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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
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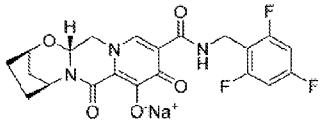
(54) Title: POLYMORPHIC FORMS OF BICTEGRAVIR SODIUM



(57) Abstract: The present disclosure relates to novel crystalline forms of bictegravir sodium and processes for their preparation.

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POLYMORPHIC FORMS OF BICTEGRAVIR SODIUM

CROSS-REFERENCE TO RELATED APPLICATIONS

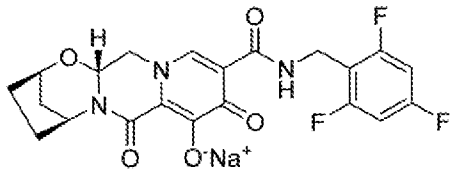
This application claims the benefit of the earlier filing date of Indian Provisional Patent Application No. IN202241035593 filed on June 21, 2022.

FIELD OF THE DISCLOUSRE

The present disclosure relates to novel crystalline forms of bictegravir sodium and processes for their preparation.

DESCRIPTION OF THE RELATED ART

Bictegravir sodium is approved as part of a single tablet regimen in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) for the treatment of HIV-1 infection under the brand name of BIKTARVY®, marketed by Gilead Sciences. Bictegravir sodium is chemically known as (2R,5S,13aR)- 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9, 13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), having the structure below:



Bictegravir is disclosed in U.S Patent No. 9,216,996 B2, which is hereby incorporated by reference.

Bictegravir sodium salt and crystalline Form I of bictegravir sodium disclosed in U.S Patent No. 9,708,342B2.

Different polymorphs may provide different advantages in a variety of capacities, for example, in ease of formulation, stability of the polymorphic form, stability of the formulation, and in pharmacokinetic profiles. These advantages may arise

from the different properties present in each polymorph. The present invention provides novel polymorphic forms of bictegravir sodium and process for the preparation thereof.

SUMMARY OF THE DISCLOSURE

A first aspect of the present invention is to provide crystalline Form M1 of bictegravir sodium.

One aspect of the present invention is to provide crystalline Form M1 of bictegravir sodium, which is characterized by powdered X-ray diffraction pattern as shown in Fig 1.

Another aspect of the present invention is to provide a process for the preparation of crystalline Form M1 of bictegravir sodium comprising the steps of:

a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
b) optionally adding sodium source and stirring the reaction mass at the same temperature;
c) cooling the reaction mass to 20-35 °C; and
d) isolating crystalline Form M1 of bictegravir sodium.

A second aspect of the present invention is to provide crystalline Form M2 of bictegravir sodium.

In another aspect, the present invention is to provide crystalline Form M2 of bictegravir sodium, which is characterized by powdered X-ray diffraction pattern as shown in Fig 2.

Other aspect of the present invention is to provide a process for the preparation of crystalline Form M2 of bictegravir sodium comprising the steps of:

a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
b) optionally adding sodium source and stirring the reaction mass at the same temperature;
c) optionally cooling the reaction mass to 0-5 °C; and
d) isolating crystalline Form M2 of bictegravir sodium.

A third aspect of the present invention is to provide crystalline Form M3 of bictegravir sodium.

In another aspect, the present invention is to provide crystalline Form M3 of bictegravir sodium, which is characterized by powdered X-ray diffraction pattern as shown in Fig 3.

Other aspect of the present invention is to provide a process for the preparation of crystalline Form M3 of bictegravir sodium comprising drying the crystalline Form M1 or crystalline Form M2 of bictegravir sodium at 100-150 °C.

BRIEF DESCRIPTION OF THE FIGURES

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

Figure. 1 is an X-ray powder diffractogram of crystalline Form M1 of bictegravir sodium.

Figure. 2 is an X-ray powder diffractogram of crystalline Form M2 of bictegravir sodium.

Figure. 3 is an X-ray powder diffractogram of crystalline Form M3 of bictegravir sodium.

DETAILED DESCRIPTION OF THE DISCLOSURE

It is to be understood that the description of the present invention has been simplified to illustrate elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that may be well known.

