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Process for the preparation of Tenofovir Alafenamide Monofumarate

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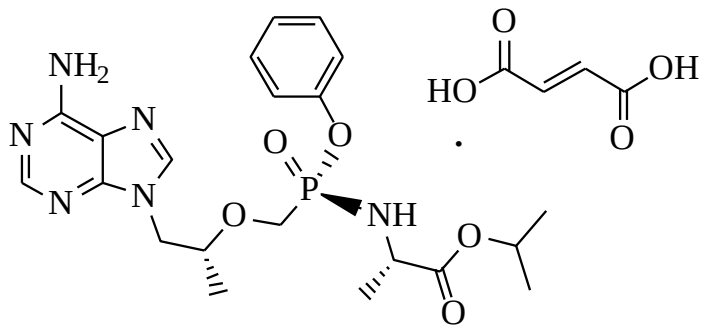
A process for the preparation of propan-2-yl-N-[(S)-({[(2R)-1-(6-amino-9Hpurin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate,(2E)-but-2-enedioate of formula-1, which is represented by the following structural formula.



Formula-1

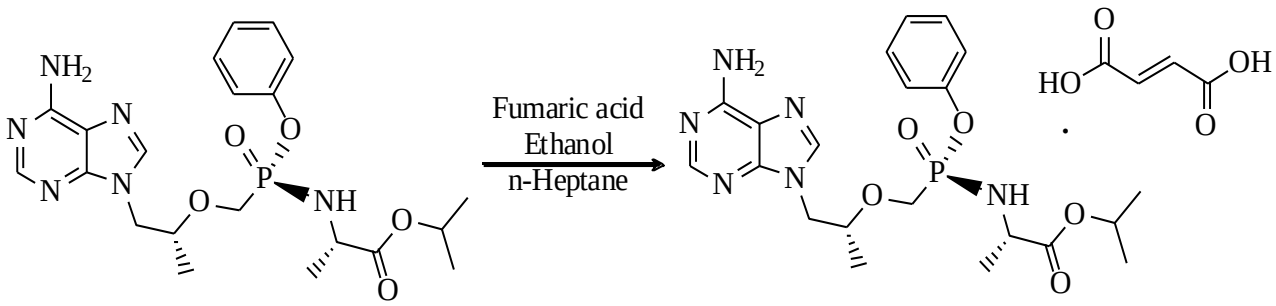
Tenofovir alafenamide monofumarate is chemically known as propan-2-yl-N-[(S)-({[(2R)-1-(6-amino-9Hpurin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2E)-but-2-enedioate. Tenofovir alafenamide is a prodrug of tenofovir. It was developed by Gilead Sciences based on the protide technology of Chris McGuigan for use in the treatment of HIV/AIDS and chronic hepatitis B, and is applied in the form of tenofovir alafenamide fumarate (TAF).

WO2002008241A1 discloses process for the preparation of Tenofovir alafenamide monofumarate in example- 4, by dissolving Tenofovir alafenamide and fumaric acid in acetonitrile solvent, Tenofovir alafenamide monofumarate obtained as a white powder with melting point of 119.7°C - 121.1°C.

WO2015040640A2 discloses the preparation of Tenofovir alafenamide monofumarate in example- 6 with PXRD pattern as figure-2, by dissolving Tenofovir alafenamide and fumaric acid in acetonitrile solvent, Tenofovir alafenamide monofumarate obtained as a white crystalline powder.

WO2017134089A1 describes the polymorphic forms of form-I, form-II, form-III and form-S of Tenofovir alafenamide monofumarate.

The present disclosure provides an improved process for the preparation of Tenofovir alafenamide monofumarate with reproducibly in good purity and yield, which is schematically disclosed as follows.



Tenofovir Alafenamide **Tenofovir Alafenamide Monofumarate**

The present disclosure provides a pharmaceutical composition comprising Tenofovir alafenamide monofumarate of formula-1, which is prepared according to the present invention and one or more pharmaceutically acceptable excipients.

The excipient can be selected from one or more described in *Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems 2006*.

As used herein, the term "pharmaceutical compositions" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Tenofovir alafenamide monofumarate produced by the present disclosure can be micronized or milled using conventional techniques to get the desired particle size and surface area to achieve desired solubility profile to suit to pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball milling, roller milling and hammer milling, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

P-XRD Method of Analysis:

PXRD analysis of Tenofovir alafenamide monofumarate of formula-1 was carried out by using BRUKER/D8 ADVANCE diffractometer using Cu Kα radiation of wavelength 1.5406 A° and continuous scan speed of 0.03°/min.

PXRD pattern of Tenofovir alafenamide monofumarate produced by the present disclosure is similar to the PXRD pattern disclosed in WO2015040640A2.

The following examples specifies the conditions of the process for the preparation of Tenofovir Alafenamide Monofumarate.

Reference Example-1: Process for the preparation of Tenofovir alafenamide fumarate (example-6 of WO2015040640A2).

To a solution of 9-[(R)-2-[[(S)-[[(S)-l-(isopropoxycarbonyl) ethyl] amino] phenoxy phosphinyl] methoxy] propyl] adenine (100 gms, 0.209 mol) in acetonitrile (1890 gms), fumaric acid (22 gms, 0.188 mol) was added and heated to reflux to dissolve the solids. The reaction mass was filtered in hot condition, cooled to 5°C and maintained for 16 hours. The product was isolated by filtration, rinsed with acetonitrile and dried under reduced pressure to get product as a white crystalline powder.

Yield: 92 g

HPLC purity: 99.78%.

The PXRD pattern of the obtained compound was depicted in Figure-1.

