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Novel Crystalline Polymorph Of Baloxavir Marboxil And Process For Preparation Thereof

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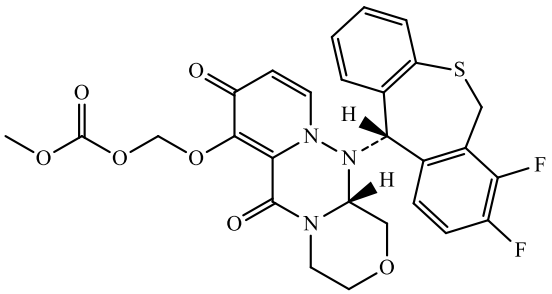
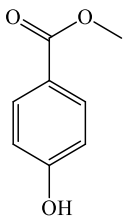
Novel crystalline polymorph of Baloxavir marboxil and process for preparation thereof

Field of the Invention:

The present invention provides novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil compound of formula-1 and Methylparaben compound of formula-2 and process for preparation thereof.



Formula-1



Formula-2

Background of the Invention:

({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate, commonly known as Baloxavir marboxil is an antiviral polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza. Baloxavir marboxil has been approved by USFDA on October 24, 2018 and by PMDA (The Pharmaceuticals and Medical Devices Agency, Japan) on February 23, 2018.

US8987441B2 and US10392406B2 describes Baloxavir marboxil, its analogs and processes for their preparation.

US10759814B2 describes three crystalline polymorphs of Baloxavir marboxil namely form-I, form-II, form-III and processes for their preparation.

WO2020181025A1 describes six crystalline polymorphs of Baloxavir marboxil namely form-BM1, form-BM2, form-BM3, form-BM4, form-BM5, form-BM6 and amorphous form and also describes processes for their preparation.

CN111875619A describes new crystal form of Baloxavir marboxil and processes for its preparation.

CN111961064A describes ‘α’ crystal form of Baloxavir marboxil and its process for preparation.

CN111377944 A describes two crystalline polymorphs of Baloxavir marboxil namely form-A, form-B and processes for their preparation.

Still, there is a significant need in the art to develop novel polymorph of Baloxavir marboxil.

The present inventors after significant efforts have surprisingly found novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben.

Brief description of the invention:

The first embodiment of the present invention is to provide a novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben.

The second embodiment of the present invention is to provide a process for the preparation of novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben.

Brief Description of the Drawing:

Figure-1: Illustrates the PXRD pattern of novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben.

Detailed description of the Invention:

The first embodiment of the present invention is to provide a novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben, which is herein designated as form-R.

The novel crystalline form-R of Baloxavir marboxil of the present invention is characterized by its PXRD pattern having peaks at 4.0, 7.9 and 11.0 ± 0.2° of 2θ values.

The crystalline form-R of Baloxavir marboxil of the present invention is further characterized by its PXRD pattern having peaks at 11.4, 12.0 and 17.9 ± 0.2° of 2θ values.

The crystalline form-R of Baloxavir marboxil of the present invention is further characterized by its PXRD pattern as illustrated in figure-1.

The second embodiment of the present invention provides a process for the preparation of novel crystalline form-R of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben. The said process comprising;

a) providing a solution of Baloxavir marboxil and Methylparaben in a solvent at a suitable temperature,
b) obtaining novel crystalline form-R of Baloxavir marboxil.

An aspect of the present invention provides a process for the preparation of crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben. The said process comprising;

a) providing a solution of Baloxavir marboxil and Methylparaben in a solvent at a suitable temperature,
b) obtaining crystalline polymorph of Baloxavir marboxil.

The solvent in step-a) is selected from chloro solvents such as dichloromethane, chloroform, carbon tetrachloride or their mixtures; and the temperature ranges from about 25°C to about 100°C.

The solution of step-a) of the above process can be optionally filtered to make it particle free.

In an aspect of the present invention, the solution of step-a) of the above process can be optionally treated with charcoal to remove the colour/to clarify the solution.

In one aspect of the present invention, the solution in step-a) of the above described process can be provided by dissolving Baloxavir marboxil and Methylparaben in a solvent.

The crystalline polymorph of Baloxavir marboxil in step-b) can be obtained by removal of the solvent from the mixture by various techniques. The techniques include but not limited to decantation, filtration, evaporation, distillation, cooling the reaction mixture to a lower temperature, holding the mixture for sufficient time to precipitate the solid followed by removal of the solvent by any of the above techniques.

In an aspect of the second embodiment, the said crystalline polymorph is prepared by adding a second solvent to a solution comprising Baloxavir marboxil and Methylparaben in a solvent, filtration of the precipitated solid followed by drying the solid.

Wherein, the second solvent is selected from hydrocarbon solvents. In one aspect, the second solvent is preferably n-heptane.

The solvent may be removed optionally under reduced pressures, at temperatures less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C, less than about -60°C or at less than about -80°C.

The first aspect of the second embodiment of the present invention provides a process for the preparation of crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben. The said process comprising;

a) providing a solution of Baloxavir marboxil and Methylparaben in dichloromethane,
b) evaporation of the solvent to provide crystalline polymorph of Baloxavir marboxil.

The second aspect of the second embodiment of the present invention provides a process for the preparation of novel crystalline polymorph of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben. The said process comprising;

a) providing a solution of Baloxavir marboxil and Methylparaben in dichloromethane,
b) combining the solution with n-heptane to provide crystalline polymorph of Baloxavir marboxil.

