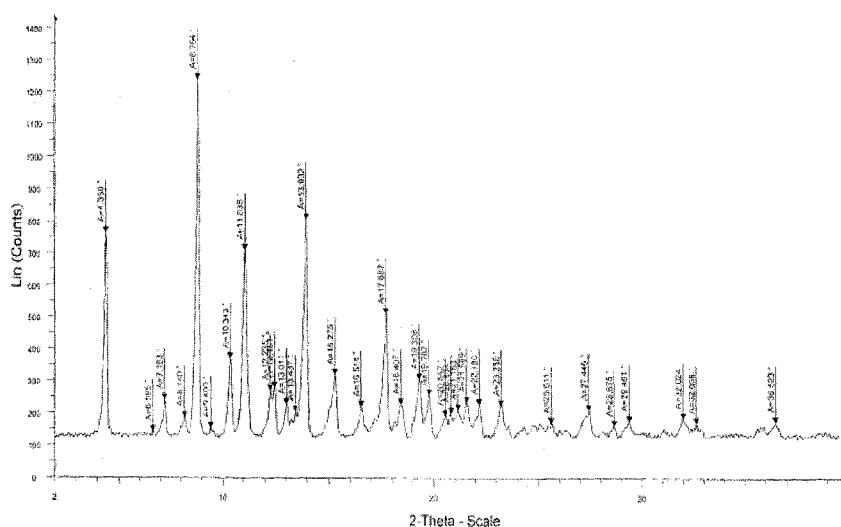




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(54) Title: PROCESS FOR PREPARING DOCETAXEL TRIHYDRATE POLYMORPH

**FIG.1**

(57) Abstract: A crystalline form of docetaxel trihydrate designated as Form-VK and process for preparation thereof are provided. A substantially pure trihydrate crystalline product obtained by the process is also provided. The crystalline product of the process which has an XRPD pattern as per Fig-1 is useful as an active pharmaceutical in pharmaceutical composition and has anti-cancer activity.



GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

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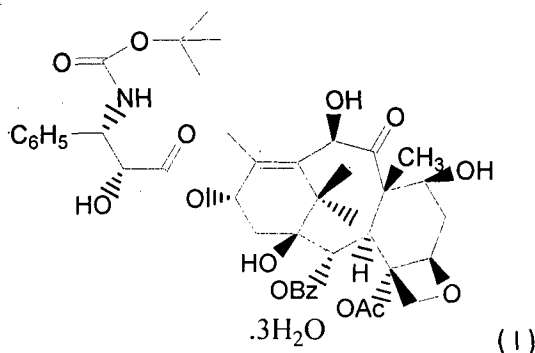
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

PROCESS FOR PREPARING DOCETAXEL TRIHYDRATE POLYMORPH**FIELD OF THE INVENTION**

Particular aspects of the present application encompass the novel polymorphic form of docetaxel trihydrate and process for preparation thereof. Further, the present invention of this application also relates to pharmaceutical compositions comprising of novel polymorphic form of docetaxel trihydrate that are useful in the treatment of various cancerous disorders.

BACKGROUND OF THE INVENTION

- Particular aspects of the present application encompass the novel polymorphic form of docetaxel trihydrate and process for preparation thereof. Further, the present invention of this application also relates to pharmaceutical compositions comprising of novel polymorphic form of docetaxel trihydrate that are useful in the treatment of various cancerous disorders.
- DOCETAXEL TRIHYDRATE is the generic name for the compound (2R, 3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5(β)-20-epoxy-1,2(α), 4,7(β), 10(β), 13(α)-hexahydroxy tax-11-en-9-one 4-acetate 2-benzoate, trihydrate and is represented by the formula (I)



- Docetaxel possess activity against different kinds of cancer, including breast cancer, non-small cell lung cancer and other malignant tumors. It is well known anticancer agent of taxoid family and is sold under the trade name TAXOTERE® in the form of a sterile, non-pyrogenic injection in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) of the drug. TAXOTERE® injection comprises a two part component formulation that requires two-step dilution before infusion. The first step involves dilution with the contents of a diluents

vial (about 13% w/w ethanol in water for injection) without significant foaming, and the second step involves further dilution with infusion fluid for parenteral administration.

5 Colin et al. in US 4,814,470 first time disclosed docetaxel, its pharmaceutical compositions and their use in the treatment of acute leukemias and solid tumors.

Zaske et al in Journal de Physique IV France, Vol. 11, Pr10-221 - 226 (2001) discloses the solid-state characterization of anhydrous, hemihydrate and trihydrate forms of docetaxel.

10 Durand et al, in US 6,197,980 discloses 4-acetoxy-2 α -benzoyloxy-5 β , 20-epoxy-1 β ,7 β ,10 β -tri hydroxy-9-oxo-11-taxen-13 α -y1(2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxy propionate trihydrate (i.e. docetaxel trihydrate) obtained by a process of centrifugal partition chromatography, comprising centrifuging impure 4-acetoxy-2 α -benzoyloxy-5 β ,20-epoxy-1 β ,7 β , 10 β -trihydroxy-9-oxo-11-taxen-13 α -y1(2R,3S)-3-t-butoxycarbonyl amino-3-phenyl-2-
15 hydroxy propionate (docetaxel) utilizing at least four solvents, wherein the solvents are selected from an aliphatic hydrocarbon, an ester, an alcohol, and water.

Authelin et al, in US 6,022,985, discloses a process for the preparation of Docetaxel trihydrate, wherein Docetaxel is crystallized using a mixture of water and an aliphatic alcohol
20 containing 1 to 3 carbon atoms, and then the product obtained is subjected to drying under defined conditions of temperature, pressure and humidity. Further, the patent discloses that 4-acetoxy-2 α -benzoyloxy-5 β , 20-epoxy-1 β ,7 β ,10 β -trihydroxy-9-oxo-11-taxen-13 α -y1(2R,3S)-3-t-butoxy carbonyl amino-3-phenyl-2-hydroxy propionate trihydrate has a better stability than that of the anhydrous docetaxel product.

25

Sharma et al in US 6,838,569, discloses a process for converting paclitaxel or docetaxel to its trihydrate in a mixture of alkane and chlorinated alkane to provide a crude product of 65-75% purity and the crude product subsequently dissolved in an alkyl ketone, followed by addition of an alkane to provide a product of enhanced chromatographic purity. This product with an
30 aliphatic nitrile solvent, followed by addition of water provides taxane trihydrate.

WO 2005/061474 A1 discloses a process for the preparation of amorphous, anhydrous, and trihydrate forms of docetaxel. The process for docetaxel trihydrate involves solubilizing docetaxel in a solvent which is chemically inert. This solvent may be a linear or branched alcohol (containing between 1 and 8 carbons), an organic acid, an aliphatic or cyclic ether, a polar, aprotic solvent, a halogenated solvent, an aromatic solvent, a polyethoxylated sorbitol, lecithin or castor oil, or another solvent of adequate polarity to effect the complete solubilization of docetaxel and is capable of solubilizing, or is miscible with, at least 3 molar equivalents of water. The solution so obtained is admixed with an amount of distilled water between 3 and 200,000 molar equivalents relative to docetaxel. Crystallization is induced and the docetaxel trihydrate is isolated by means of conventional processes such as filtration, decantation or centrifugation.

Li Jinliang et al in US2006/0217436A1, discloses a process for preparing docetaxel trihydrate, which involves repeated dissolution and removal of the solvent by concentration of docetaxel in acetone. The final precipitation of the product is by addition of water to the solution of the compound in acetone.