Example-1: Process for the preparation of Tenofovir alafenamide monofumarate.

Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9Hpurin-9-yl)propan-2-yl]-oxy}methyl) (phenoxy)phosphoryl]-L-alaninate (50 g) was added to the mixture of Fumaric acid (12.17 g) in ethanol (500 ml) at 25-30°C. Heated the mixture at 45-50°C and stirred for 10 minutes. Mixture added to the pre-cooled n-Heptane (1250 ml) at 0-5°C and stirred for 3 hours. Filtered the solid and dried to get the titled product.

Yield: 50 g

Assay by HPLC: 99.63%

Fumaric acid content by Potentiometry: 19.39%.

The PXRD pattern of the obtained compound was depicted in Figure-2.

Figures:

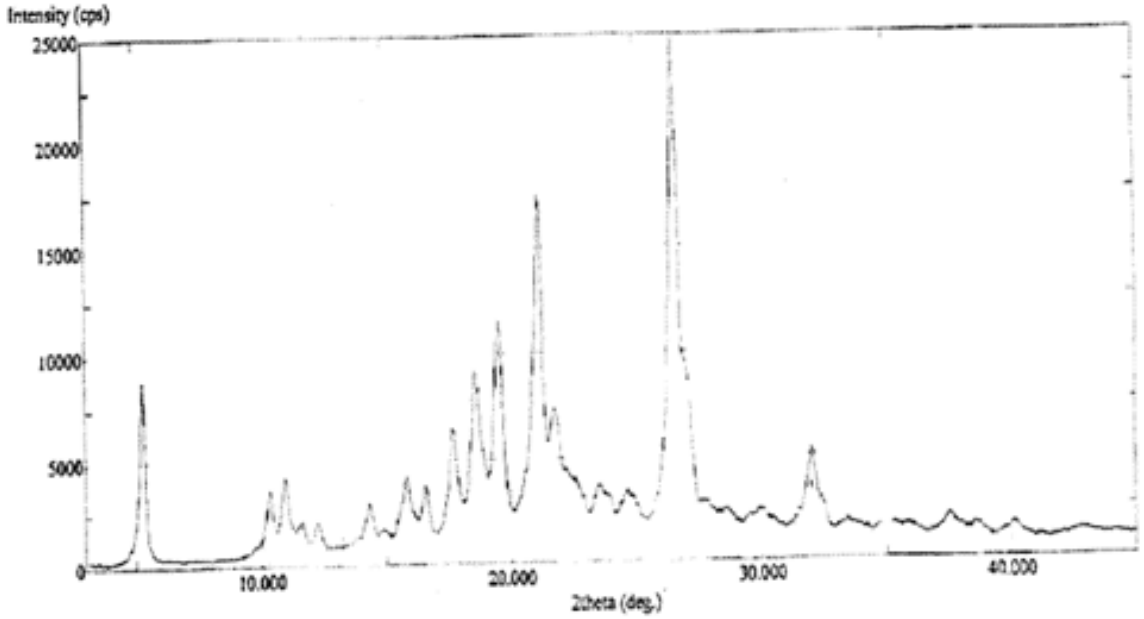


Figure-1

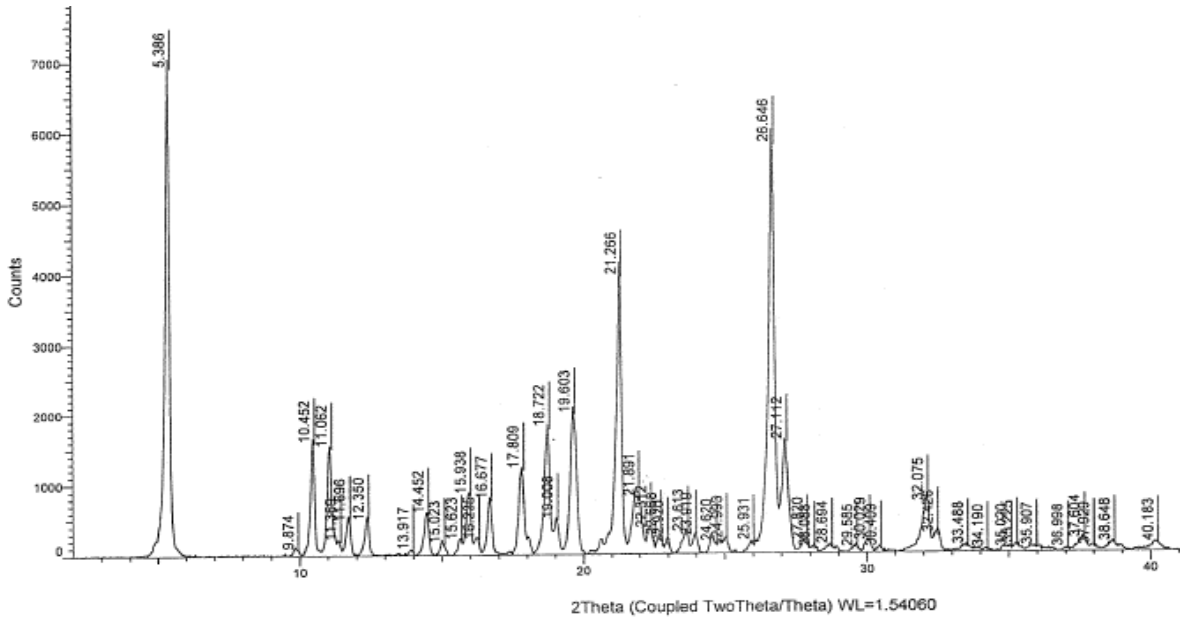


Figure-2

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