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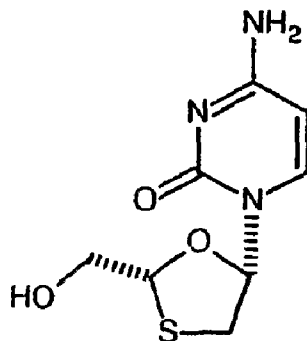
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(54) Title: NOVEL CRYSTALLINE FORM OF LAMIVUDINE



(I)

(57) Abstract: The present invention relates to a novel crystalline form of lamivudine, i.e. Formula (I). The novel crystalline form of the present invention is designated as Form IV. The present invention further relates to a process for the preparation of crystalline Form IV of lamivudine.

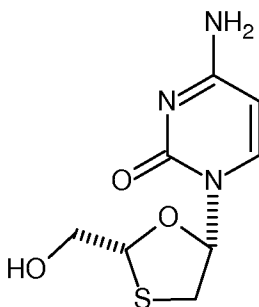
NOVEL CRYSTALLINE FORM OF LAMIVUDINE

Field of the Invention

The present invention relates to a novel crystalline form of lamivudine. The novel crystalline form of the present invention is designated as Form IV. The present invention
5 further relates to a process for the preparation of crystalline Form IV of lamivudine.

Background of the Invention

Lamivudine is a substituted 1,3-oxathiolane and it is presently available in the market as an antiretroviral agent. Lamivudine is a cis-(-)-isomer and it is chemically (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one of
10 Formula I having the structure as depicted below.



FORMULA I

U.S. Patent No. 5,905,082 provides a process for preparing lamivudine by enzymatic separation of (±)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidine-2-one. However, according to U.S. Patent No. 5,905,082, lamivudine so
15 obtained has an enantiomeric excess of only about 90% and it is referred as “Intermediate 5”. The Intermediate 5 is dissolved in water by heating to 45°C and cooled to 30°C. The solid product crystallized as unstirrable mass is broken up, stirred at 10°C, filtered and washed two times with industrial methylated spirit. The washed material is dried and the
20 product obtained is referred as Form I. The Form I so obtained is further suspended in industrial methylated spirit, stirred at 50°C for 1 hour and a small amount of sample is removed. The remaining mixture is dried under vacuum at 50°C and the product obtained is referred as 100% Form II. U.S. Patent No. 5,905,082 patent also provides a process of converting Form I to Form II in industrial methylated spirit by seeding.

J. Pharm. Sci., 85(2), 1996, 193-199 and J. Chem. Soc., Perkin Trans. 2, 1997, 2653-2659 provide characterization methods of Form I and Form II by XRPD, DSC, Scanning Electron Micrographs and single crystal analysis.

U.S. Patent No. 6,329,522 provides a process for purification of lamivudine by the
5 formation of salicylate salt and a crystallization method for lamivudine from isopropyl acetate. However, both the preparation of lamivudine salicylate and crystallization of lamivudine involve seeding, and US '522 patent does not disclose any method to obtain the seed crystals of lamivudine salicylate as well as lamivudine. PCT Publication No. WO 03/027106 provides a process for preparing Form II of lamivudine from lamivudine
10 salicylate using ethyl acetate and acetonitrile as solvents and triethylamine as a base. However, WO 03/027106 application does not disclose any specific method to obtain lamivudine salicylate.

PCT Publication No. WO 2007/119248 provides a process for the preparation of Form III of lamivudine. Form III is prepared by dissolving Form II in water by heating to
15 45°C and subsequent cooling to 30°C. However, the time involved for reducing the temperature from 45°C to 30°C varies from 15 minutes to 1 hour 40 minutes. The mixture so obtained is further stirred at 10°C for 1 hour, filtered and dried in vacuum at 45°C for 24 hours to obtain Form III. The process also involves optional washing with ethanol or industrial methylated spirit. Form III is also prepared by dissolving Form I in water by
20 heating to 45°C and subsequent cooling to 10°C. However, the time involved for reducing the temperature from 45°C to 10°C is 10 minutes. The mixture so obtained is stirred at 10°C for 1 hour, filtered and dried in vacuum at 45°C for 24 hours to obtain Form III. Form III is also prepared by stirring a suspension of Form I or Form II in water at 25°C for 24 hours or 48 hours. The mixture is further stirred at 10°C for 1 hour, filtered and dried
25 in vacuum at 45°C for 24 hours to obtain Form III.