WO 2007/044950 A2 discloses crystalline forms of docetaxel and processes for their preparation. One of the claimed form of docetaxel is characterized by data selected from the group consisting of a powder XRD pattern having peaks at about 7.3, 8.8, 13.7, 17.2 and $20.2 \pm 0.2^\circ 2\theta$, and an FTIR spectrum having peaks at about 1098, 1165, 1248, 1701 and 1720 (cm^{-1})

Kim Namdu et al in US2010/00099897A1, discloses stable anhydrous crystalline docetaxel and method for the preparation thereof. Said form of anhydrous docetaxel is characterized by XRD pattern having major peaks at about 2θ values of 4.88, 9.22, 9.72, 10.38, 11.30, 11.88, 13.34, 14.56, 15.14, 16.62, 17.28, 17.66, 19.02, 19.62, 19.86, 20.86, 21.86, 24.58, and 26.98; and which contains 0.1% or less of the 7-epimer thereof. The process comprises dissolving docetaxel in a dichloromethane-methanol mixture as an organic solvent followed by adding hexane to the resulting solution; and recovering the resulting crystals.

Palle et al in US2010/0197944, discloses new crystalline forms of docetaxel as Form -X and Form- XI and processes for preparation thereof. Crystalline Form X is characterized by an X-ray powder diffraction (XRPD) pattern with characteristic peaks at diffraction angles 2- θ of about 5.3, 8.9, 10.0, 10.6, 11.2, 12.2, 13.7, 14.1, 15.8, 20.4, 21.2, 21.6, and 21.9 $\pm$ 0.2 $^\circ$; differential scanning calorimetry (DSC) thermogram curve having endotherm peaks at about 106 $^\circ$ C and 175 $^\circ$ C and thermogravimetric analysis (TGA) curve corresponding to a weight loss of about 2.6%. Process for preparing Form -X comprise providing a solution of docetaxel in ethyl acetate followed by crystallizing a solid from the solution and isolating the obtained crystalline form.

- 10 Crystalline Form XI is characterized by an XRPD pattern with characteristic peaks at diffraction angles 2- θ of about 4.4, 4.5, 7.0, 8.0, 8.7, 9.1, 11.0, 11.4, 12.3, 12.5, 13.5, 14.1, 15.4, 16.5, 16.9, 17.4, 18.4, 19.5, and 20.4 $\pm$ 0.2 $^\circ$; DSC thermogram curve with an endotherm having an onset at about 66 $^\circ$ C and an end set at about 161 $^\circ$ C and TGA curve corresponding to a weight loss of about 1.9%. Process for preparing Form -XI comprises providing a solution of
- 15 docetaxel in acetone followed by precipitating a solid by adding ether and isolating the obtained crystalline form as Form-XI. Inventors also provided a process for preparing docetaxel trihydrate, which providing a mixture of docetaxel and water followed by maintaining the mixture at 25-30 $^\circ$ C with stirring and isolating the obtained trihydrate crystalline form, which characterized by XRPD pattern with characteristic peaks at diffraction
- 20 angles 2 θ of about 4.5, 7.3, 8.9, 10.5, 11.2, 12.4, 12.7, 13.1, 13.6, 14.1, 15.4, 16.6, 17.2, 17.8, 18.5, 19.4 and 19.9 $\pm$ 0.2 $^\circ$.

- Polymorphism is a phenomenon, wherein existence of different physical forms including shape, size, and arrangement of molecules in the physical state or polymorphs of same
- 25 compound is known in the nature. A single compound, or a salt complex, may give rise to a variety of solids having distinct physical properties, which often results in substantial differences in bioavailability, stability, and other differences between production lots of formulated pharmaceutical products. Due to this reason, since polymorphic forms can vary in their chemical and physical properties, regulatory authorities often require that efforts be
- 30 made to identify all polymorphic forms, e.g., hydrate or anhydrate, crystalline or amorphous, solvated or un-solvated forms, etc. of the drug substances. However, the existence, and possible numbers, of polymorphic forms for a given compound cannot be predicted. In

addition, there are no "standard" procedures that can be used to prepare polymorphic forms of a substance.

5 New forms of pharmaceutically active / useful compounds provide an opportunity to improve the drug performance characteristics of such product. Further, discovery of additional polymorphic forms may help in the identification of the polymorphic content of a batch of an active pharmaceutical ingredient. Therefore, there is a need for preparing new crystalline forms of a drug substance and processes for preparation thereof. Though the review of the above mentioned literature disclose diverse polymorphic crystalline forms and processes for the preparation of docetaxel and its trihydrate, but due to one more reasons they are not particularly convenient and amenable to industrial scale-up for preparing docetaxel trihydrate. Thus, there is an apparent need of a new stable crystalline form and its process, which may be cost-effective, industrially amenable and may overcome the drawbacks of various prior disclosed processes, e.g., multiple solvent combinations as well as multiple steps, which make the processes neither cost effective nor amenable to scale up for industrial scale production.

According to the present invention there are provided new crystalline forms of docetaxel trihydrate, and process for preparation thereof.

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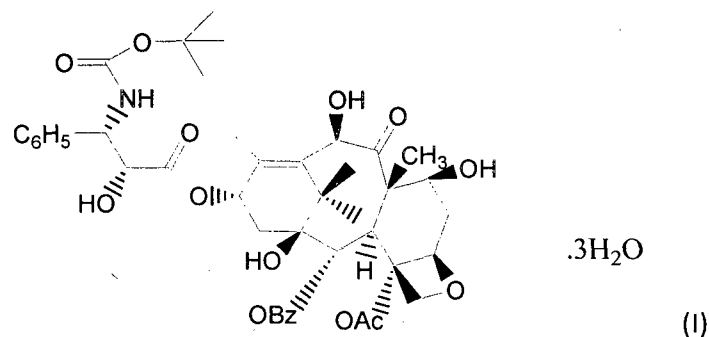
SUMMARY OF INVENTION

Particular aspects of the present specification relates to the substantially pure docetaxel trihydrate new crystalline form and process for preparation thereof.

25 In one aspect of the present invention, the present invention provides a substantially pure docetaxel trihydrate crystalline Form (hereinafter referred to as Form-VK) characterized by X-ray powder diffraction pattern comprising at least 5 characteristic $2\theta^\circ$ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 $2\theta^\circ$ and characterized by DSC isotherm comprising the endothermic peaks ranging between-

- 30 a. Peak -1- Between 135 to 145°C
b. Peak -2- Between 210 to 220°C

In another aspect, the present invention provides a process for preparation of novel crystalline polymorphic Form-VK of docetaxel trihydrate of formula (I),



characterized by at least 5 characteristic $2\theta^\circ$ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 $2\theta^\circ$ comprising the steps of-

- i) Combining docetaxel anhydrous or any hydrate form with a polar organic solvent selected from 2-alkoxy ethanol or dimethylsulfoxide
- ii) Cooling the reaction mass
- iii) Combining the reaction mass with water slowly in 1-5 hrs at 0° - 15°C .
- iv) Optionally maintain the reaction mass for about 2- 10 hrs.
- v) Isolating the material as Docetaxel trihydrate.

Further particular aspects of the invention are detailed in the description of invention, wherever appropriate.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an example of X-ray powder diffraction ("XRPD") pattern of docetaxel trihydrate-Form-VK prepared by using 2-methoxy ethanol.

Fig. 2 is an example of a differential scanning calorimetry ("DSC") curve of docetaxel trihydrate Form-VK prepared by using 2-methoxy ethanol.

Fig. 3 is an example of X-ray powder diffraction ("XRPD") pattern of docetaxel trihydrate-Form-VK prepared by using DMSO.

Fig. 4 is an example of a differential scanning calorimetry ("DSC") curve of docetaxel trihydrate Form-VK prepared by using DMSO.

DETAILED DESCRIPTION OF THE INVENTION

As set forth herein, embodiments of the present invention relates to substantially pure docetaxel trihydrate new crystalline form designated as Form- VK and process for preparation thereof.