The polymorph of the present disclosure is characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of the polymorphs of the disclosure were measured on ***BRUKER D-8 Discover*** powder diffractometer equipped with goniometer of θ/2θ configuration and ***Lynx Eye*** detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 0.4 seconds step time.

The present disclosure relates to crystalline forms of bictegravir sodium. The present disclosure also relates to process for the preparation of crystalline forms of bictegravir sodium.

In one embodiment, the present disclosure is to provide crystalline Form M1 of bictegravir sodium.

In another embodiment, the present disclosure is to provide crystalline Form M1 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.94, 19.78, 20.97, 23.64, 25.20, and 26.10 ±0.2° degrees two-theta.

In yet another embodiment, crystalline Form M1 of bictegravir sodium is further characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.94, 11.93, 12.38, 13.59, 17.06, 20.97, 22.30, 23.64, 25.20, 26.09 and 31.67 ±0.2° degrees two-theta.

In yet another embodiment, crystalline Form M1 of bictegravir sodium is further characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.94, 6.13, 7.09, 11.92, 12.38, 12.76, 13.59, 14.24, 15.11, 16.48, 16.89, 17.06, 17.73, 17.95, 18.68, 19.34, 19.78, 20.54, 20.97, 21.30, 21.43, 21.75, 22.30, 23.28, 23.64, 24.17, 25.20, 26.10, 26.33, 27.16, 27.43, 28.01, 28.32, 28.67,, 29.63, 29.86, 30.12, 31.67, 32.37, 34.52, 39.05 and 45.39 ±0.2° degrees two-theta.

In still another embodiment the present invention is to provide a process for the preparation of crystalline Form M1 of bictegravir sodium comprising the steps of:

a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
b) optionally adding sodium source and stirring the reaction mass at the same temperature;
c) cooling the reaction mass to 20-35 °C; and
d) isolating crystalline Form M1 of bictegravir sodium.

Within the context of this embodiment, the organic solvent employed may include chloroethanol solvent. In particular useful embodiments organic solvent is 2-chloroethanol.

Within the context of this embodiment, sodium source employed may include sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide. Sodium source may be dissolved in water and added to the reaction mass. In particular useful embodiments sodium source is sodium hydroxide.

Within the context of this embodiment, isolation can be done using any techniques in the art such as, decantation, filtration by gravity or suction, centrifugation. In particular useful embodiments the solid is isolated by filtration followed by drying under vacuum.

According to the present disclosure, bictegravir sodium is suspended in an organic solvent and heated to elevated temperature of about 40-70 °C and stirred for about

16-20 hours. The reaction mass is cooled to 20-30 °C, filtered and then dried under vacuum. The obtained solid is crystalline Form M1 of bictegravir sodium.

According to the present disclosure, bictegravir is dissolved in an organic solvent and heated to elevated temperature of about 40-70 °C. To the reaction mass sodium source is added and stirred for about 12-16 hours. The reaction mass is cooled to 20-30 °C, filtered and then dried under vacuum. The obtained solid is crystalline Form M1 of bictegravir sodium.

In another embodiment, the present disclosure is to provide crystalline Form M2 of bictegravir sodium.

Another embodiment, the present disclosure is to provide crystalline Form M2 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.90, 12.30, 19.78, 23.71 and 25.19 ±0.2° degrees two-theta.

In yet another embodiment, crystalline Form M2 of bictegravir sodium is further characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.90, 6.56, 10.67, 11.97, 12.30, 12.71, 13.33, 15.59, 16.09, 16.70, 17.79, 18.26, 18.67, 18.97, 19.40, 19.80, 20.18, 20.55, 21.39, 21.66, 22.29, 22.81 23.70, 25.19, 26.02, 26.36, 26.70, 28.36, 28.63, 29.08, 29.64, 30.31, 31.03, 31.63, 33.66, 41.14, 43.47 and 45.32 ±0.2° degrees two-theta.

In still another embodiment the present invention is to provide a process for the preparation of crystalline Form M2 of bictegravir sodium comprising the steps of:

a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
b) optionally adding sodium source and stirring the reaction mass at the same temperature;
c) optionally cooling the reaction mass to 0-5 °C; and

d) isolating crystalline Form M2 of bictegravir sodium.

