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(54) Title: APALUTAMIDE POLYMORPHS

(57) Abstract: The present invention discloses novel crystalline polymorphic forms of Apalutamide, methods of preparation, pharmaceutical compositions and methods of therapeutic treatment involving polymorphic forms thereof.



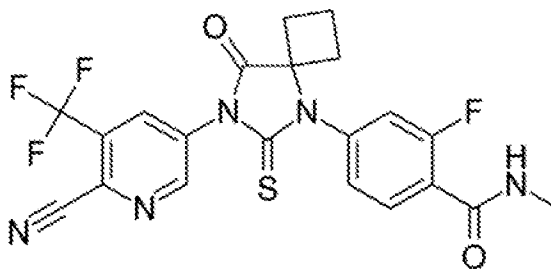
“APALUTAMIDE POLYMORPHS”

TECHNICAL FIELD OF INVENTION

The present invention relates to new crystalline polymorphs of Apalutamide, processes for their preparation and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Apalutamide, chemically known 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is a nonsteroidal antiandrogen medication used in the treatment of prostate cancer. It is sold under the brand name Erleada. Apalutamide has the following chemical structure;



Apalutamide is an Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. Apalutamide is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer.

Apalutamide or its salts is first disclosed in EP2368550.

WO2013184681 discloses crystalline Forms viz. Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I and Form J of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide and to process for preparation thereof.

WO2016124149 discloses crystal Form I and Form II of Apalutamide, method of preparation thereof.

Further, various solid state crystalline forms of Apalutamide and its salts, solvates are disclosed in WO2018112001.

Drug Polymorphism relates to the occurrence of two or more types of different crystal forms of the substance molecule having significant differences in solubility, melting point, stability, bioavailability, curative effect and safety of the medicine. These different degrees of multi-crystal type phenomena in the drug molecule are widely used in medicines for improving the performance characteristic of a pharmaceutical product.

For the same reason, a need still exists in the art to provide novel polymorphs of Apalutamide which is the objective of the present invention.

SUMMARY OF THE INVENTION

In light of the above, the present invention provides novel crystalline polymorphs of Apalutamide.

In one aspect, the present invention provides crystalline forms of Apalutamide, hereinafter referred to as Form-C2, Form-C3, Form-C4, Form-C5, Form-C6, Form-C7, Form-C8, Form-C9 and Form-C10.

In another aspect, the present invention provides a process for preparation of said novel polymorphs of Apalutamide.

The novel polymorphs of Apalutamide of the present invention can be formulated into pharmaceutical composition for the treatment of prostate cancer.

In yet another aspect, the method for treating the prostate cancer comprises administering therapeutic amount of pharmaceutical composition containing novel polymorphs of Apalutamide of the present invention to a subject in need thereof.

DESCRIPTION OF FIGURES

Fig 1 depicts a powder X-ray diffraction pattern (PXRD) of Form-C2 of Apalutamide

Fig 2 depicts a powder X-ray diffraction pattern (PXRD) of Form-C3 of Apalutamide

Fig 3 depicts a Differential Scanning Calorimetry (DSC) of Form-C3 of Apalutamide

Fig 4 depicts a thermogravimetric analysis (TGA) of Form-C3 of Apalutamide

Fig 5 depicts an Infra-Red (IR) absorption spectrum of Form-C3 of Apalutamide

Fig 6 depicts a powder X-ray diffraction pattern PXRD of Form-C4 of Apalutamide

Fig 7 depicts a powder X-ray diffraction pattern (PXRD) of Form-C5 of Apalutamide

Fig 8 depicts a powder X-ray diffraction pattern (PXRD) of Form C6 of Apalutamide

Fig 9 depicts a powder X-ray diffraction pattern (PXRD) of Form-C7 of Apalutamide

Fig 10 depicts a powder X-ray diffraction pattern (PXRD) of Form-C8 of Apalutamide

Fig 11 depicts a powder X-ray diffraction pattern (PXRD) of Form-C9 of Apalutamide

Fig 12 depicts a powder X-ray diffraction pattern (PXRD) of Form-C10 of Apalutamide

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in its various preferred as well as optional embodiments, so that the various aspects therein will be more clearly understood and appreciated.

The present invention relates to crystalline Apalutamide polymorphs, the process for preparation thereof and pharmaceutical compositions containing said polymorphs as active ingredient.

As used herein, the term "PXRD" refers to powder X-ray diffraction, the term "IR" refers to infrared, the term "NMR" refers to nuclear magnetic resonance, the term "TGA" refers to thermogravimetric analysis, the term "DSC" refers to differential scanning calorimetry and the term "DVC" refers to dynamic vapour sorption isotherm.

As used herein, the term "substantially the same X-ray powder diffraction pattern" is understood to mean that those X-ray powder diffraction patterns having diffraction peaks with 2θ values within $\pm 0.2^\circ$ of the diffraction pattern referred to herein are within the scope of the referred to diffraction pattern.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C2 as having PXRD pattern as shown in fig. 1.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C2 comprising of PXRD with two theta values including but not limiting to 12.0, 16.1, 19.4 and $22.6 \pm 0.2^\circ 2\theta$.

In a further embodiment, there is disclosed herein crystalline Apalutamide Form-C2 comprising of PXRD with two theta values including but not limiting to 9.6, 13.9, 17.9 and $21.8 \pm 0.2^\circ 2\theta$.

The present disclosure further comprises crystalline Apalutamide Form-C3 as having PXRD pattern as shown in fig. 2.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C3 comprising of PXRD with two theta values including but not limiting to 4.8, 9.6, 14.3, 17.6, 19.2 and $22.2 \pm 0.2^\circ 2\theta$.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C3 comprising of PXRD with two theta values including but not limiting to 12.1, , 24.1 and $27.8 \pm 0.2^\circ 2\theta$.

Crystalline Form-C3 of Apalutamide may also be characterized as having a DSC spectrum. The DSC plot for the sample shows one endotherm with an onset at 150.20°C , a peak maximum at 154.62°C ; and a second endotherm with a peak maximum at 195.41°C .

In an embodiment, crystalline Form-C3 of Apalutamide is characterized by having a DSC spectrum as shown in Figure 3.

In another embodiment, crystalline Form-C3 of Apalutamide is characterized by having a thermogravimetric analysis (TGA) profile as shown in Figure 4.

Crystalline Form-C3 of Apalutamide may also be characterized as having an IR spectrum comprising characteristic IR spectra peaks at about 3438 cm^{-1} , 3236 cm^{-1} , 3095 cm^{-1} , 3003 cm^{-1} , 2965 cm^{-1} , 2947 cm^{-1} , 2905 cm^{-1} , 2877 cm^{-1} , 2528 cm^{-1} , 2242 cm^{-1} , 1765 cm^{-1} , 1662 cm^{-1} , 1634 cm^{-1} , 1622 cm^{-1} , 1599 cm^{-1} , 1567 cm^{-1} , 1502 cm^{-1} , 1461 cm^{-1} , 1432 cm^{-1} , 1409 cm^{-1} , 1379 cm^{-1} , 1313 cm^{-1} , 1272 cm^{-1} , 1243 cm^{-1} , 1215 cm^{-1} , 1171 cm^{-1} , 1152 cm^{-1} , 1111 cm^{-1} , 1097 cm^{-1} , 1058 cm^{-1} , 1030 cm^{-1} , 1004 cm^{-1} , 981 cm^{-1} , 931 cm^{-1} , 909 cm^{-1} , 878 cm^{-1} , 830 cm^{-1} , 805 cm^{-1} , 771 cm^{-1} , 748 cm^{-1} , 721 cm^{-1} , 690 cm^{-1} , 678 cm^{-1} and 644 cm^{-1} .