- 5 In one embodiment of the present application, it provides a substantially pure Docetaxel trihydrate crystalline Form, designated as Form-VK (hereinafter referred to as Form-VK) characterized by X-ray powder diffraction pattern comprising at least 5 characteristic $2\theta^\circ$ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 $\pm 0.1^\circ 2\theta^\circ$ and characterized by DSC isotherm comprising the
- 10 endothermic peaks ranging between-
- a. Peak -1- Between 135 to 145°C
 - b. Peak -2- Between 210 to 220°C

- Substantially pure Crystalline Docetaxel trihydrate 'Form-VK' exhibits an X-ray powder diffraction pattern substantially as shown in FIG. 1 and 3. The prominent and characteristic $2\theta^\circ$ and 'd' spacing values for the Form-VK of the present invention, includes 4.29 (20.58 d value), 7.11 (12.42 d value), 10.30 (8.59 d value), 12.21 (7.24 d value), 13.87 (6.38 d value), 15.21 (5.82 d value), 17.62 (5.03 d value), 19.26 (4.61 d value), 21.51 (4.13 d value), 22.19 (4.00 d value), 23.16 (3.83 d value) and 27.34 (3.26 d value) $\pm 0.1^\circ 2\theta^\circ$.
- 15
- 20 The Crystalline Docetaxel trihydrate 'Form-VK' produced by the inventors of the present application was characterized by the 2 theta values (in degrees) in the X-ray diffractograms are shown in Table 1.

Table 1: Characteristic X-ray diffractograms- $2\theta^\circ$ Values of Docetaxel trihydrate Form-VK

25

S.No.	$2\theta^\circ$ Peaks
1.	3.14
2.	4.29
3.	7.11
4.	8.01
5.	8.70

S.No.	2 θ° Peaks
6.	10.30
7.	12.21
8.	12.97
9.	13.38
10.	13.87
11.	15.21
12.	16.42
13.	17.07
14.	17.62
15.	18.09
16.	18.37
17.	19.26
18.	19.73
19.	20.49
20.	20.77
21.	21.51
22.	22.13
23.	22.56
24.	23.16
25.	24.16
26.	24.72
27.	25.52
28.	27.12
29.	27.34
30.	28.04
31.	29.34
32.	32.67
33.	35.72
34.	36.49

It should be kept in mind that typical minor variation in the observed 2 theta angles values may be expected based on the sample preparation, the analyst, the specific diffractometer employed and technique. Sometimes, more variation may also be expected for the relative peak intensities, which is largely affected often by the particle size of the sample. Thus, identification of the exact crystalline form of a compound should be based primarily on observed 2 theta angles with lesser importance attributed to relative peak intensities. D-spacing values are calculated with observed 2 theta angles and copper K(α) wavelength using the Bragg equation well known to those of skill in the art.

10 Characteristic XRPD based observed 2 theta angles and corresponding D-spacing values for the substantially pure Crystalline Docetaxel trihydrate Form-VK of the present invention are tabulated in the Table-2.

15 Table 2: Characteristics observed 2 theta angles and corresponding D-spacing values of Form-VK

S. No.	2 θ°	d(A°)
1)	4.29	20.58
2)	7.11	12.42
3)	10.30	8.59
4)	12.21	7.24
5)	13.87	6.38
6)	15.21	5.82
7)	17.62	5.03
8)	19.26	4.61
9)	21.51	4.13
10)	22.19	4.00
11)	23.16	3.83
12)	27.34	3.26

In the crystalline Form-VK of the present application, some margin of error may be present in each of the 2 theta angle assignments reported herein. The assigned margin of error in the 2 theta angles for the crystalline Form-VK of Docetaxel trihydrate is approximately ± 0.10 $2\theta^\circ$ for each of the peak assignments. In view of the assigned margin of error, in a preferred

variant, the crystalline Form-VK of Docetaxel trihydrate may be characterized by an X-ray diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.29 ± 0.10 , 7.11 ± 0.10 , 10.30 ± 0.10 , 12.21 ± 0.10 , 13.87 ± 0.10 , 15.21 ± 0.10 , 17.62 ± 0.10 , 19.26 ± 0.10 , 21.51 ± 0.10 , 22.19 ± 0.10 , 23.16 ± 0.10 , 27.34 ± 0.10 $2\theta^\circ$

The samples of Docetaxel trihydrate Form-VK were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu K α radiation using the wavelength 1.5418 Å and lynx Eye detector.

The crystalline Form-VK of Docetaxel trihydrate is hydrated form. A sample of the crystalline Form-VK prepared by the inventors of the present application had moisture content is in between 5.0% -7.0% by Coulometric KF method on a Metrohm 831 KF titrando, which confirmed the hydrated nature of the compound possessing trihydrate (3 Molecules of H₂O).

While the invention is not limited to any specific theory, it should be understood however that the crystalline Form-VK of Docetaxel trihydrate may contain additional residual, unbound moisture without losing its hydrate character and/or its crystalline Form-VK characteristics. In a particular embodiment, the water content measured by Karl Fischer Coulometer method for crystalline Form-VK was 5.4% w/w. It is believed that additional residual moisture may be present in the form of water molecules present in the channel of the crystals, rather than being bound and joined inside the crystal lattice as in hydrated forms. Whenever the novel crystalline Form-VK remains more wet, the entire lattice of crystal may expand due to the space occupied by the other water molecules and hence the X-ray powder diffraction pattern of the more wet hydrated crystalline form may also expand. In such case, the X-ray powder diffraction patterns of two different moisture trapped crystalline forms may not be perfectly overlapped. Nevertheless, one skilled in the art should be able to determine whether they are same crystalline forms or not, by looking at the overall view of the X-ray powder diffraction pattern optionally with help of other spectroscopy data such as Infrared spectroscopy (IR).

Crystalline Form-VK is further characterized by DSC isotherm comprising at least three endothermic peaks ranging between-

- a. Peak -1- Between 135 to 145°C

b. Peak -2- Between 210 to 220°C

The Differential Scanning Calorimetry (DSC) thermogram of crystalline form of Docetaxel trihydrate obtained by the inventors is shown in Fig. 2 and 4. It exhibits a significant endo-exo pattern with 2 well identified peaks around 137.97°C and 214.04 °C. The DSC thermogram was measured on a Perkin Elmer instrument model Zade DSC. It is known to one of skill in the art that the endothermic peak location may be affected by the heating rate in the DSC. Thus, slight variation of the peak may be acceptable.

- 10 Illustrative examples of analytical data for the crystalline 'Form-VK' obtained in the Examples are set forth in the Figs. 1-4.

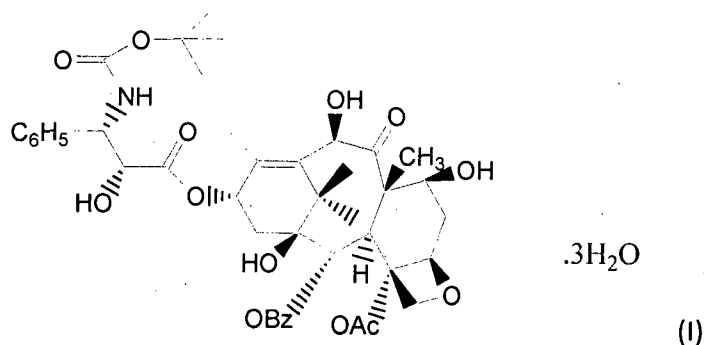
In a further embodiment, the invention also relates to a composition containing crystalline Docetaxel trihydrate of which at least 95%, by total weight of the crystalline form of Docetaxel trihydrate in the composition, is the crystalline Form-VK. In yet another embodiment of the invention, the composition may substantially free of any other known forms of Docetaxel trihydrate.