Within the context of this embodiment, the organic solvent employed may include chloroethanol solvent. In particular useful embodiments organic solvent is 2-chloroethanol.

Within the context of this embodiment, sodium source employed may include sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide. Sodium source may be dissolved in water and added to the reaction mass. In particular useful embodiments sodium source is sodium hydroxide.

Within the context of this embodiment, isolation can be done using any techniques in the art such as, decantation, filtration by gravity or suction, centrifugation. In particular useful embodiments the solid is isolated by filtration followed by drying under vacuum.

According to the present disclosure, bictegravir sodium is suspended in 2-chloroethanol and heated to elevated temperature of about 40-70 °C and stirred for about 16-20 hours. The reaction mass is filtered at the same temperature and then dried under vacuum. The obtained solid is crystalline Form M2 of bictegravir sodium.

According to the present disclosure, bictegravir is dissolved in 2-chloroethanol and heated to elevated temperature of about 60-70 °C. To the reaction mass sodium source is added. The reaction mass is cooled to 0-5 °C, filtered, and then dried under vacuum at 40-70 °C. The obtained solid is crystalline Form M2 of bictegravir sodium.

In another embodiment, the present disclosure is to provide crystalline Form M3 of bictegravir sodium.

Another embodiment, the present disclosure is to provide crystalline Form M3 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 7.14, 13.95, 19.33, 20.92 and 31.70 ±0.2° degrees two-theta.

In yet another embodiment, crystalline Form M3 of bictegravir sodium is further characterized by Powder X-ray diffraction pattern having 2θ angle positions at about
7.14, 12.45, 13.95, 15.54, 18.71, 18.92, 19.34, 19.77, 20.15, 20.92, 21.95, 26.47 and 31.70 ±0.2° degrees two-theta.

In yet another embodiment, crystalline Form M3 of bictegravir sodium is further characterized by Powder X-ray diffraction pattern having 2θ angle positions at about
7.14, 12.45, 13.95, 14.33, 15.54, 16.93, 18.35, 18.71, 18.92, 19.34, 19.77, 20.15, 20.92, 21.95, 22.55, 23.57, 24.14, 24.52, 25.44, 26.47, 27.33, 31.70 and 45.44 ±0.2° degrees two-theta.

In still another embodiment the present invention is to provide a process for the preparation of crystalline Form M3 of bictegravir sodium comprising drying the crystalline Form M1 or crystalline Form M2 of bictegravir sodium at 110-140 °C.

Within the context of this embodiment, drying is performed under atmospheric pressure or under reduced pressure. In particular useful embodiments drying is performed under reduced pressure.

According to the present invention, the input bictegravir or bictegravir sodium is prepared by any prior-art process for example PCT publication No. WO2015196116A1.

In yet another embodiment, the physical and chemical stability of the crystalline bictegravir sodium Form M3 was determined by storing the samples at 25°C and 60% RH and 40°C and 75% RH conditions for three months, followed by analysis of the samples by PXRD and HPLC purity. The results of the study are summarized in the below table. The novel Bictegravir sodium Form M3 was found to be physically and chemically stable at 25°C and 60% RH and at 40°C and 75% RH conditions stable up to 3months.

Conditions/Polymorph	**Crystalline Bictegravir sodium Form M3**	
	PXRD	**HPLC**
at 25°C/60% RH		
Initial	Form M3	99.91
1 month	Stable	99.89
2 months	Stable	--
3 months	Stable	99.88
at 40°C/75% RH		
Initial	Form M3	99.91
1 month	Stable	99.88
2 months	Stable	--
3 months	Stable	99.87

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions and Formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

EXAMPLES

Example 1: Preparation of crystalline Form M1 of Bictegravir sodium:

Bictegravir Sodium (7g) was suspended in 2-chloroethanol (56 mL) at 25±2 °C. The reaction mass was heated to 50-55 °C and the resulting suspension was stirred

at 50-55 °C for 18 hours. The reaction mass was cooled to 25-30 °C, filtered and suck-dried under vacuum for 30 minutes. The solid obtained was identified by PXRD as novel crystalline bictegravir sodium Form M1.