In an embodiment, crystalline Form-C3 of Apalutamide is characterized by having an IR spectrum as shown in Figure 5.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C2 and Form-C3.

Accordingly, the process for preparing Apalutamide Form-C2 comprises dissolving Apalutamide in dimethyl carbonate to obtain thick paste followed by precipitating from solvents such as acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether (MTBE), cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate, and tetrahydrofuran; preferably tert-butylmethyl ether (MTBE).

Alternatively, crystalline Form-C2 may be obtain by suspending Apalutamide in a suitable solvent or solvent mixture . Suitable solvent is selected from but not limited to heptane, hexane, dimethyl carbonate, diethyl carbonate, diethyl ether, dimethyl ether and MTBE.

The obtained suspension is preferably stirred at about 25°C to the boiling point of the solvent/s used. More preferably, stirring is done at about 25°C to about 50°C, for a period of about 1 hour to about 10 hours, preferably 2 hours to about 5 hours, more preferably for about 2 hours. Optionally suspension is cooled to 0°C to 5°C before isolation by filtration.

In another embodiment, Apalutamide Form-C2 is subjected to drying in a tray dryer to obtain Apalutamide Form-C3

In an embodiment, the operation temperature in the said tray dryer is about 30°C to about 80°C, preferably about 40°C to about 70°C, more preferably about 50°C to about 70°C.

In an embodiment, the residence time in the said tray dryer is typically anywhere between a period of about 1 hour to about 10 hours, preferably 2 hours to about 7 hours, more preferably for about 3 hours to about 5 hours.

Alternatively, crystalline Form-C3 may be obtained by suspending Apalutamide in a suitable solvent or solvent mixture. Suitable solvent is selected from but not limited to heptane, hexane, dimethyl carbonate, diethyl carbonate, diethyl ether, dimethyl ether and MTBE.

The obtained suspension is preferably stirred at about 0°C to the boiling point of the solvent/s used. More preferably, stirring is done at about 2°C to about 10°C, for a period of about 2 hours to about 25 hours, preferably 5 hours to about 20 hours, more preferably for about 10 hours to about 15 hours.

Preferably, removing the precipitate is done by filtration. Preferably, the obtained solid is dried under reduced pressure at 25°C to about 80°C, preferably at 30°C to about 40°C, for a period of about 2 hours to about 10 hours, preferably 4 hours to about 8 hours, more preferably for about 6 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C4 having PXRD pattern as shown in fig.6.

In an embodiment, crystalline Apalutamide Form-C4 is characterised by PXRD comprising of two theta values including but not limiting to 7.3, 8.07, 10.28 and $16.34 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprise further peaks at 3.73, 11.05, 16.77, 17.22 and $20.40 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C4, comprising dissolving Apalutamide in a suitable solvent, treating with an antisolvent, isolating the precipitated solid and drying the solid.

In an embodiment solvent is selected from polar solvent such as DMF, DMSO, DMA, NMP, acetonitrile, THF and the like. In an embodiment anti-solvent is selected from nonpolar solvent such as heptane, hexane, MDC, EDC, MTBE, CPME, chloroform, diethyl ether, dibutyl ether, diisopropyl ether, and the like.

Preferably, Apalutamide is dissolved in DMF and precipitated by adding antisolvent mixture of heptane and MTBE. The obtained precipitate is preferably stirred at about 20°C to 40°C. More preferably, stirring is done at about 25°C to about 30°C, for a period of about 1 hour to about 10 hours, preferably 2 hours to about 6 hours, more preferably for about 3 hours to about 5 hours.

Preferably, removing the precipitate is done by filtration. Preferably, the obtained solid is dried under reduced pressure at 25°C to about 80°C, preferably at 30°C to about 40°C, for a period of about 2 hours to about 10 hours, preferably 4 hours to about 8 hours, more preferably for about 6 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C5 having PXRD pattern as shown in fig.7.

In an embodiment, crystalline Apalutamide Form-C5 is characterised by PXRD comprising of two theta values including but not limiting to 4.06, 8.12, 16.34, 17.25 and $19.28 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C5, comprising drying Apalutamide, preferably crystalline Apalutamide Form C4, at about 25°C to about 80°C, preferably at 30°C

to about 60°C, for a period of about 2 hours to about 10 hours, preferably 3 hours to about 8 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C6 having PXRD pattern as shown in fig.8.

In an embodiment, crystalline Apalutamide Form-C6 is characterised by PXRD comprising of two theta values including but not limiting to 7.89, 10.26, 13.55, 15.28 and $22.84 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprises further peaks at 3.94, 14.52, 16.43, 17.74, 21.03, 25.51 and $28.97 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C6, comprising dissolving Apalutamide in a suitable solvent, treating with an antisolvent, isolating the precipitated solid and drying the solid.

In an embodiment solvent is selected from polar solvent such as DMF, DMSO, DMA, NMP, acetonitrile, THF and the like. In an embodiment anti-solvent is selected from nonpolar solvent such as heptane, hexane, MDC, EDC, MTBE, CPME, chloroform, diethyl ether, dibutyl ether, diisopropyl ether, and the like.

Preferably, Apalutamide is dissolved in NMP and precipitated by adding antisolvent mixture of heptane and MTBE. The obtained precipitate is preferably stirred at about 20°C to 40°C. More preferably, stirring is done at about 25°C to about 30°C, for a period of about 1 hour to about 10 hours, preferably 2 hours to about 6 hours, more preferably for about 3 hours to about 5 hours.

Preferably, removing the precipitate is done by filtration. Preferably, the obtained solid is dried under reduced pressure at 25°C to about 80°C, preferably at 30°C to about 40°C, for a period of about 2 hours to about 10 hours, preferably 4 hours to about 8 hours, more preferably for about 6 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C7 having PXRD pattern as shown in fig.9.

In an embodiment, crystalline Apalutamide Form-C7 is characterised by PXRD comprising of two theta values including but not limiting to 8.65, 10.79, 13.02, 15.51, 17.32 and $22.77 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprises further peaks at 4.33, 7.82, 14.53, 21.03 and $22.08 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C7, comprising drying Apalutamide, preferably crystalline Apalutamide Form C6, at about 25°C to about 80°C, preferably at 30°C to about 60°C, more preferably at about 40°C to about 50°C for a period of about 1 hour to about 10 hours, preferably 2 hours to about 8 hours, more preferably at about 3 hours to about 6 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C8 having PXRD pattern as shown in fig.10.

In an embodiment, crystalline Apalutamide Form-C8 is characterised by PXRD comprising of two theta values including but not limiting to 7.46, 8.04, 10.34 and $17.357 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprises further peaks at 3.77, 4.06, 15.82, 21.48, 24.86 and $26.382 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C8, comprising dissolving Apalutamide in a suitable solvent, stirring for sufficient time to form a precipitate, isolating the precipitated solid and drying the solid.

In an embodiment solvent is selected from polar solvent such as acetonitrile, propionitrile, DMF, DMSO, DMA, NMP, THF and the like. Preferably,

Apalutamide is dissolved in a nitrile solvent such as acetonitrile or propionitrile and stirred for a sufficient time to form a precipitate.

More preferably, stirring is done at about 25°C to about 30°C, for a period of about 5 hours to about 30 hours, preferably 10 hours to about 25 hours, more preferably for about 15 hours to about 25 hours.