WO 2007/119248 application also provides processes for preparing Form I and Form II of lamivudine. Form I is prepared by dissolving lamivudine in water by heating to 45°C and subsequent cooling to 30°C in 0.5 minute. The solid product crystallized as
unstirrable mass is broken up, stirred at 10°C, filtered and washed with industrial
30 methylated spirit. The washed material is dried in vacuum at 45°C for 24 hours to obtain Form I. Form I is also prepared in a similar way from a mixture of water and denaturated

spirit. However, in this process, the time involved for reducing the temperature from 45°C to 30°C is 12 minutes and it also involves seeding with Form I crystals. The washing at the final step is also carried out with a mixture of water and denaturated spirit. Form II is prepared refluxing lamivudine in ethanol and partially removing the solvent by distillation.

5 The concentrated solution is cooled to 15°C in 35 minutes, stirred at 15°C for 1 hour, filtered and washed with ethanol. The washed product is dried in vacuum at 50°C for 12 hours to obtain Form II.

Brief Description of the Figures

10 Figure 1 depicts X-Ray Powder Diffractogram (XRPD) of crystalline Form IV of lamivudine.

Figure 2 depicts Differential Scanning Calorimetry (DSC) thermogram of crystalline Form IV of lamivudine.

Figure 3 depicts Fourier-Transform Infra-red (FTIR) spectrum of crystalline Form IV of lamivudine.

15 Figure 4 depicts Thermogravimetric Analysis (TGA) of crystalline Form IV of lamivudine.

Figure 5 depicts comparative XRPD of crystalline Form IV, Form I and Form II of lamivudine.

Summary of the Invention

20 The present inventors have now prepared a novel crystalline form of lamivudine designated as Form IV. The crystalline Form IV of lamivudine has different physical characteristics as compared to the known crystalline forms of lamivudine. The crystalline form of the present invention is reproducible and stable to develop pharmaceutical dosage forms.

Detailed Description of the Invention

25 A first aspect of the present invention provides crystalline Form IV of lamivudine. The crystalline Form IV of lamivudine has an XRPD pattern substantially as depicted in Figure 1 of the accompanied drawing. The XRPD of Form IV shows characteristic d-spacing values substantially at 16.933, 13.223, 10.381, 9.174, 8.938, 8.692, 8.478, 7.852,

7.734, 7.612, 7.173, 7.024, 6.891, 6.696, 6.140, 6.069, 5.903, 5.654, 5.481, 5.350, 5.045, 4.934, 4.894, 4.738, 4.651, 4.593, 4.495, 4.432, 4.380, 4.238, 4.168, 4.078, 3.928, 3.867, 3.789, 3.655, 3.624, 3.563, 3.514, 3.463, 3.446, 3.349, 3.310, 3.262, 3.234, 3.194, 3.161, 3.128, 3.033, 2.993, 2.961, 2.908, 2.883, 2.860, 2.826, 2.773, 2.744, 2.689, 2.640, 2.577, 2.551, 2.297, 2.482, 2.448, 2.424, 2.391, 2.369 and 2.346. The crystalline Form IV of lamivudine has a DSC thermogram substantially as depicted in Figure 2 of the accompanied drawing. The DSC thermogram shows a first endotherm at about 130° to about 135°C followed by an exotherm at about 136° to about 144°C and a second endotherm at about 173° to about 183°C. The crystalline Form IV of lamivudine has an FTIR pattern substantially as depicted in Figure 3 of the accompanied drawing. The TGA of the crystalline Form IV of lamivudine shows a single step weight loss of about 1.8%.