Yield: 8.5g

Example 2: Preparation of crystalline Form M1 of Bictegravir sodium:

Bictegravir (3g) was dissolved in 2-chloroethanol (24 mL) at 25±2 °C. The reaction mass was heated to 50-55 °C and added slowly drop-wise aqueous sodium hydroxide solution (Dissolved 534mg sodium hydroxide in 6 mL water at 25±2 °C) at 50-55 °C for 5 minutes. The resulting clear solution was further maintained under stirring at 50-55°C for 14 hours. The reaction mass was then cooled to 25-30 °C, maintained for 1 hour, filtered and suck-dried under vacuum for 30 minutes. The solid obtained was identified by PXRD as novel crystalline bictegravir sodium Form M1.

Yield: 2.0g

Example 3: Preparation of crystalline Form M2 of Bictegravir sodium:

Bictegravir Sodium (7 g) was suspended in 2-chloroethanol (56 mL) at 25±2 °C. The reaction mass was heated to 50-55 °C and the resulting suspension was stirred at 50-55 °C for 17 hours. The reaction mass was filtered at 50-55 °C and suck-dried for 30 minutes. The solid obtained was identified by PXRD as novel crystalline bictegravir sodium Form M2.

Yield: 6.5g

Example 4: Preparation of crystalline Form M2 of Bictegravir sodium:

Bictegravir (5 g) dissolved in 2-chloroethanol (50 mL) at 25±2 °C. The reaction mass was heated to 65±2 °C and added slowly drop-wise aqueous sodium hydroxide solution (Dissolved 445 mg sodium hydroxide in 11mL water at 25±2 °C) at 65±2 °C for 15 minutes. The clear solution was then cooled to 0-5 °C in 30 minutes and maintained under stirring at 0-5 °C for 3 hours. The resulting reaction mass was filtered, suck-dried for 30 minutes and dried under vacuum at 60 °C for

21 hours. The solid obtained was identified by PXRD as novel crystalline bictegravir sodium Form M2.

Yield: 3.0g

Example 5: Preparation of crystalline Form M3 of Bictegravir sodium:

The Bictegravir sodium Form M1 or Form M2 obtained as per above example 1-4 was dried under vacuum at 130 °C for 10-15 hours. The solid obtained was identified by PXRD as novel crystalline bictegravir sodium Form M3.

Example 6: Preparation of crystalline Form M3 of Bictegravir sodium:

Bictegravir (2g) was dissolved in 2-chloroethanol (12 mL) at 25-30 °C and the obtained clear solution was heated to 35-40 °C. Added aqueous sodium hydroxide solution (dissolved 267 mg NaOH in 2 mL water) at 35-40 °C for 5-10minutes. The thick reaction mass was then maintained under stirring at 35-40 °C for 6-8 hours. The thick reaction mass was then cooled to 25-30 °C, added water (6 mL) slowly for 5-10 minutes at 25-30 °C and stirred the reaction mass at 25-30 °C for 60 minutes. The resulting reaction mass was filtered, washed with mixture of 3 mL 2-chloroethanol and 1 mL water and suck dried for 1hour under vacuum. The PXRD of the wet material was identified by PXRD as crystalline form of bictegravir sodium Form M1. The wet material was further dried under vacuum at 130°C for 8-12 hours. The solid obtained was identified by PXRD as novel crystalline form of Bictegravir sodium Form M3.

Yield: 1.56g

We claim:

1. A crystalline Form M3 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 7.14, 13.95, 19.33, 20.92 and 31.70 ±0.2° degrees two-theta.

2. A crystalline Form M3 of bictegravir sodium, characterized by Powder X-ray diffraction pattern as depicted in FIG. 3.

3. A process for the preparation of crystalline Form M3 of bictegravir sodium comprising drying the crystalline Form M1 or crystalline Form M2 of bictegravir sodium at 110-140 °C.

4. A crystalline Form M1 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.94, 19.78, 20.97, 23.64, 25.20, and 26.10 ±0.2° degrees two-theta.

5. A process for the preparation of crystalline Form M1 of bictegravir sodium comprising the steps of:
    a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
    b) optionally adding sodium source and stirring the reaction mass at the same temperature;
    c) cooling the reaction mass to 20-35 °C; and
    d) isolating crystalline Form M1 of bictegravir sodium.