In an embodiment, there is disclosed herein crystalline Apalutamide Form-C9 having PXRD pattern as shown in fig.11.

In an embodiment, crystalline Apalutamide Form-C9 is characterised by PXRD comprising of two theta values including but not limiting to 9.74, 14.98, 17.46 and $22.71 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprises further peaks at 7.72, 12.27, 20.15, 20.49, 22.21, 24.01 and $26.65 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C9, comprising suspending Apalutamide in a suitable solvent or solvent mixture. Suitable solvent is selected from but not limited to dimethyl carbonate, diethyl carbonate, propylene carbonate, ethylene carbonate, ethyl methyl carbonate and the like.

Preferably, Apalutamide is stirred in diethyl carbonate. The obtained suspension is preferably stirred at about 25°C to the boiling point of the solvent/s used. More preferably, stirring is done at about 25°C to about 35°C, for a period of about 1 hour to about 10 hours, preferably 2 hours to about 5 hours, more preferably for about 2 hours to about 3 hours before isolation by filtration.

In an embodiment, there is disclosed herein crystalline Apalutamide Form -C10 having PXRD pattern as shown in fig.12.

In an embodiment, crystalline Apalutamide Form-C10 is characterised by PXRD comprising of two theta values including but not limiting to 9.64, 12.69, 15.36, 17.64, 20.80 and $22.95 \pm 0.2^\circ 2\theta$. The PXRD diffractogram may comprises further peaks at 6.90, 7.67, 13.22, 14.29, 21.56, $21.97 \pm 0.2^\circ 2\theta$.

In another embodiment the present invention relates to a process for preparing the crystalline Apalutamide Form-C10, comprising drying Apalutamide, preferably crystalline Aplautamide Form-C9, at about 25°C to about 80°C, preferably at 40°C to about 70°C, more preferably at about 50°C to about 60°C for a period of about 1 hour to about 10 hours, preferably 2 hours to about 8 hours, more preferably at about 2 hours to about 5 hours.

Those skilled in the art would recognize that the above crystalline forms of Aplautamide may be further characterized by other methods including, but not limited to IR, solid state NMR, DSC, TGA, intrinsic dissolution and Raman spectroscopy.

The Aplautamide base used for the above process, as well as for the following processes, may be in any polymorphic form or in a mixture of any polymorphic forms such as hydrated, solvated, non-solvated or mixture of hydrated, solvated or non-solvated forms thereof.

The process of the present invention may be used as a method for purifying any form of Apalutamide, as well as for the preparation of the new polymorphic forms or salts thereof.

The present Apalutamide polymorphs have the distinctive advantageous properties such as polymorphic purity, solubility, bioavaialability, dissolution rate, stability with respect to polymorphic conversion, low content of residual solvent and such other properties useful in formulating the pharmaceutical compositions.

The present invention comprises 1) a pharmaceutical composition comprising any one, or combination of Apalutamide crystalline forms C2, C3, C4, C5, C6, C7, C8, C9 or C10 described above and at least one pharmaceutically acceptable excipient; and 2) the use of any one, or combination, of the above-described Apalutamide crystalline forms C2, C3, C4, C5, C6, C7, C8, C9 or C10 in the manufacture of a pharmaceutical composition, wherein the pharmaceutical composition can be useful for the treatment or prevention of cancer.

The pharmaceutical composition can be prepared by a process comprising combining any one, or combination of the above-described Apalutamide crystalline forms C2, C3, C4, C5, C6, C7, C8, C9 or C10; with at least one pharmaceutically acceptable excipient.

Any one, or combination, of the above-mentioned Apalutamide crystalline forms C2, C3, C4, C5, C6, C7, C8, C9 or C10 particularly in a pharmaceutical composition and dosage form, can be used to treat or prevent cancer in a mammal such as a human, comprising administering a treatment effective amount of the one, or combination, of the Apalutamide crystalline forms C2, C3, C4, C5, C6, C7, C8, C9 or C10 in the mammal.

EXAMPLES

Various embodiments of invention are described in more detail by means of the following examples. These are provided by way of illustration and not by way of limitation.

Example 1: Preparation of Form- C2 of Apalutamide

Dissolved Apalutamide (2g) in dimethyl carbonate (10ml) at 25-30°C. Solution was kept for stirring until thick paste material was obtained. To the material, 60 ml of MTBE was added and stirred for 3 hrs. The isolated product Form-C2 was characterized with PXRD.

Example 2: Preparation of Form- C3 of Apalutamide

The Form-C2 obtained in example 1 was dried in Air Tray Dryer (ATD) at 60°C for 3-5 hrs to obtain the Form -C3 characterized with its PXRD.

Example 3: Alternate process for the preparation of Form-C2

Suspended Apalutamide Form-T12 (10 gm) in 200 mL of n-Heptane (20v) at 45°C-50°C. Maintained this reaction mass for 2 hrs at 45°C to 50°C. Filtered the material and suck dried under vacuum to obtain the title compound.

Yield: 8 gm

Apalutamide Form-C2 has been confirmed by PXRD as presented in figure 1.

Example 4: Alternate process for the preparation of Form-C2

Suspended Apalutamide Form-T1(12 gm) in 300 mL of MTBE (25v) at 25°C-30°C. Then charged (0.16 v) of dimethyl carbonate and maintained this reaction mass for 2 hrs at 25°C to 30°C. Cooled the reaction mass to 2-8°C and maintained this reaction mass for 2 hrs at 2-8°C. Filtered the material and suck dried under vacuum to obtain the title compound.

Yield: 11 gm

Apalutamide Form-C2 has been confirmed by PXRD as presented in figure 1.

Example 5: Alternate process for the preparation of Form-C3

Suspended Apalutamide Form-T15 (5gm) in 120 mL of n-Heptane (24v) at 2-8°C. Maintained this reaction mass for 12-14 hrs at 2-8°C, followed by filtration and drying to get the title compound.

Yield: 4.3 gm

Apalutamide Form-C3 has been confirmed by PXRD as presented in figure 2, DSC as presented in figure 3, TGA as presented in figure 4 and IR as presented in figure 5.

Example 6: Process to prepare Form-C4

Dissolved Apalutamide (2 gm) in N, N Dimethyl Formamide (2ml) at 25-30°C. To the clear solution 40 mL of Heptane and 40 mL of MTBE added and stirred for 3-4 hrs. Filtered the material and suck dried under vacuum to obtain the title compound.

Apalutamide Form-C4 has been confirmed by PXRD as presented in figure 6.

Example 7: Process to prepare Form-C5

Apalutamide Form-C4 was dried in Air Tray Dryer (ATD) at 40-50°C for 3-5 hrs resulted the titled compound.

Yield:1.5 gm

Apalutamide Form-C5 has been confirmed by PXRD as presented in figure 7.

Example 8: Process to prepare Form-C6

Dissolved Apalutamide (2 gm) in N-Methyl Pyrrolidine (4ml) at 25-30°C. To the clear solution 40 mL of Heptane and 40 mL of MTBE added and stirred for 3-4 hrs. Filtered the material and suck dried the material under vacuum to obtain the title compound.

Apalutamide Form-C6 has been confirmed by PXRD as presented in figure 8.

Example 9: Process to prepare Form-C7

Apalutamide Form-C6 was dried in Air Tray Dryer (VTD) at 40-50°C for 3-5 hrs resulted the titled compound.

Yield:1.6 gm

Apalutamide Form-C7 has been confirmed by PXRD as presented in figure 9.