A second aspect of the present invention provides a process for the preparation of crystalline Form IV of lamivudine, wherein the process comprises,

- a) dissolving lamivudine in methanol,
- b) cooling the solution obtained in step a) to a temperature of about 15°C or below, and
- c) isolating crystalline Form IV of lamivudine from the mixture thereof.

Lamivudine existing in any solid form known in the art may be used as a starting material. Lamivudine is dissolved in methanol. Methanol may also be used as a mixture with any other organic solvent. The dissolution process may be carried out at about 25°C or above, for example, at about 25° to about 65°C. The solution obtained is cooled in about 10 minutes to about 40 minutes to a temperature of about 15°C or below, for example, about 0° to about 15°C. The solution is further stirred at a temperature of about 0° to about 5°C for sufficient time to obtain crystalline Form IV of lamivudine. The crystalline Form IV of lamivudine is isolated from the mixture thereof by filtration, concentration, distillation, decantation, evaporation or a combination thereof.

A third aspect of the present invention provides a process for the preparation of crystalline Form IV of lamivudine,

wherein the process comprises,

- a) dissolving lamivudine in methanol,

- b) treating the solution obtained in step a) with an antisolvent, and
- c) isolating crystalline Form IV of lamivudine from the mixture thereof.

Lamivudine existing in any solid form known in the art may be used as a starting material. Lamivudine is dissolved in methanol. The dissolution process may be carried out at about 25°C or above, for example, at about 25° to about 65°C. The solution obtained is treated with an antisolvent. The antisolvent is selected from the group consisting of aliphatic or aromatic hydrocarbons, esters, ketones, nitriles, halogenated hydrocarbons and ethers, or a mixture thereof. The antisolvent may be, for example, n-hexane, cyclohexane, toluene, acetone, ethylacetate, acetonitrile, diethyl ether, methyl t-butyl ether, heptane or petroleum ether, or a mixture thereof. The treatment with antisolvent may be carried out at a temperature of about 20° to about 35°C. The mixture obtained is cooled to about 15°C or below, for example, about 0° to about 15°C and stirred for sufficient time to obtain crystalline Form IV of lamivudine. The crystalline Form IV of lamivudine is isolated from the mixture thereof by filtration, concentration, distillation, decantation, evaporation or a combination thereof.

A fourth aspect of the present invention provides a pharmaceutical composition comprising crystalline Form IV of lamivudine optionally containing an excipient/ diluent.

A fifth aspect of the present invention provides a method of treating HIV or HBV infections which comprises of administering to a human in need thereof a therapeutically effective amount of crystalline Form IV of lamivudine.

The XRPD was determined by using Panalytical X'Pert Pro X-Ray Powder Diffractometer in the range 3° to 40° 2θ and under tube voltage and current of 45 Kv and 40 mA respectively. Copper radiation of wavelength 1.54 angstrom and Xceleor detector was used.

The TGA was recorded on TA (Q500) (Rate of heating = 10°C/minute). The DSC was recorded on Mettler Toledo (DSC 821) (Rate of heating = 10°C/minute). Moisture content was determined on a Metrohm 831KF coulometer. The FTIR was recorded in KBr on Perkin Elmer FTIR (Spectrum One) instrument.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

5

EXAMPLES

Example 1: Preparation of Crystalline Form IV of Lamivudine:

Lamivudine (50 g) was dissolved in methanol (500 ml) at reflux temperature. The solution obtained was cooled to 0° to 15°C in 20 to 30 minutes and stirred at 0° to 5°C for 1 hour. The solid obtained was filtered and dried at 45° to 50°C to obtain the title

10 compound.

Yield: 40.5 g

Moisture content: 0.4%

Example 2: Preparation of Crystalline Form IV of Lamivudine:

15 Lamivudine (50 g) was dissolved in methanol (500 ml) at reflux temperature. The solution obtained was added to cyclohexane (1000 ml), kept at 20° to 25°C and stirred for 2 hours. The suspension obtained was cooled to 5° to 10°C in 15 to 20 minutes and stirred for 2 hours. The solid obtained was filtered and dried at 45° to 50°C to obtain the title compound.