6. A crystalline Form-M2 of bictegravir sodium, characterized by Powder X-ray diffraction pattern having 2θ angle positions at about 5.90, 12.30, 19.78, 23.71 and 25.19 ±0.2° degrees two-theta.

7. A process for the preparation of crystalline Form M2 of bictegravir sodium comprising the steps of:

    a) providing bictegravir or its sodium salt in organic solvent at elevated temperature;
    b) optionally adding sodium source and stirring the reaction mass at the same temperature;
    c) optionally cooling the reaction mass to 0-5 °C; and
    d) isolating crystalline Form M2 of bictegravir sodium.

8. The process as claimed in claim 5 and claim 7 wherein organic solvent is selected from 2-chloroethanol.

9. The process as claimed in claim 5 and claim 7, wherein sodium source is selected from sodium hydroxide, sodium carbonate, sodium bicarbonate or sodium alkoxide.

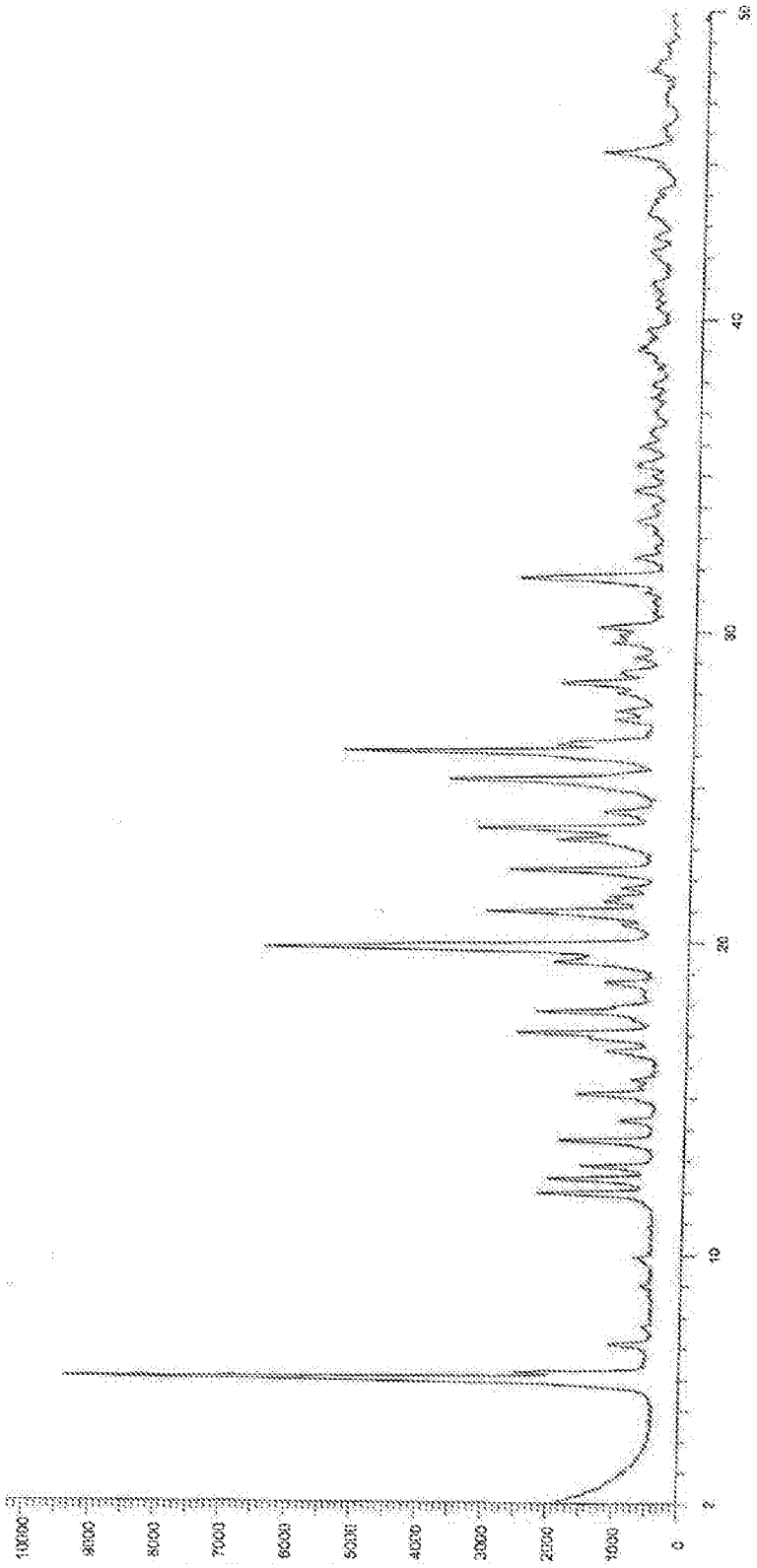


Figure 1 - X-ray powder diffractogram of crystalline Form-M1 of bictegravir sodium

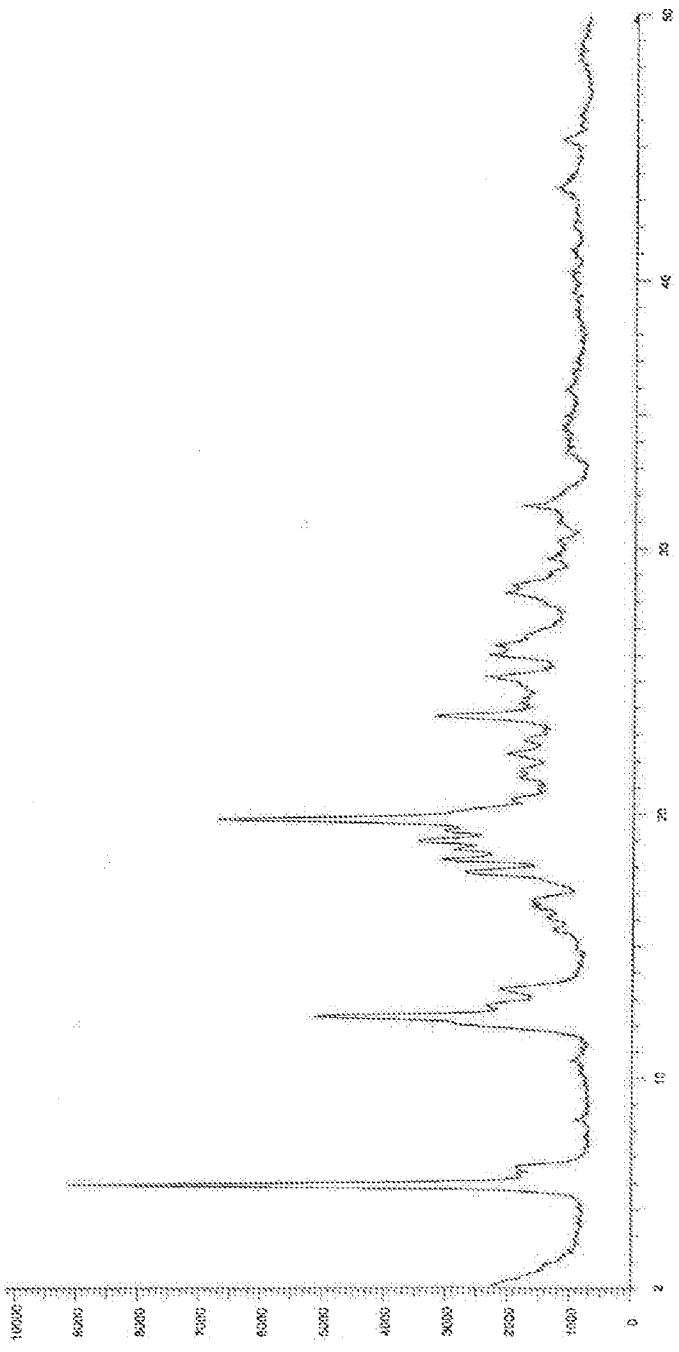


Figure 2 - X-ray powder diffractogram of crystalline Form-M2 of bictegravir sodium