The Baloxavir marboxil compound of formula-1 which is used as the input in the above process for the preparation of novel crystalline form-R of Baloxavir marboxil of the present invention can be synthesized by any of the processes known in the art.

Methylparaben which is used as the input in the above process can be obtained from any commercial sources available.

The novel crystalline form-R of compound of formula-1 of the present invention is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of compound of formula-1 is present in the composition in particular polymorphic form mentioned.

The third embodiment of the present invention provides the use of novel crystalline form-R of compound of formula-1 of the present invention for the preparation of pharmaceutical formulations.

The fourth embodiment of the present invention provides a pharmaceutical composition comprising novel crystalline form-R of compound of formula-1 of the present invention and at least one pharmaceutically acceptable excipient.

The fifth embodiment of the present invention provides a method of treating a patient in need thereof comprising administering to the said patient a therapeutically effective amount of novel crystalline form-R of compound of formula-1 of the present invention.

The novel crystalline form-R of compound of formula-1 produced by the process of the present invention may have particle size distribution of D_{90} less than about 400 µm, preferably less than about 300 µm, more preferably less than about 200 µm. In one aspect of the present invention, the novel crystalline form-R of compound of formula-1 may have particle size distribution of D_{90} less than about 100 µm, preferably less than about 50 µm.

The crystalline compound of formula-1 produced by the process of the present invention 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.

P-XRD Method of Analysis:

The PXRD analysis of compound of formula-1 of the present invention was carried out by using BRUKER/D8 ADVANCE diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

The best mode of carrying out the present invention is illustrated by the below mentioned example. This example is provided as illustration only and hence should not be construed as limitation to the scope of the invention.

Example:

Example-1: Preparation of novel crystalline form-R of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben

Baloxavir marboxil (1.0 gm) and Methylparaben (0.266 gm) were dissolved in dichloromethane (5 ml) at 25-30°C. The solution was held at 25-30°C for 3 hr. Evaporated the solvent, collected the solid and dried to get the title compound.

The PXRD pattern of the obtained compound is shown in figure-1.

Yield: 1.05 gm.

Example-2: Preparation of crystalline form-R of Baloxavir marboxil comprising Baloxavir marboxil and Methylparaben

A mixture of Baloxavir marboxil (5 gm), Methylparaben (1.33 gm) and dichloromethane (25 ml) was stirred for 15 min at 25-30°C. n-Heptane (150 ml) was slowly added to the solution at 25-30°C and stirred for 2 hr 15 min at the same temperature. Filtered the solid, washed with n-heptane and dried the material to get the title compound.

The PXRD pattern of the obtained compound is similar to figure-1.

Yield: 4.8 gm.

Drawing:

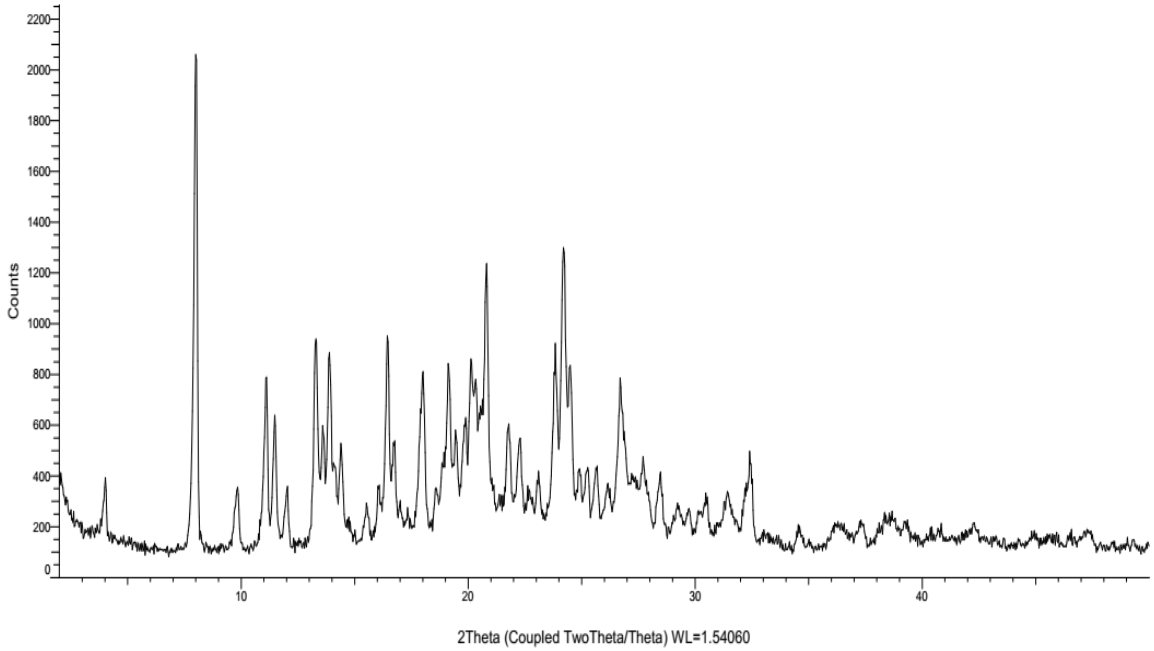


Figure-1