X-ray diffraction provides a convenient and practical means for quantitative determination of the relative amounts of crystalline forms in a solid mixture. X-ray diffraction is adaptable to quantitative applications because the intensities of the diffraction peaks, particularly long range peaks of a given compound in a mixture are proportional to the fraction of the corresponding powder in the mixture. The percent composition of crystalline Docetaxel trihydrate in an unknown composition can be determined. Preferably, the measurements are made on solid powder Docetaxel trihydrate. The X-ray powder diffraction patterns of an unknown composition can be compared to known quantitative standards containing the pure crystalline Form-VK of Docetaxel trihydrate to identify the percent ratio of a particular crystalline form. This may be done by comparing the relative intensities of the peaks from the diffraction pattern of the unknown solid powder composition with a calibration curve derived from the X-ray diffraction patterns of pure known samples. The curve can be calibrated based on the X-ray powder diffraction pattern for the strongest peak or any distinctive peak from a pure sample of the crystalline Form-VK of Docetaxel trihydrate. The calibration curve may be

created in a manner known to those of skill in the art. For example, five or more artificial mixtures of crystalline forms of Docetaxel trihydrate, at different amounts, may be prepared. In a non-limiting example, such mixtures may contain, 2%, 5%, 10% and 15% of the Form-VK of Docetaxel trihydrate. Then, X-ray diffraction patterns are obtained for each artificial mixture using standard X-ray diffraction techniques. Slight variations in peak positions, if any, may be accounted for by adjusting the location of the peak to be measured. The intensities of the selected characteristic peak(s) for each of the artificial mixtures are then plotted against the known weight percentages of the crystalline form. The resulting plot is a calibration curve that allows determination of the amount of the crystalline form Form-VK of Docetaxel trihydrate in an unknown sample. For the unknown mixture of the crystalline forms of Docetaxel trihydrate, the intensities of the selected characteristic 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 given crystalline form in the composition.

- 15 Similar quantitative analysis may be carried out using IR spectroscopy, particularly with attenuating total reflectance (ATR) technology.

In another embodiment of the present application, it provides a process of preparation of novel crystalline polymorphic form of docetaxel trihydrate of formula (I) designated as Form-VK,



characterized by at least 5 characteristic $2\theta^\circ$ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 $2\theta^\circ$ comprising the steps of-

- 25 i) Combining docetaxel anhydrous or any hydrate form with a polar organic solvent selected from 2-alkoxy ethanol or dimethylsulfoxide

- ii) Cooling the reaction mass
- iii) Combining the reaction mass with water slowly in 1-5 hrs at 0°-15°C.
- iv) Optionally maintain the reaction mass for about 2- 10 hrs.
- v) Isolating the material as Docetaxel trihydrate as Form-VK.

5 The individual steps of the process of the present invention for preparing Form-VK are detailed separately herein below.

Though the specifics of the process of the detailed in the example section, however, they may not construed to be limiting the scope of the invention.

10

Step i) of the process involves the combining docetaxel anhydrous or any hydrate form with a polar organic solvent selected from 2-alkoxy ethanol or dimethylsulfoxide. Combining the docetaxel or any hydrated form and polar organic solvent comprise preparing solution of docetaxel or its hydrate with polar organic solvent selected from 2-alkoxy ethanol or
15 dimethylsulfoxide. The solution is prepared by combining docetaxel with polar solvent upto the range between 10 to 18 times by weight of docetaxel. In a particular embodiment, docetaxel solution was prepared in 2-methoxy ethanol only by combining 40 gm of docetaxel with 664 ml (specific gravity 0.965 gm/ml) of 2-methoxy ethanol (16.6 times w/v or 16 time w/w).

20 **Step ii)** of the process involves cooling the combined mixture of step i)

This step of cooling the combined mixture of step a) involves slow cooling upto less than 15°C but more than 5°C comprise a slow and constant cooling. A fast cooling rate of more than 10 °C may be avoided in view of any probable inconsistency in the further steps.

25 **Step iii)** of the process involves combining the reaction mass with water slowly in 1-5 hrs at 0°-15°C

Adding the water into a solution docetaxel in a polar solvent (as per step i) for preparing Form-VK comprise lot wise addition of the water in two to four lots at a time interval of 10 to 30 mins, however, it may be added in continuous ways also, with slow addition rate. In one of
30 the preferred embodiment, the time interval used was 10 minutes for two lots of water addition. Water addition was carried out at a temperature of not more than 15°C.

The water is combined with the reaction mass or solution mixture of step i) upto the range between 20 to 35 times by weight of docetaxel. In a particular embodiment, 1660 gm of water was combined with reaction mixture containing 50 gm of docetaxel with 660 gm of 2-methoxy ethanol (~33 time w/w).

5 Step iv) of the process involves optionally maintain the reaction mass for about 2- 10 hrs.

The combined mixture may be maintained for about 1-5 hrs, however, this time may be more, but, depending upon achieving the desired solution nature and equilibration to impurity profile compliance.

The process related impurities, including unreacted intermediates, side products, degradation products and other medium dependent impurities, that appears in the impurity profile of the Docetaxel trihydrate can be substantially removed by the process of the present invention resulting in the formation crystalline Form-VK. In view of maintaining the equilibrium to the impurity profile compliance, the process may require in-process quality checks.

Step v) of the process involves isolating the crystalline Form-VK.

15

Process of isolating Form-VK comprise processes but not limited to conventional processes including filtering and optional drying, which may be carried out at room temperature for the suitable durations to retain the crystalline polymorphic form characteristics.

20 Substantially pure Crystalline Docetaxel trihydrate Form-VK obtained according to the process of the present invention results in matter purity by HPLC of more than 99% w/w.

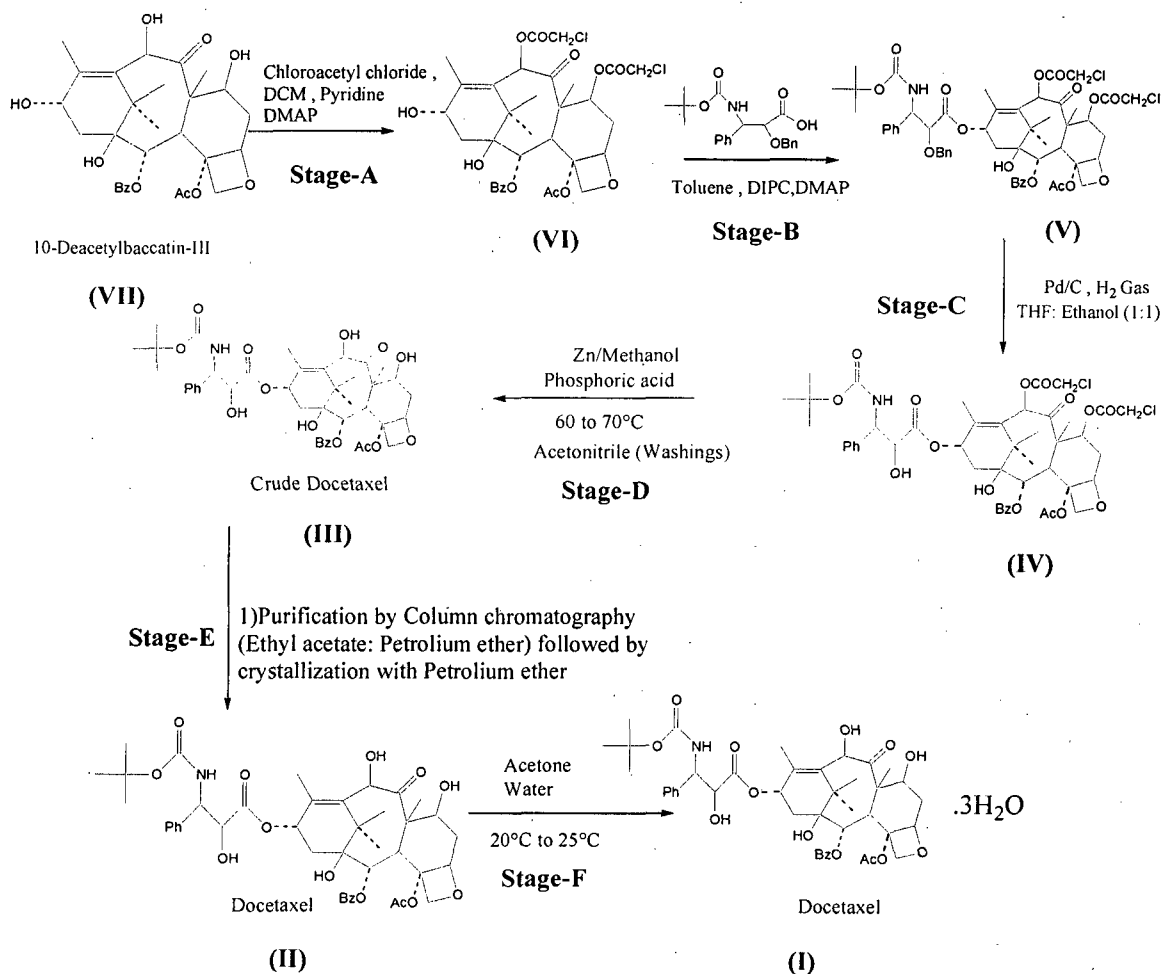
Though the specifics of the process of the detailed in the example section, however, they may not construed to be limiting the scope of the invention.

