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Solid state forms of Apalutamide and their process for the preparation thereof

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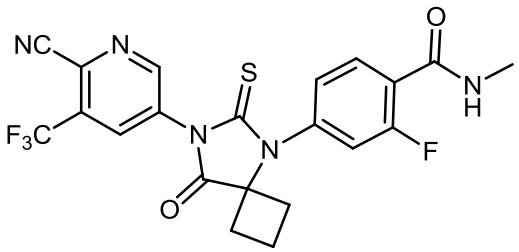
Apalutamide of formula-1 is chemically known as (4-[7-(6-Cyano-5-trifluoromethyl pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methyl benzamide). Apalutamide was approved in US and Europe under the brand name of ERLEADA™ and it is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer. The structural formula 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) is given below:



Formula-1

US patent number 8445507 (hereinafter described as US'507) describes the process for the preparation of Apalutamide. Various crystalline polymorphs of Apalutamide are known in the literature. US patent number 9481663 (hereinafter referred as the US' 663 patent) discloses the polymorphic forms of compound of formula-1, characterized by XRD, DSC, single crystal X-Ray diffraction and TGA. US patent publication US2023233529A1 describes solid dispersion of comprising Apalutamide and HPMC-AS. PXRD pattern of amorphous solid dispersion comprising Apalutamide and HPMC-AS was not disclosed in US’529A1. The patent applications/publications WO2016124149A1, WO2018112001A1, WO2019016747A1, WO2019135254A1, IN201741043701 and IN201841002315 also discloses the polymorphs of Apalutamide.

The present disclosure relates to an amorphous solid dispersion comprising Apalutamide of formula-1 and HPMC-AS; process for the preparation thereof.

In the present disclosure, the ratio of the weight of Apalutamide to the weight of the HPMC-AS within the solid dispersion ranges from but not limited to about 1:0.05 to about 1:5.

In the present disclosure, amorphous solid dispersion is further characterized by its powder X-Ray diffraction {PXRD} pattern which is illustrated in figure-1.

The present disclosure provides a process for the preparation of amorphous solid dispersion comprising Apalutamide of formula-1 and HPMC-AS, comprising:

a) providing a solution of Apalutamide in a solvent,
b) combining the above solution with HPMC-AS,
c) isolating amorphous solid dispersion comprising Apalutamide and HPMC-AS.

Providing a solution of Apalutamide of compound of formula-1can be directly obtained from the reaction mixture or it can be obtained by dissolving the compound of formula-1 in a suitable solvent at a temperature ranging about 25°C to reflux temperature of the solvent used, a solvent used in step-a) is selected from alcohol solvents, chloro solvents or the mixture thereof.

Isolating amorphous solid dispersion in step-c) of the above process can be done by removing the solvent from the reaction mixture. The technique used for the removal of the solvent from the reaction mixture includes but not limited to evaporation, evaporation under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying.

The amorphous solid dispersion is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used.

The present disclosure also provides the use of amorphous solid dispersion of the present disclosure for the preparation of pharmaceutical formulations.

The present disclosure also provides pharmaceutical composition comprising amorphous solid dispersion of the present disclosure and at least one pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The present disclosure also provides a pharmaceutical composition comprising amorphous solid dispersion of the present disclosure and one or more pharmaceutically acceptable carriers for the treatment of patients with non-metastatic castration-resistant prostate cancer.

The solid dispersion produced by various processes of the present disclosure can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction includes but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling/micronization may be performed before drying or after drying of the product.

PXRD Method of Analysis:

The PXRD analysis of compounds of the present disclosure was carried out by using BRUKER-Axis/D8 ADVANCE (DAVINCI) X-Ray diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

Examples:

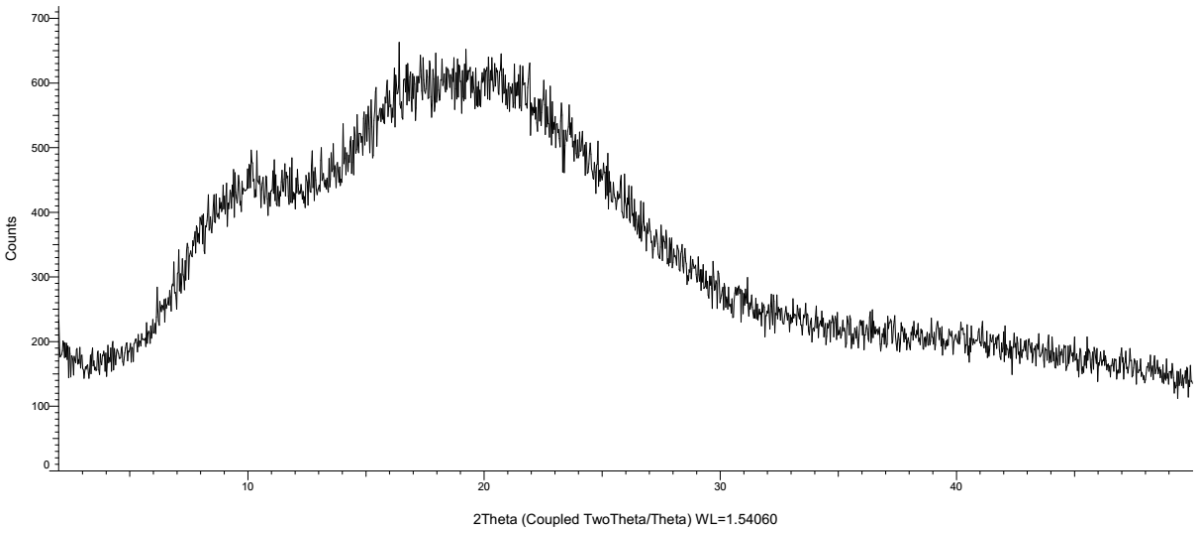
Example-1: Preparation of amorphous solid dispersion of Apalutamide and HPMC-AS.

Apalutamide (25 g) is dissolved in mixture of methanol (250 ml) and dichloromethane (250 ml) at 25-30°C. Filtered the solution for making it particle free. HPMC-AS (25 g) added to the above obtained filtrate at 25-30°C and stirred at the same temperature. Spray dried the obtained solution using spray dryer as following conditions:

Internal temperature: 60-65°C; Feed rate: 6 ml/min; Aspirator flow rate: 70%; N2 Pressure: 2.0 Kg. Obtained material is dried to get the title compound.

Yield: 33 g; PXRD of the obtained compound is illustrated to the figure-1.

Figure-1


Counts
700
600
500
400
300
200
100
0
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

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