Example 10: Process to prepare Form-C8

Dissolved Apalutamide (1 gm) in propionitrile (2ml) at 25-30°C. Clear solution stirred for 20-25 hrs at room temperature. Filtered the material and suck dried the material under vacuum to obtain the title compound.

Yield:1.5 gm

Apalutamide Form-C8 has been confirmed by PXRD as presented in figure 10.

Example 11: Process to prepare Form-C9

Suspended Apalutamide (0.5 gm) in 3 mL of diethyl carbonate and stirred for 2-3 hrs at Room temperature. Filtered the material and suck dried the material under vacuum to obtain the title compound.

Apalutamide Form-C9 has been confirmed by PXRD as presented in figure 11.

Example 12: Process to prepare Form-C10

Apalutamide Form-C9 was dried in Air Tray Dryer (ATD) at 55-60°C for 2-3 hrs resulted the titled compound.

Yield: 0.38 gm

Apalutamide Form-C10 has been confirmed by PXRD as presented in figure 12.

We Claim,

1. Crystalline polymorphic forms of Aaplutamide, selected from the group consisting of Form-C2, Form-C3, Form-C4, Form-C5, Form-C6, Form-C7, Form- C8, Form-C9 and Form-C10.
2. The crystalline Form-C3 of Aaplutamide as claimed in claim 1, characterized by having a PXRD pattern comprising peaks at 4.8, 9.6, 14.3, 17.6, 19.2 and $22.2 \pm 0.2^\circ 2\theta$.
 $\pm 0.2^\circ 2\theta$, substantially as depicted in Figure 2.
3. The crystalline Form-C3 of Aaplutamide as claimed in claim 2, characterized by having a PXRD pattern comprising further peaks at 12.1, 22.2, 24.1 and $27.8 \pm 0.2^\circ 2\theta$, substantially as depicted in Figure 2.
4. The crystalline Form-C3 of Aaplutamide as claimed in claim 1, characterized by having a DSC spectrum exhibiting one endotherm with an onset at 150.20°C , a peak maximum at 154.62°C ; and a second endotherm with a peak maximum at 195.41°C .
5. The crystalline Form-C3 of Aaplutamide as claimed in claim 4, characterized by having a DSC spectrum as depicted in Figure 3.
6. The crystalline Form-C3 of Aaplutamide as claimed in claim 1, characterized by having a thermogravimetric analysis (TGA) profile as shown in Figure 4.
7. The crystalline Form-C3 of Aaplutamide as claimed in claim 1, characterized by having an IR spectrum comprising characteristic IR spectra peaks at about 3438 cm^{-1} , 3236 cm^{-1} , 3095 cm^{-1} , 3003 cm^{-1} , 2965 cm^{-1} , 2947 cm^{-1} , 2905 cm^{-1} , 2877 cm^{-1} , 2528 cm^{-1} , 2242 cm^{-1} , 1765 cm^{-1} , 1662 cm^{-1} ,

1634 cm⁻¹, 1622 cm⁻¹, 1599 cm⁻¹, 1567 cm⁻¹, 1502 cm⁻¹, 1461 cm⁻¹, 1432 cm⁻¹, 1409 cm⁻¹, 1379 cm⁻¹, 1313 cm⁻¹, 1272 cm⁻¹, 1243 cm⁻¹, 1215 cm⁻¹, 1171 cm⁻¹, 1152 cm⁻¹, 1111 cm⁻¹, 1097 cm⁻¹, 1058 cm⁻¹, 1030 cm⁻¹, 1004 cm⁻¹, 981 cm⁻¹, 931 cm⁻¹, 909 cm⁻¹, 878 cm⁻¹, 830 cm⁻¹, 805 cm⁻¹, 771 cm⁻¹, 748 cm⁻¹, 721 cm⁻¹, 690 cm⁻¹, 678 cm⁻¹ and 644 cm⁻¹.

8. The crystalline Form-C3 of Aaplutamide as claimed in claim 7, characterized by having an IR spectrum as shown in Figure 5.
9. A process for preparing crystalline Form-C3 of Aaplutamide, as claimed in any one of claims 2 to 8, wherein, the process comprises, drying Aaplutamide Form-C2 in a tray dryer.
10. The process according to the claim 9, wherein the operation temperature in the said tray dryer is about 30°C to about 80°C, preferably about 40°C to about 70°C, more preferably about 50°C to about 70°C.
11. The process as claimed in claim 9 or 10, wherein the residence time in the said tray dryer is typically anywhere between a period of about 1 hour to about 10 hours, preferably 2 hours to about 7 hours, more preferably for about 3 hours to about 5 hours.
12. A process for preparing crystalline Form- C3 of Apalutamide as claimed in claim 2 to 8, wherein, the process comprises, suspending Apalutamide in a suitable solvent or solvent mixture, isolating the precipitated solid and drying the solid.
13. The process according to the claim 12, wherein the suspension is stirred at about 0°C to the boiling point of the solvent used.

14. The process according to the claim 13, wherein the suspension is stirred at about 2°C to about 10°C, for a period of about 2 hours to about 25 hours, preferably 5 hours to about 20 hours, more preferably for about 10 hours to about 15 hours.
15. The process according to the claim 12, wherein suitable solvent is selected from, but not limited to heptane, hexane, dimethyl carbonate, diethyl carbonate, diethyl ether, dimethyl ether and MTBE.
16. The process according to the claim 15, wherein solvent is heptane.
17. The process according to the claim 12, wherein the precipitated solid is isolated by filtration and dried under reduced pressure at 25°C to about 80°C, preferably at 30°C to about 40°C, for a period of about 2 hour to about 10 hours, preferably 4 hours to about 8 hours, more preferably for about 6 hours.
18. Crystalline Form- C3 of Apalutamide prepared by a process according to any one of the claims 9 to 11 or 12 to 17.
19. A pharmaceutical composition comprising: (a) a therapeutically effective amount of a crystalline Form-C3 of Apalutamide according to any of claims 2 to 8 3 or 18; and (b) at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient.
20. A method for the prevention or treatment of cancer which method comprises administering therapeutically effective amounts to a patient in need thereof crystalline Form-C3 of Apalutamide according to any of claims 2 to 8 or 18.