25

The crystalline solid 'Form VK' described herein may be characterized by X-ray powder diffraction pattern (XRPD) and Thermal techniques such as differential scanning calorimetry (DSC) analysis. The samples of docetaxel trihydrate Form-VK were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source - Cu K α radiation using the
30 wavelength 1.5418 Å and lynx Eye detector.

Illustrative examples of analytical data for the crystalline solid 'Form-VK' obtained in the Examples are set forth in the Figs. 1-4.

Docetaxel or (2R, 3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5, 20-epoxy-1,2,4,7,10,13-hexahydroxy tax-11-en-9-one 4-acetate 2-benzoate (I) or its any hydrate including any trihydrate may be obtained by any of the processes known in the prior art or any of its less stable form or impure form available from any source may be utilized. However in the present invention for polymorphic form and its process for preparation, materials obtained by the process schematically shown in scheme-I was utilized.



Scheme-I: Preparation of docetaxel

In another embodiment, the crystalline "Form-VK" of docetaxel trihydrate 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.

5

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.

10

- 15 Pharmaceutically acceptable excipients used in the compositions comprising Crystalline Form-VK of docetaxel trihydrate of the present application include, but are but 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;
- 20 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
- 25 to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

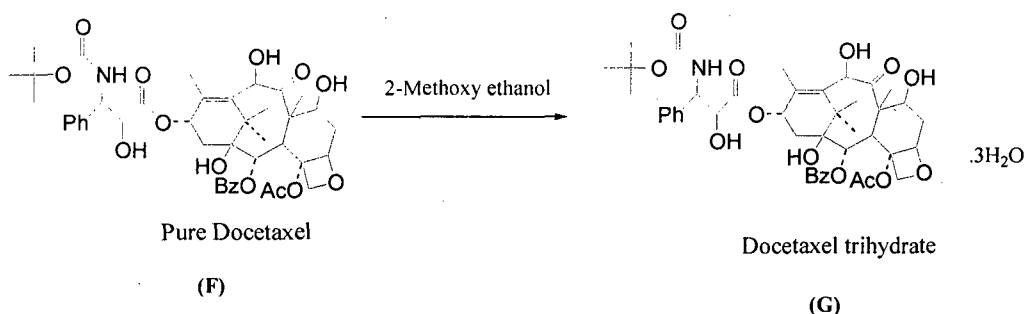
Pharmaceutically acceptable excipients used in the compositions of Crystalline Form-VK of docetaxel trihydrate of the present application may also comprise to include the

30 pharmaceutically acceptable carrier used for the preparation of solid dispersion, wherever utilized in the desired dosage form preparation.

Certain specific aspects and embodiments of the present application will be explained in more detail with reference to the following examples, which are provided by way of illustration only and should not be construed as limiting the scope of the invention in any manner.

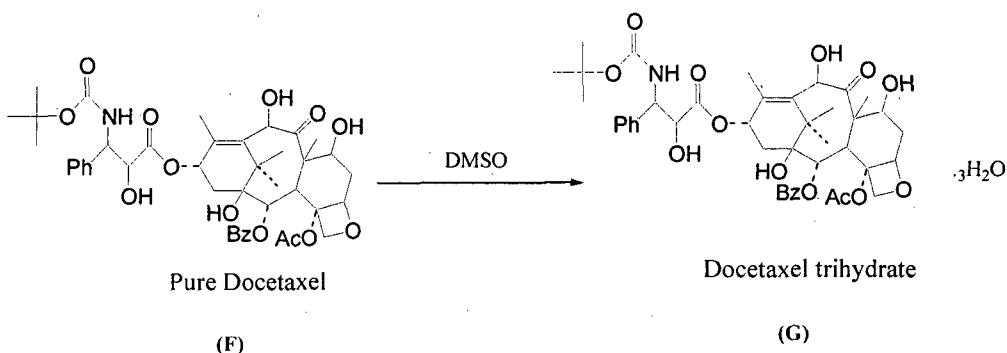
5 EXAMPLE

Example -01: Preparation of Pure Docetaxel Trihydrate Crystalline Form-VK by using the polar solvent as 2-Methoxy Ethanol



Charged 4.0 gm of anhydrous docetaxel and 66.4 ml of 2-methoxy ethanol into a round bottom flask. Stirred the reaction mass to dissolve completely at room temperature. Cooled the reaction mass to 10-15°C and start addition of 664 ml of water slowly in 1-2 hrs at 10-15°C. Maintain the temperature for 6 hrs. Filter the mass and suck dried. Then washed with water, air dried the material to get moisture content 5.4%.

Example-02: Preparation of Pure Docetaxel Trihydrate Crystalline Form-VK by using the polar solvent as Dimethylsulfoxide (DMSO)

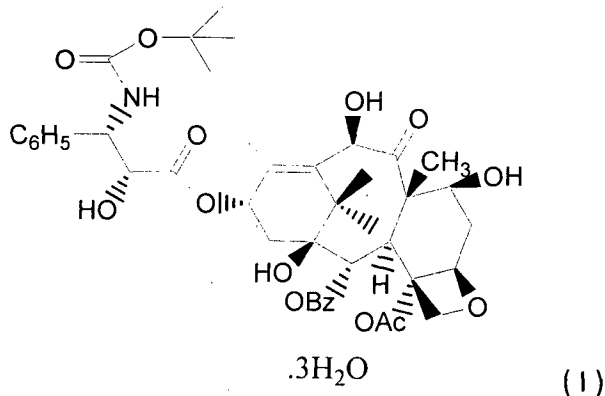


Charged 5.0 gm of docetaxel anhydrous and 16.5 ml of DMSO into a round bottom flask. Stirred the reaction mass to dissolve completely. Cool to 10-15°C and start addition of 166 ml of water slowly for 1-2 hrs at 10-15 °C. Maintain the temperature for 6 hrs. Filter the mass and suck dried. Then washed with water, air dried the material to get moisture content 5.29%.