20 Yield: 42 g

Moisture content: 0.5%

Example 3: Preparation of Crystalline Form IV of Lamivudine:

25 Lamivudine (50 g) was dissolved in methanol (500 ml) at reflux temperature. The solution obtained was added to diisopropyl ether (1000 ml), kept at 20° to 25°C and stirred for 2 hours. The solution obtained was cooled to 5° to 10°C in 15 to 20 minutes and stirred for 2 hours. The solid obtained was filtered and dried at 45° to 50°C to obtain the title compound.

Yield: 42 g

Moisture content: 0.5%

Example 4: Preparation of Crystalline Form IV of Lamivudine:

Lamivudine (50 g) was dissolved in methanol (500 ml) at reflux temperature. The
5 solution obtained was added to ethyl acetate (1000 ml) and kept at 20° to 25°C for 2 hours.
The solution obtained was cooled to 5° to 10°C in 15 to 20 minutes and stirred for 2 hours.
The solid obtained was filtered and dried at 45° to 50°C to obtain the title compound.

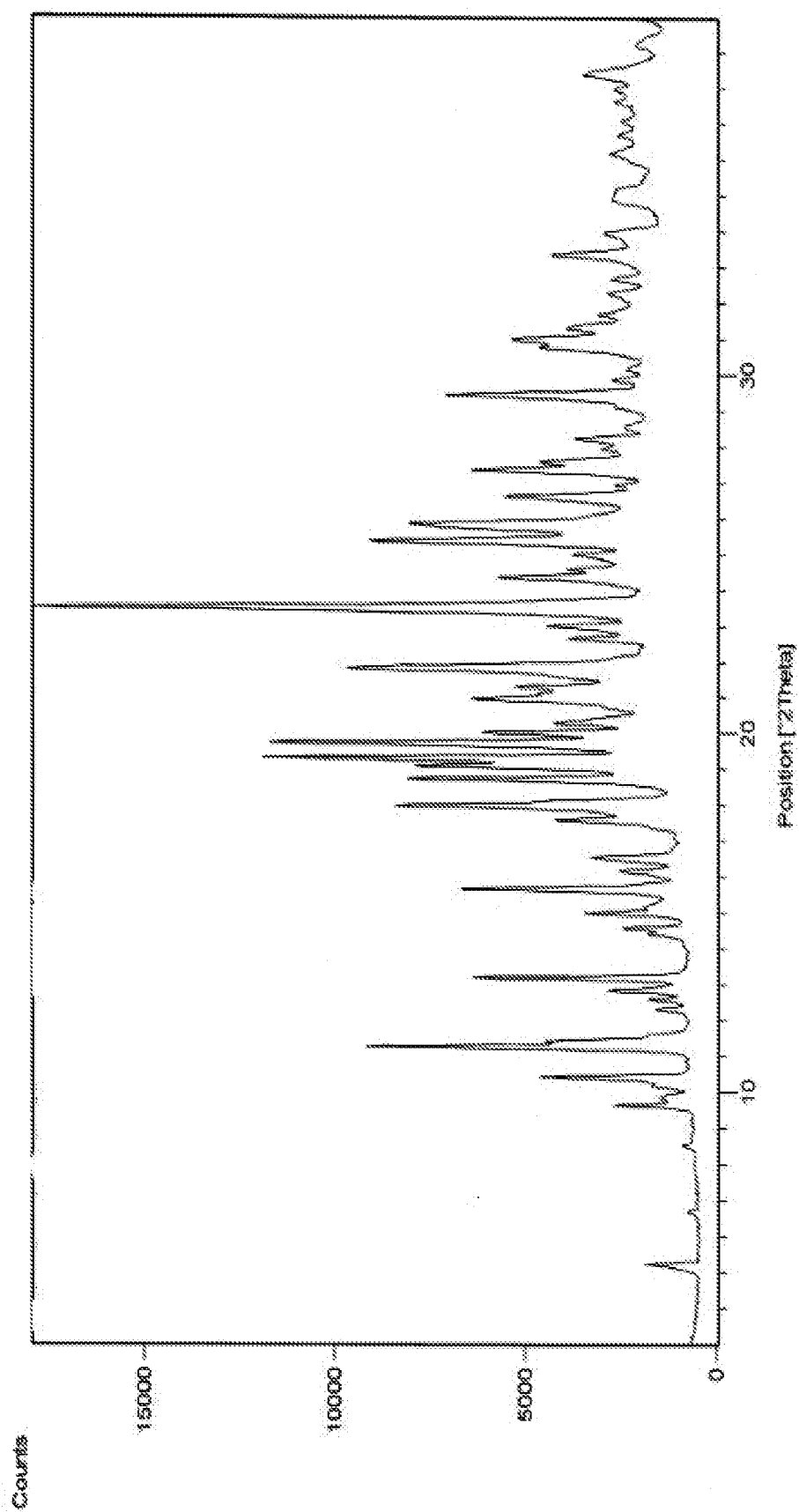
Yield: 39.5 g

Moisture content: 0.4%

We claim:

- 1 1. Crystalline Form IV of lamivudine having an XRPD pattern substantially as
2 depicted in Figure 1.
- 1 2. Crystalline Form IV of lamivudine having an XRPD pattern, wherein the
2 characteristic d-spacing values are obtained substantially at 16.933, 13.223,
3 10.381, 9.174, 8.938, 8.692, 8.478, 7.852, 7.734, 7.612, 7.173, 7.024, 6.891, 6.696,
4 6.140, 6.069, 5.903, 5.654, 5.481, 5.350, 5.045, 4.934, 4.894, 4.738, 4.651, 4.593,
5 4.495, 4.432, 4.380, 4.238, 4.168, 4.078, 3.928, 3.867, 3.789, 3.655, 3.624, 3.563,
6 3.514, 3.463, 3.446, 3.349, 3.310, 3.262, 3.234, 3.194, 3.161, 3.128, 3.033, 2.993,
7 2.961, 2.908, 2.883, 2.860, 2.826, 2.773, 2.744, 2.689, 2.640, 2.577, 2.551, 2.297,