I/VI

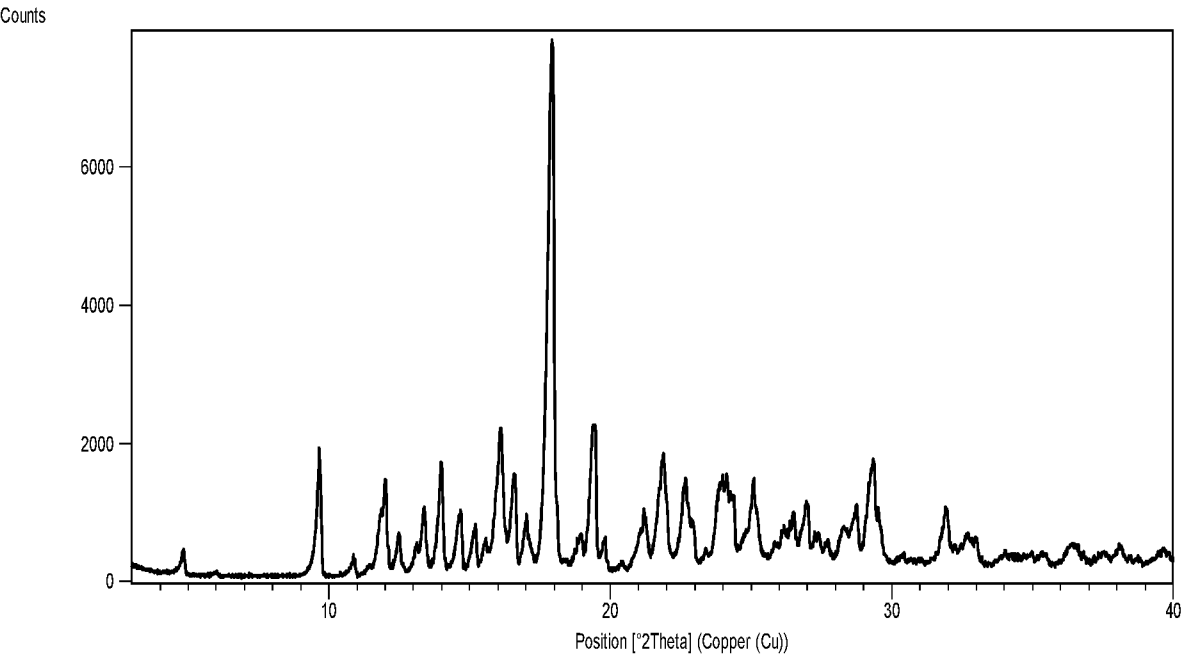


Fig 1

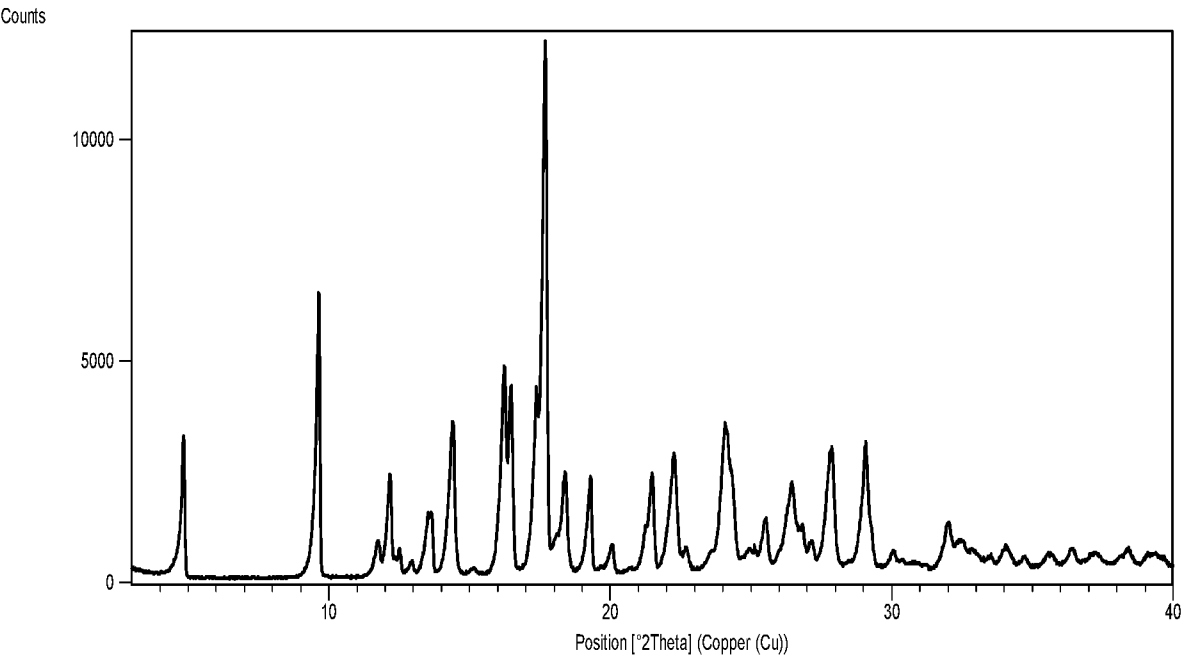


Fig 2

II/VI

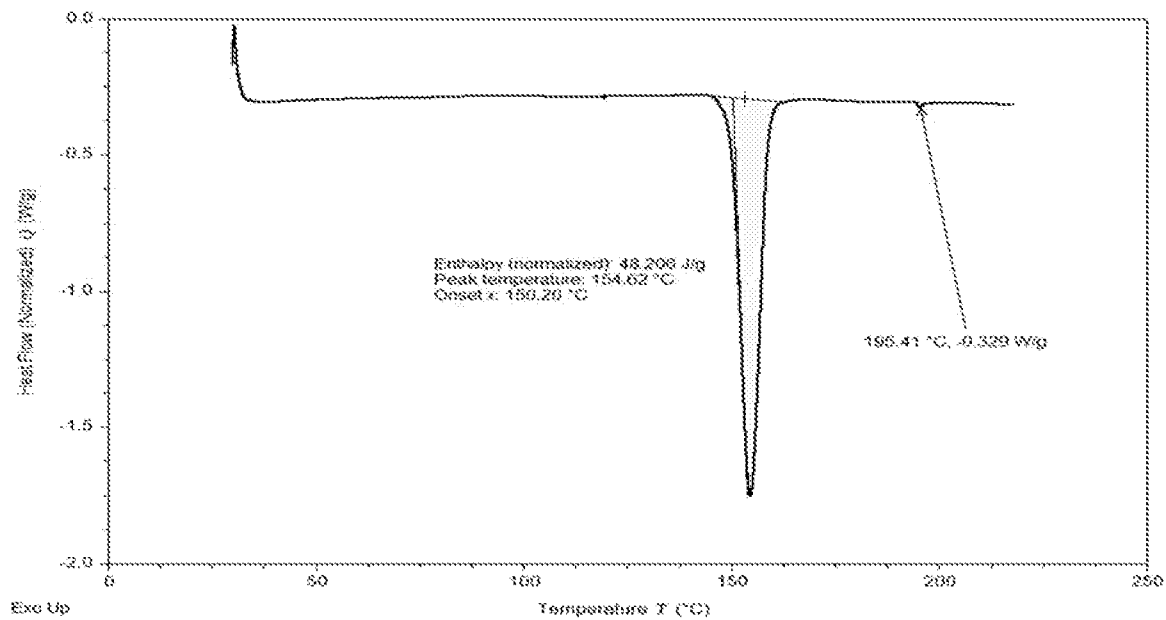


Fig 3