CLAIMS

We Claim:

- 1) A process of preparation of polymorph of docetaxel trihydrate of formula (I)



characterized by at least 5 characteristic $2\theta^\circ$ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 $2\theta^\circ$ comprising the steps of-

- i) Combining docetaxel anhydrous or any hydrate form with a polar organic solvent
 - ii) Cooling the reaction mass
 - iii) Combining the reaction mass with water slowly in 1-5 hrs at 0° - 15°C
 - iv) Optionally maintain the reaction mass for about 2- 10 hrs
 - v) Isolating the material as Docetaxel trihydrate
- 2) A process according to claim-1, wherein polar organic solvent is selected from 2-alkoxy ethanol or dimethylsulfoxide
- 3) A process according to claim-2, wherein alkoxy group in 2-alkoxy ethanol solvent is comprising of alkyl group selected from C1 to C3.
- 4) A process according to claim-1, wherein cooling step (ii) involves cooling in the range up to about 0°C to about 20°C
- 5) A process according to claim-1, wherein combining step (iii) of the reaction mass with water include either addition of water in the reaction mass or addition of reaction mass in water.

- 6) A substantially pure Docetaxel trihydrate crystalline Form-VK characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 2θ .
- 7) A substantially pure Docetaxel trihydrate crystalline Form-VK according to claim-6, which is further characterized by DSC isotherm comprising the endothermic peaks ranging between-
 - a). Peak -1- Between 135 to 145°C
 - b). Peak -2- Between 210 to 220°C
- 8) Docetaxel trihydrate crystalline Form-VK characterized by X-ray powder diffraction pattern comprising at least 7 characteristic 2θ peaks selected from the XRPD peak set of 4.29, 7.11, 10.30, 12.21, 13.87, 15.21, 17.62, 19.26, 21.51, 22.19, 23.16, 27.34 ± 0.1 2θ and DSC isotherm comprising the endothermic peaks ranging between 135 to 145°C (Peak -1) and/or 210 to 220°C (Peak -2)
- 9) Docetaxel trihydrate crystalline Form-VK according to claim -6, characterized by X-ray powder diffraction pattern substantially according to Fig-1 and Fig-3.
- 10) Docetaxel trihydrate crystalline Form-VK according to claim -6, characterized by DSC isothermal pattern substantially according to Fig-2 and 4.

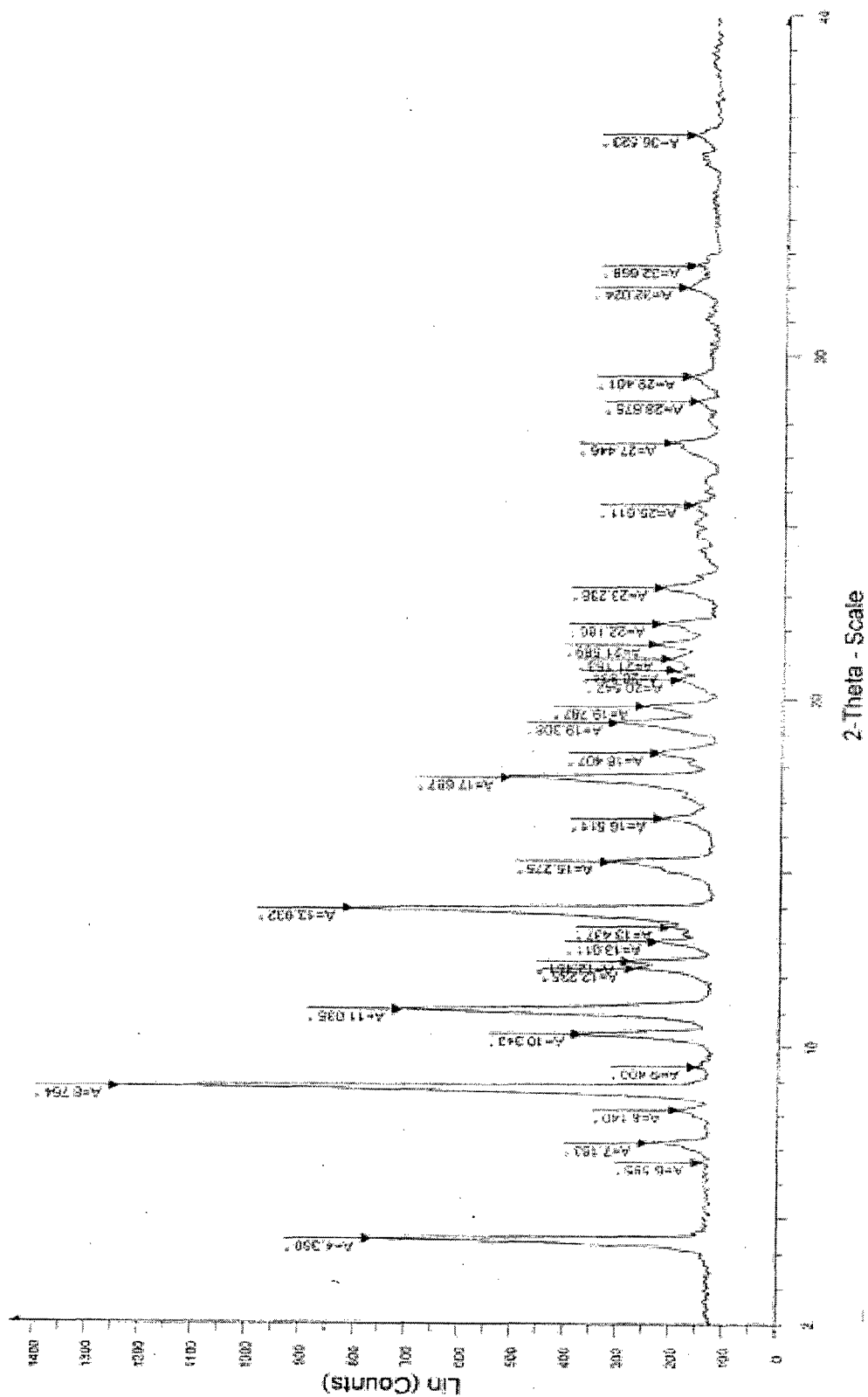
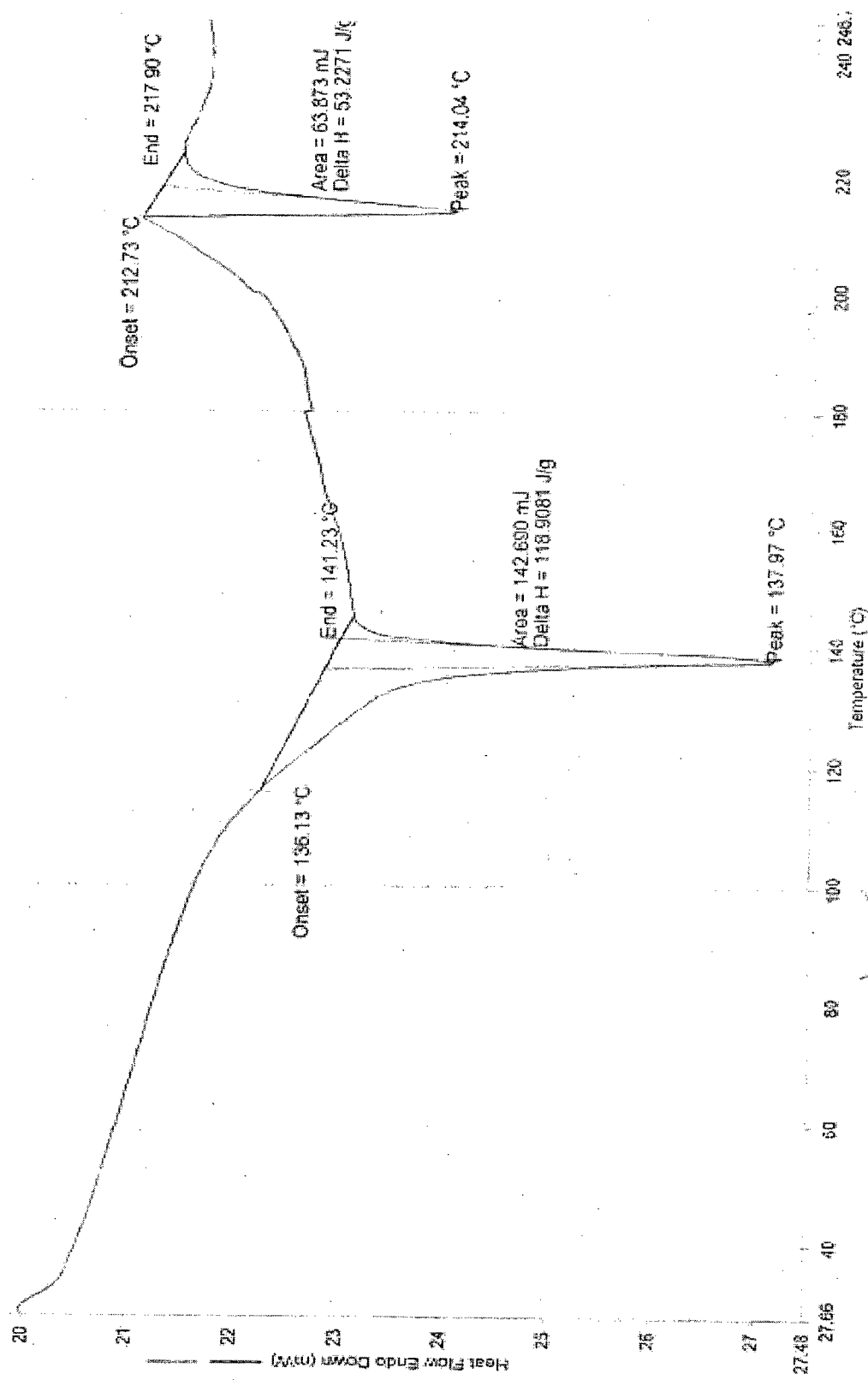