8 2.482, 2.448, 2.424, 2.391, 2.369 and 2.346.
- 1 3. Crystalline Form IV of lamivudine having a DSC thermogram substantially as
2 depicted in Figure 2.
- 1 4. Crystalline Form IV of lamivudine having a DSC thermogram, wherein the DSC
2 thermogram exhibits a first endotherm at about 130° to about 135°C followed by an
3 exotherm at about 136° to about 144°C and a second endotherm at about 173° to
4 about 183°C
- 1 5. Crystalline Form IV of lamivudine having an FTIR pattern substantially as
2 depicted in Figure 3.
- 1 6. A process for the preparation of crystalline Form IV of lamivudine, wherein the
2 process comprises,
3 a) dissolving lamivudine in methanol,
4 b) cooling the solution obtained in step a) to a temperature of about 15°C or below,
5 and
6 c) isolating crystalline Form IV of lamivudine from the mixture thereof.
- 1 7. A process according to claim 6, wherein step b) further comprises stirring at a
2 temperature of about 0° to about 5°C.

- 1 8. A process for the preparation of crystalline Form IV of lamivudine, wherein the
2 process comprises,
 - 3 a) dissolving lamivudine in methanol,
 - 4 b) treating the solution obtained in step a) with an antisolvent, and
 - 5 c) isolating crystalline Form IV of lamivudine from the mixture thereof.
- 1 9. A process according to claim 8, wherein the antisolvent is selected from the group
2 consisting of aliphatic or aromatic hydrocarbons, esters, ketones, nitriles,
3 halogenated hydrocarbons and ethers, or a mixture thereof.
- 1 10. A process according to claim 9, wherein the antisolvent is n-hexane, cyclohexane,
2 toluene, acetone, ethylacetate, acetonitrile, diethyl ether, methyl t-butyl ether,
3 heptane or petroleum ether, or a mixture thereof.