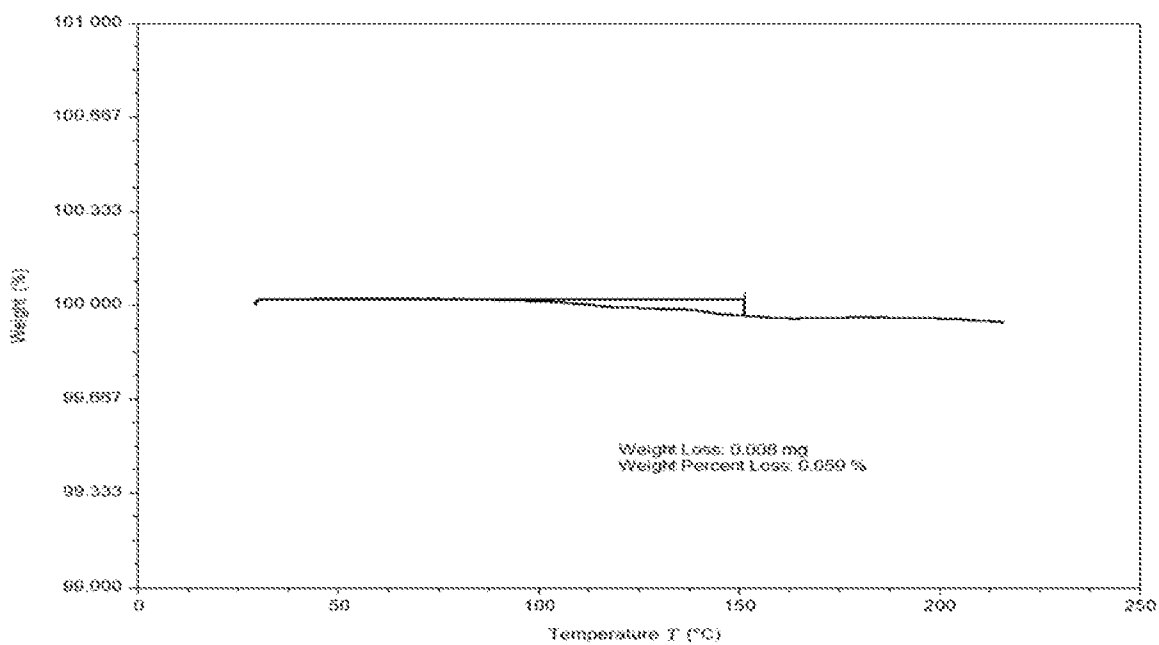


Fig 4

III/VI

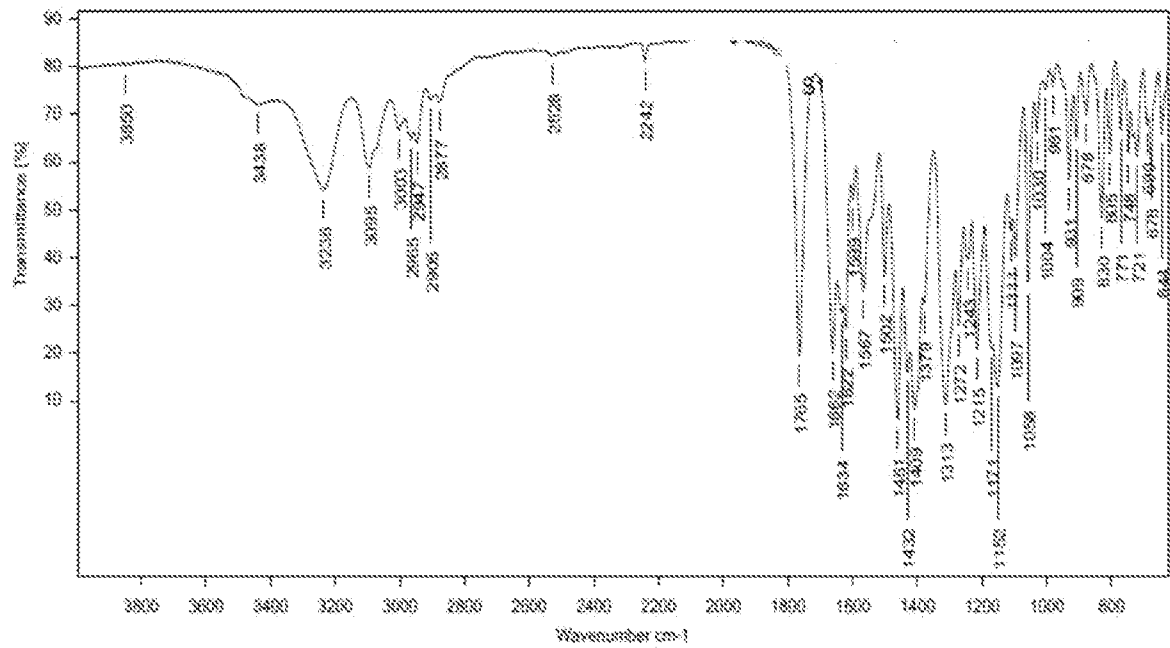


Fig 5

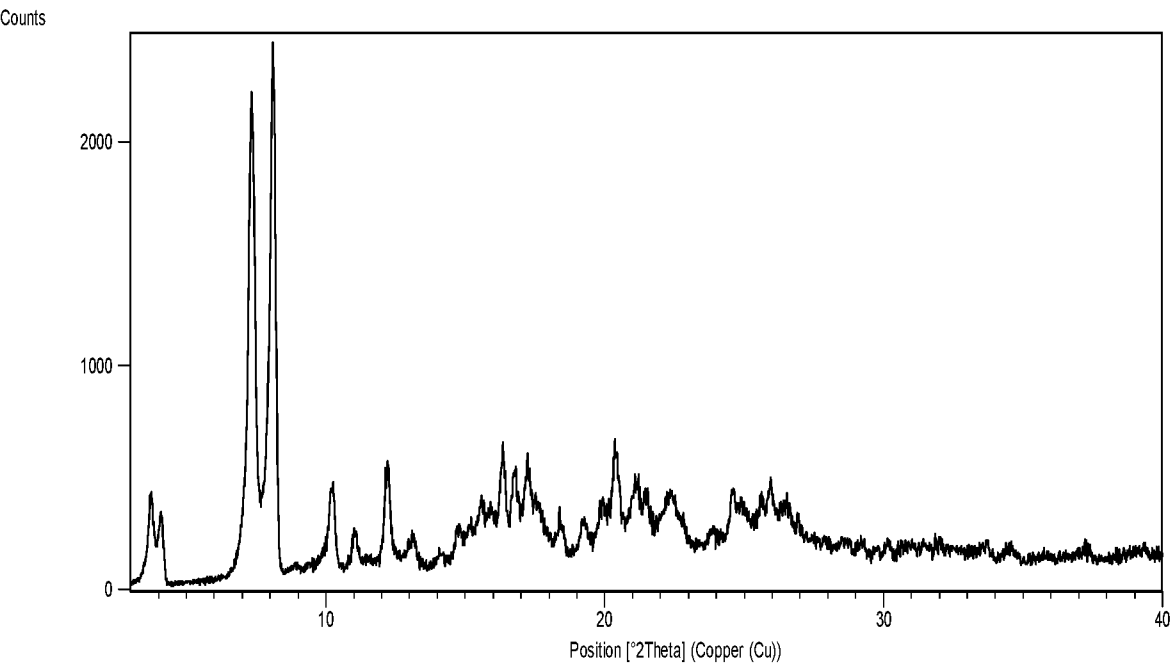


Fig 6