FIG.1



From 30° to 250°C at 10°C/min

FIG.2

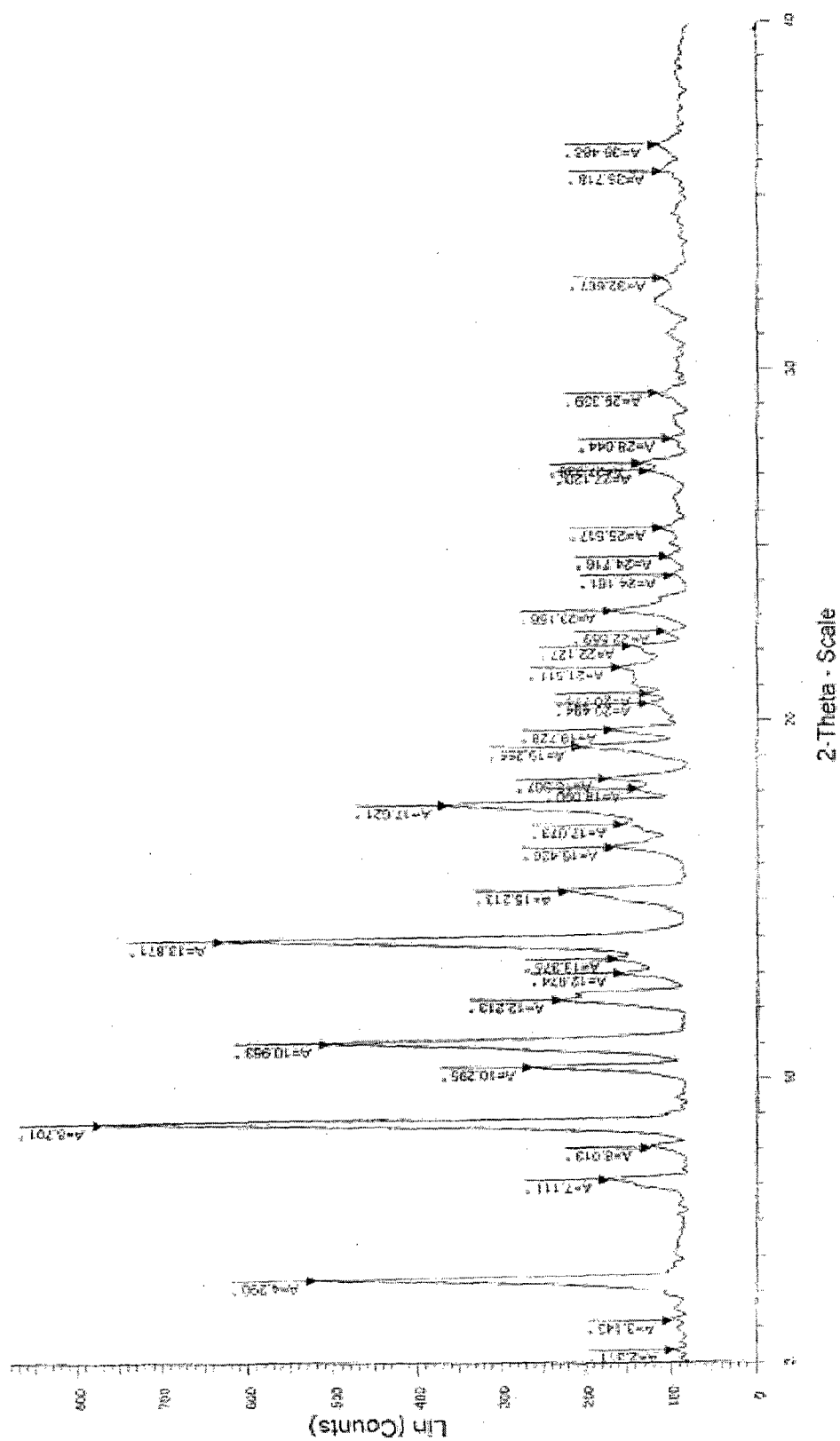


FIG.3

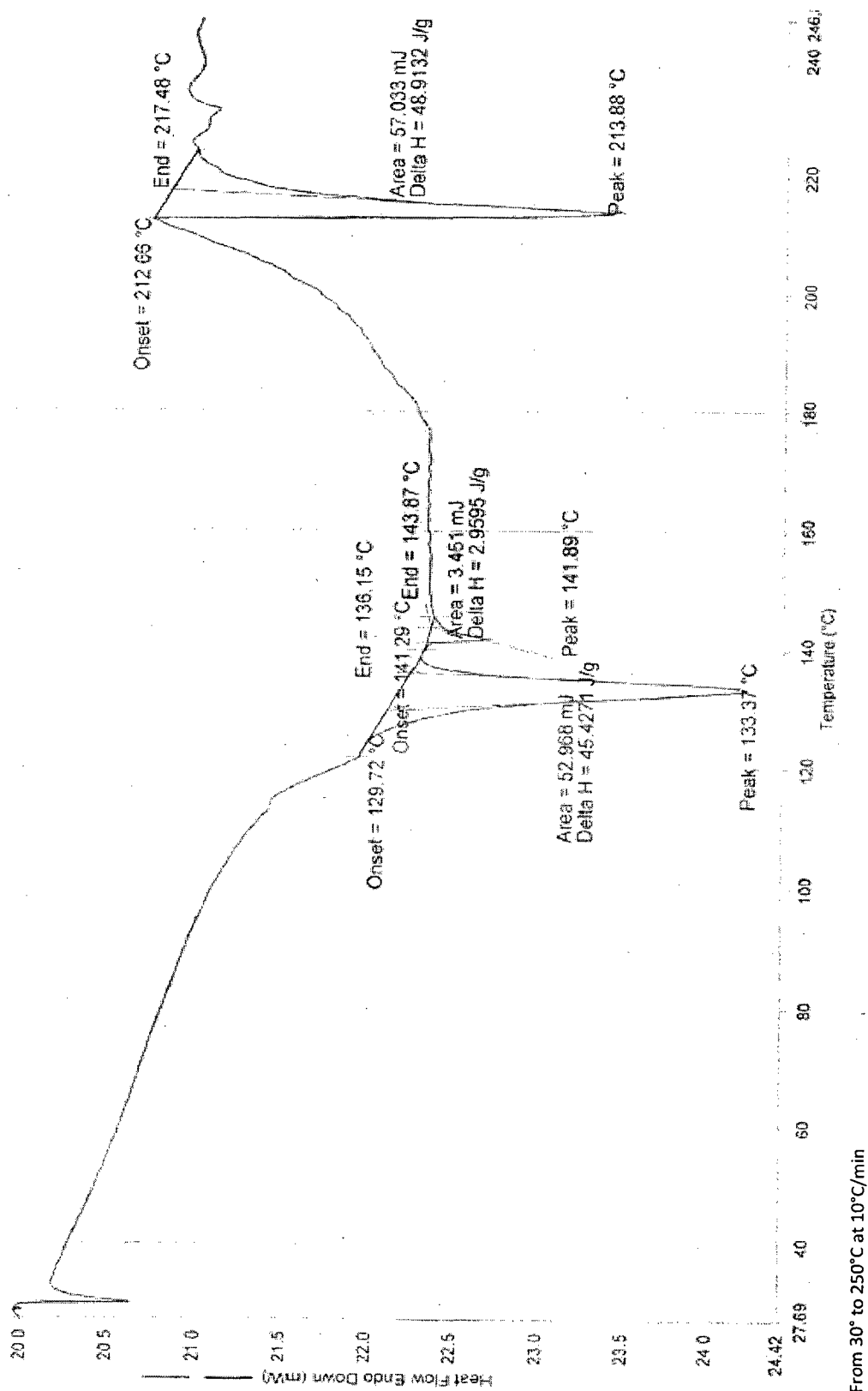


FIG.4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2011/000587

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07D305/-, A61K31/-, A61P35/-

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)

Databases: WPI; EPODOC; CNPAT; CNKI; CAplus (STN); REGISTRY (STN); CASREACT(STN); Keywords: docetaxel trihydrate, crystal+, benzenepropanoic acid, cyclodeca+, methano+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/051465 A2 (SCINOPHARM SINGAPORE PTE, LTD. ET AL) 02 May 2008 (02.05.2008) see page 10, steps 8b-8c, claims 9-13 and 21-23	1-10
X	WO 96/01815 A1 (PHONEPOULENC RORER S.A. ET AL) 25 Jan. 1996 (25.01.1996) see lines 24-33 in page 1, and examples 1-2	6-10
X	JP 2010138084 A (MERCIAN CORP) 24 Jun. 2010 (24.06.2010) see claims 1-3 and example 2	6-10
X	KR 20100000078 A (DONGWOO SYNTECH CO., LTD.) 06 Jan. 2010(06.01.2010) see working example 1, figures 1-2	6-10

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“E” earlier application or patent but published on or after the international filing date	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&”document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 Jan. 2012(12.01.2012)

Date of mailing of the international search report

01 Mar. 2012 (01.03.2012)

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Telephone No. (86-10)82246716

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2011/000587

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0197944 A1 (DR. REDDY'S LABORATORIES LIMITED ET AL) 05 Aug. 2010(05.08.2010) see examples 9-10	6-10
X	WO 2007/078050 A2 (SAMYANG GENEX CORPORATION) 12 Jul. 2007(12.07.2007) see claims 5-13, examples 5-7	6-10
X	CN 1854132 A (SHANGHAI AURISCO INTERNATIONAL TRADE CO., LTD.) 01 Nov. 2006(01.11.2006) see claim 1, examples 1-2	6-10
X	US 2011/0105598 A1 (EMCURE PHARMACEUTICALS LIMITED) 05 May 2011(05.05.2011) see examples 1-3	6-10

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2011/000587

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2008/051465 A2	02.05.2008	WO 2008051465 A3	16.04.2009
		INKOLNP 200901832 E	12.06.2009
		KR 20090080986 A	27.07.2009
		AU 2007309534 A1	02.05.2008
		EP 2094084 A2	02.09.2009
		CN 101534642 A	16.09.2009