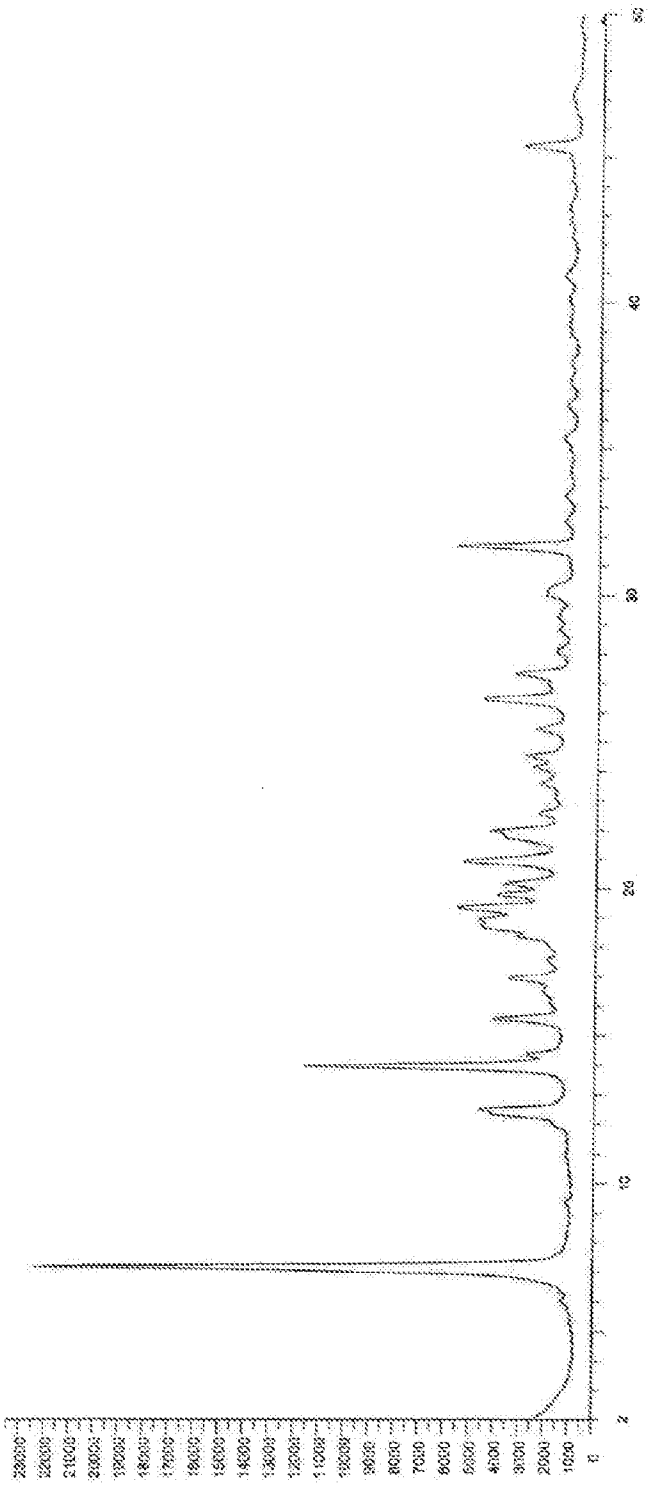


Figure 3 - X-ray powder diffractogram of crystalline Form-M3 of bictegravir sodium

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2023/050585

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/18 A61P31/18 A61K31/537
ADD.

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)
C07D A61P

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)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/196116 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) cited in the application	1,2
A	claims; table 4	3-9

X	WO 2020/255004 A1 (LAURUS LABS LTD [IN]) 24 December 2020 (2020-12-24)	1,2
A	claims 15,20,21,26,29,33,38,39,43,44; examples 1-4, 6,8,9,10,11,12,13	3-9

X	WO 2020/161744 A1 (CIPLA LTD [IN]) 13 August 2020 (2020-08-13)	1,2
A	claims; figures examples 1,5	3-9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2023	25/09/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Österle, Carmen

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2023/050585

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/196137 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23)	1,2
A	paragraph [0116] - paragraph [0117]; figures 5,16 page 66; table 1E paragraph [0249] - paragraph [0251] paragraph [0253] - paragraph [0254] paragraph [0288]	3-9

X	IN 2020 4104 6541 A (MSN LABORATORIES PRIVATE LTD) 29 April 2022 (2022-04-29)	1,2
A	claims; figures	3-9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2023/050585

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015196116 A1	23-12-2015	AR 100903 A1	09-11-2016
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