IV/VI

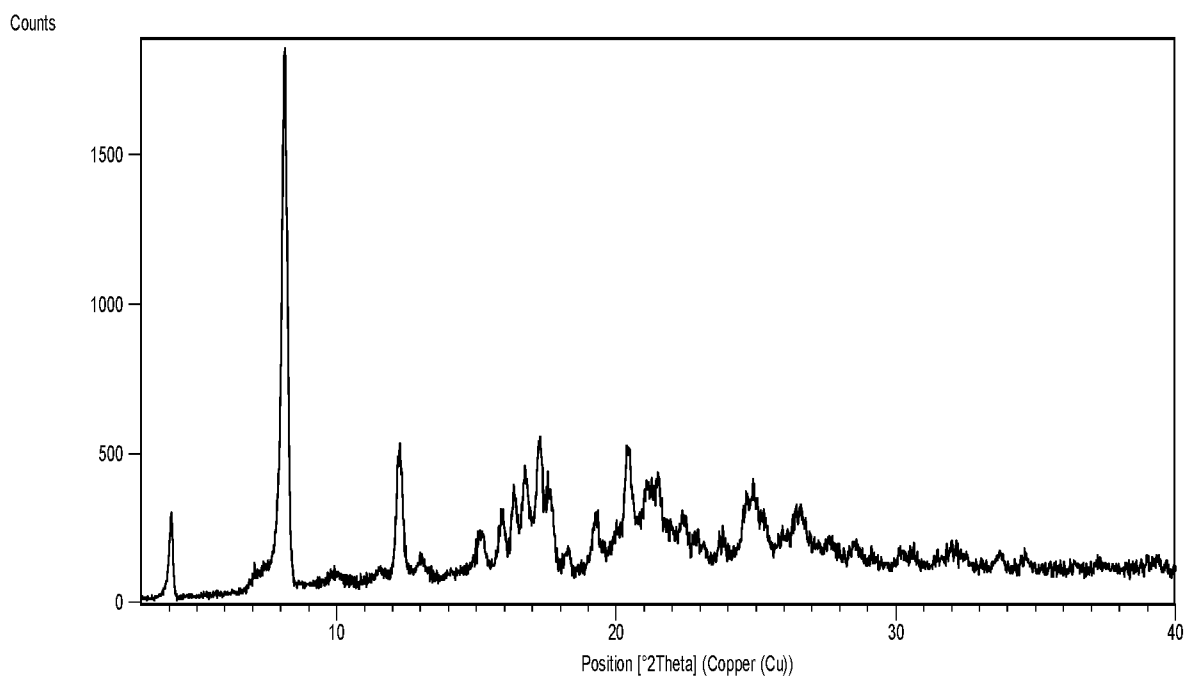


Fig 7

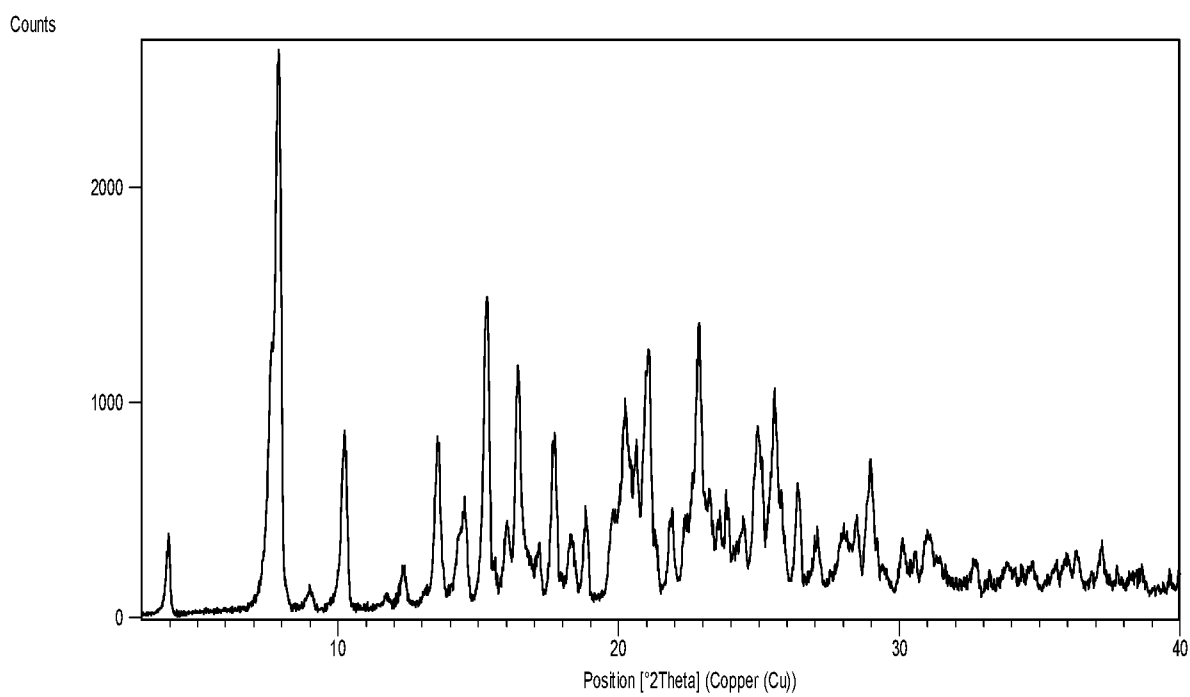


Fig 8

V/VI

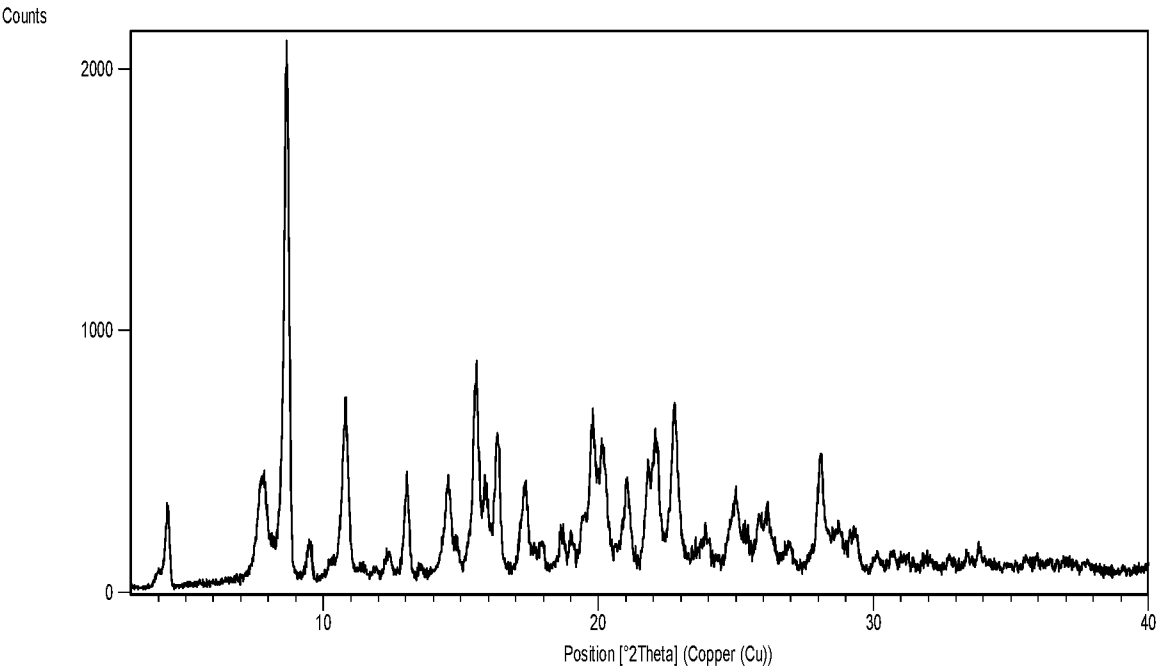


Fig 9