		US 2009275762 A1	05.11.2009
		CA 2667416 A1	02.05.2008
		JP 2010506932 A	04.03.2010
		EP 2330101 A1	08.06.2011
WO 96/01815 A1	25.01.1996	FR 2722191 A1	12.01.1996
		AU 2930595 A	09.02.1996
		ZA 9505646 A	24.04.1996
		NO 970007 A	02.01.1997
		FI 970069 A	07.01.1997
		CZ 9700035 A3	16.04.1997
		EP 0770070 A1	02.05.1997
		SK 697 A3	04.06.1997
		BR 9508789 A	21.10.1997
		NZ 289455 A	19.12.1997
		HUT 76833 A	28.11.1997
		JPH 10502627 A	10.03.1998
		MX 9700173 A1	01.04.1997
		KR 977004721 A	06.09.1997
		EP 0770070 B1	30.09.1998
		DE 69505128 E	05.11.1998
		ES 2121404 T3	16.11.1998
		CZ 284695 B6	17.02.1999
		IL 114274 A	11.04.1999
		AU 706519 B	17.06.1999

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2011/000587

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		US 6022985 A	08.02.2000
		RU 2126397 C1	20.02.1999
		SK 280520 B	13.03.2000
		CN 1151741 A	11.06.1997
		TW 419473 A	21.01.2001
		HU 220634 B1	28.03.2002
		NO 314500 B1	31.03.2003
		MX 206924 B	28.02.2002
		PH 1199550862 B1	16.04.2002
		KR 100391753 B	11.02.2004
		CN 1067996 C	04.07.2001
		JP 3753155 B2	08.03.2006
		CA 2193531 C	05.12.2006
		INDEL 9901262 A	04.04.2008
		FI 119246 B1	15.09.2008
		IN 183947 B	20.05.2000
		IN 226223 B	02.01.2009
JP 2010138084 A	24.06.2010	None	
KR 20100000078 A	06.01.2010	KR 100000783 B1	13.12.2010
US 2010/0197944 A1	05.08.2010	WO 2009006590 A2	08.01.2009
		WO 2009006590 A3	12.03.2009
		WO 2009006590 A9	07.05.2009
		EP 2173732 A2	14.04.2010
		INCHENP 201000623 E	27.08.2010
WO 2007/078050 A2	12.07.2007	KR 20070072786 A	05.07.2007
		WO 2007078050 A3	03.01.2008
		EP 1973894 A2	01.10.2008

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2011/000587

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		US 2009018353 A1	15.01.2009
		CN 101415697 A	22.04.2009
		JP 2009522351 A	11.06.2009
		MXPA 08008626 A	31.08.2008
		KR 20090074712 A	07.07.2009
		KR 20090074713 A	07.07.2009
		KR 100965866 B1	24.06.2010
		KR 100965867 B1	24.06.2010
		KR 100995390 B1	19.11.2010
CN 1854132 A	01.11.2006	CN 100420681 C	24.09.2008
US 2011/0105598 A1	05.05.2011	EP 2330100 A1	08.06.2011
		VN 26141 A	25.05.2011

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2011/000587

Continuation of “**CLASSIFICATION OF SUBJECT MATTER**”

C07D 305/14 (2006.01) i

A61K 31/335 (2006.01) i

A61K 31/337 (2006.01) i

A61P 35/00 (2006.01) i