FIGURE 1: XRPD OF CRYSTALLINE FORM IV LAMIVUDINE

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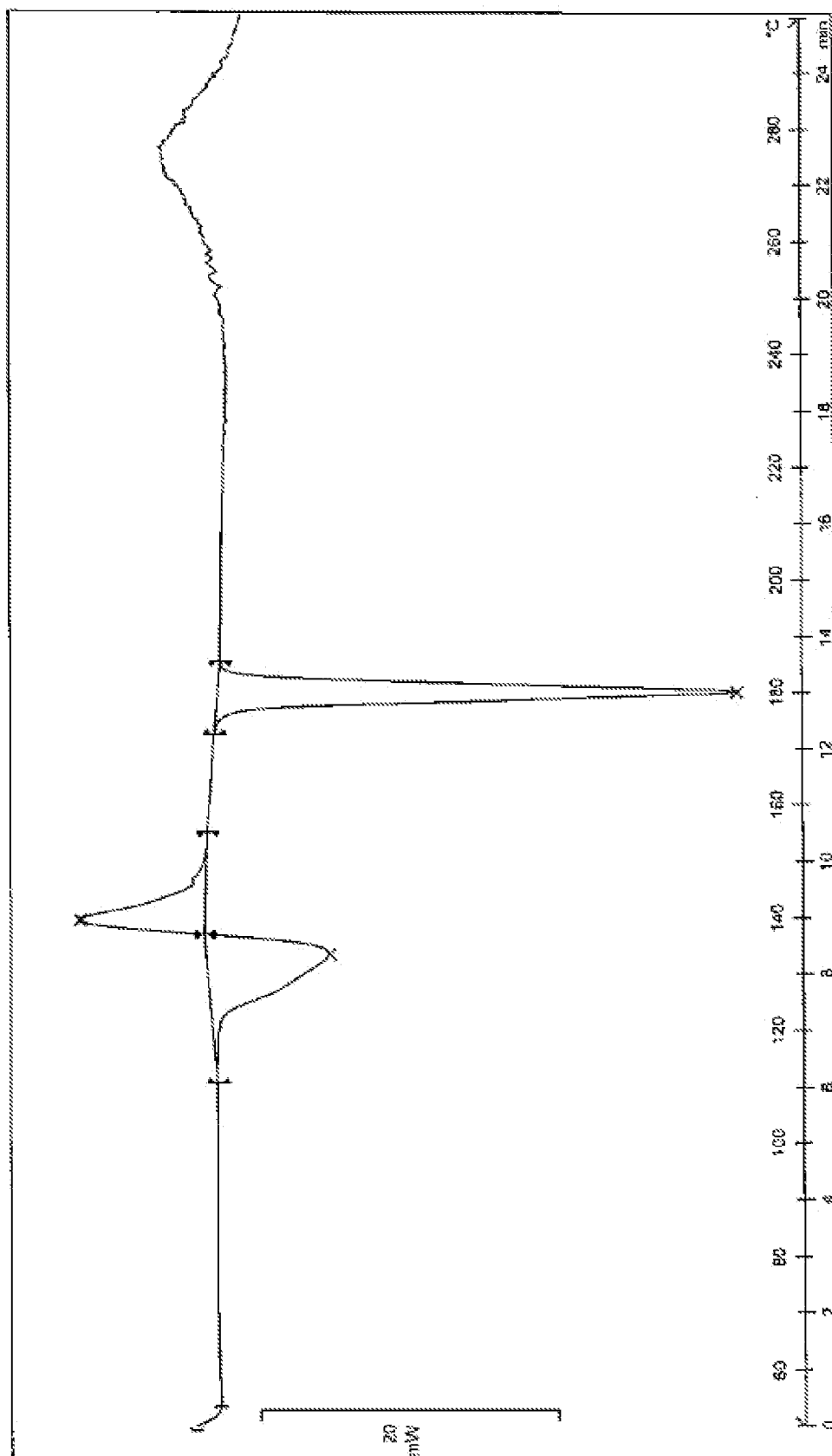
FIGURE 2: DSC OF CRYSTALLINE FORM IV LAMIVUDINE