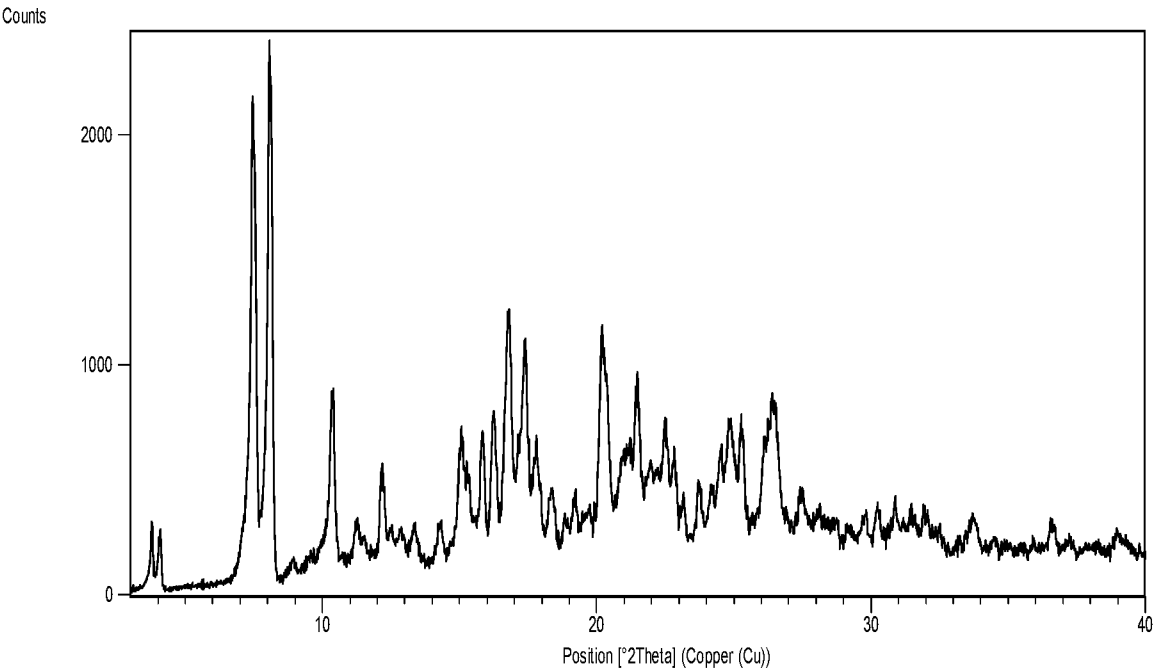


Fig 10

VI/VI

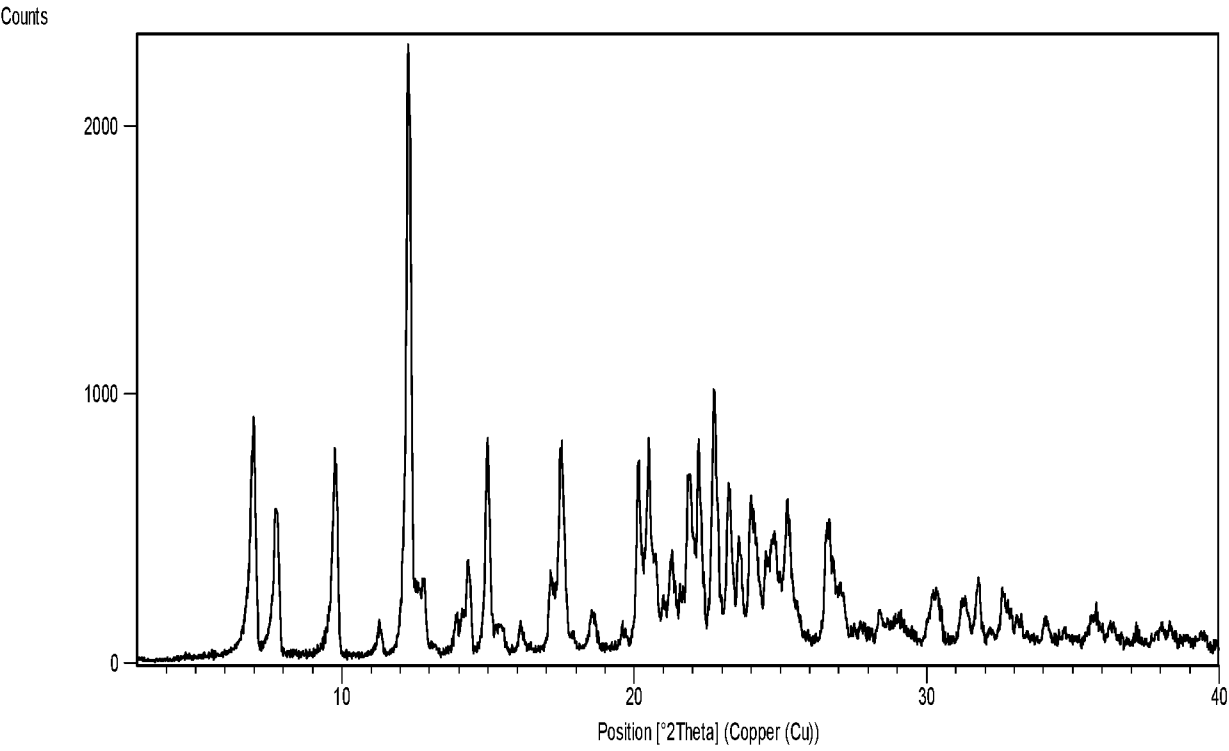


Fig 11

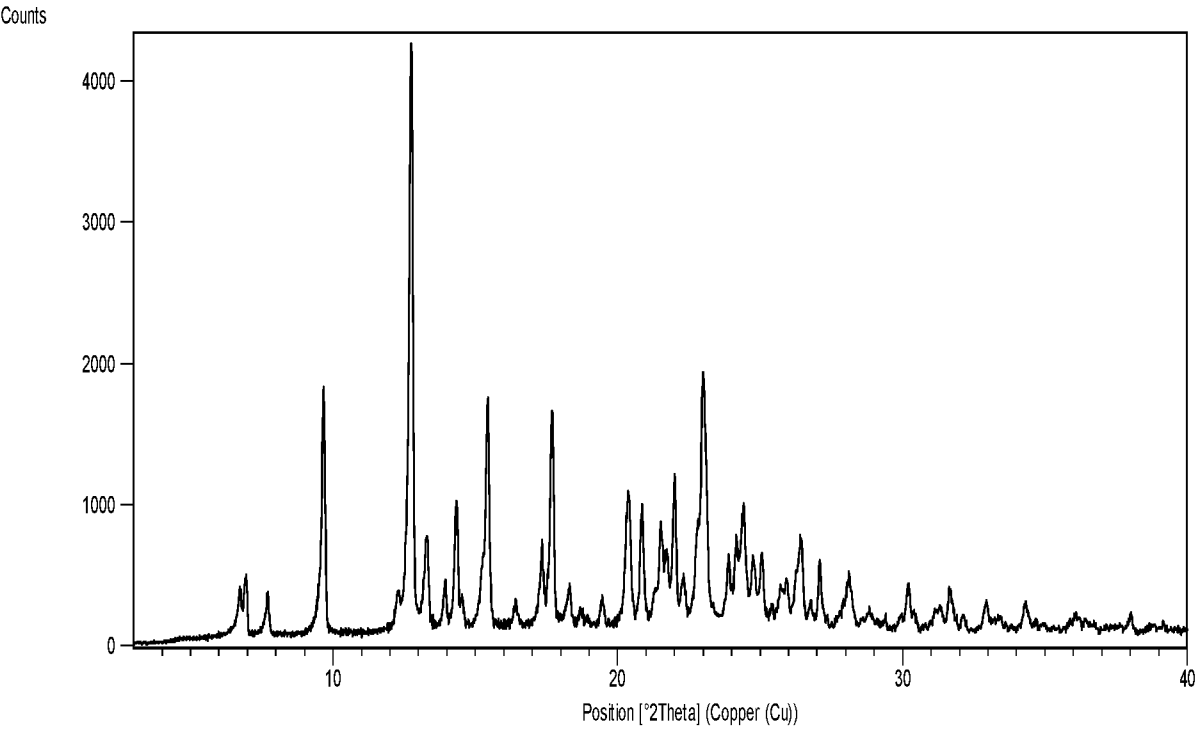


Fig 12