FIGURE 3: FTIR OF CRYSTALLINE FORM IV LAMIVUDINE

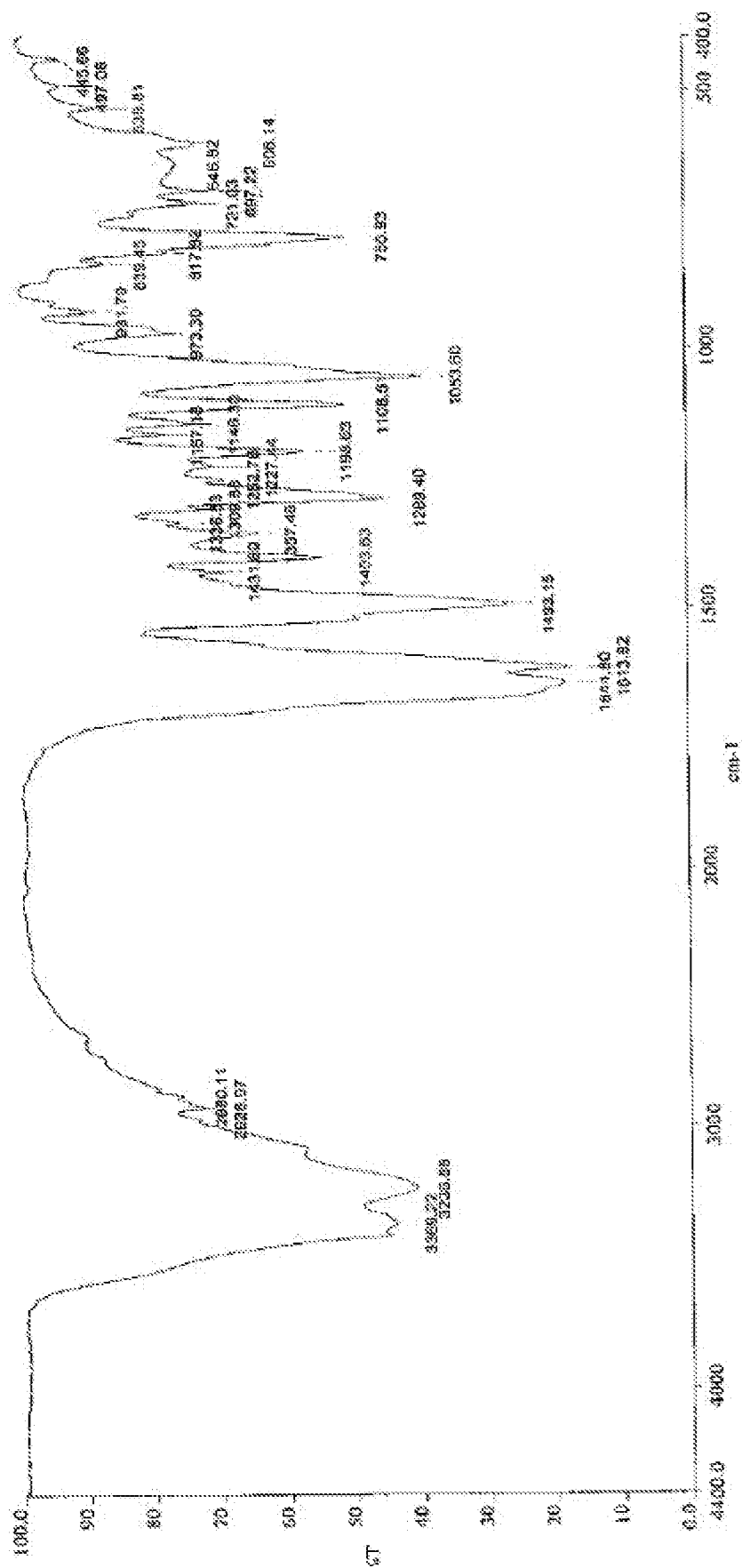


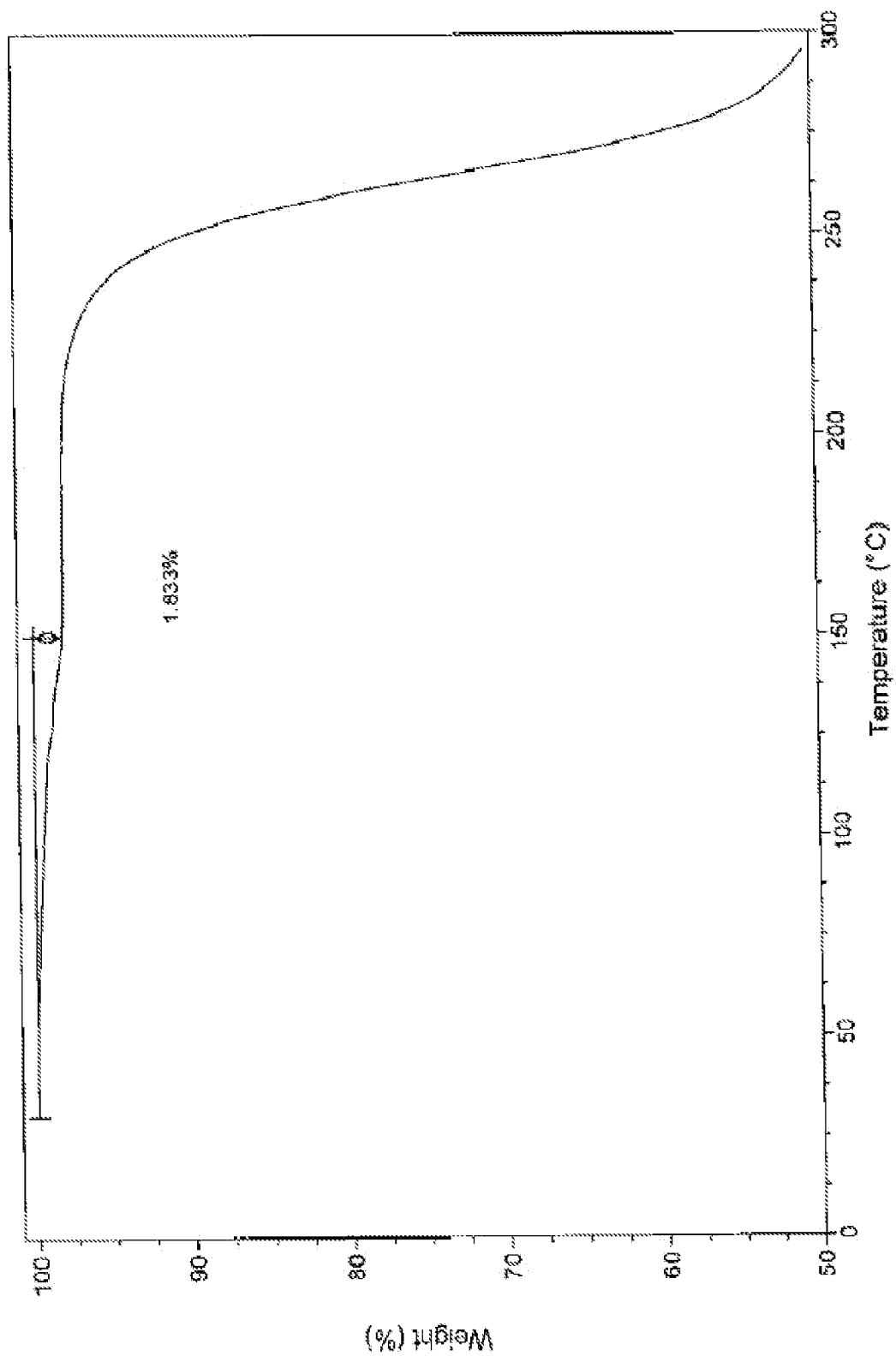
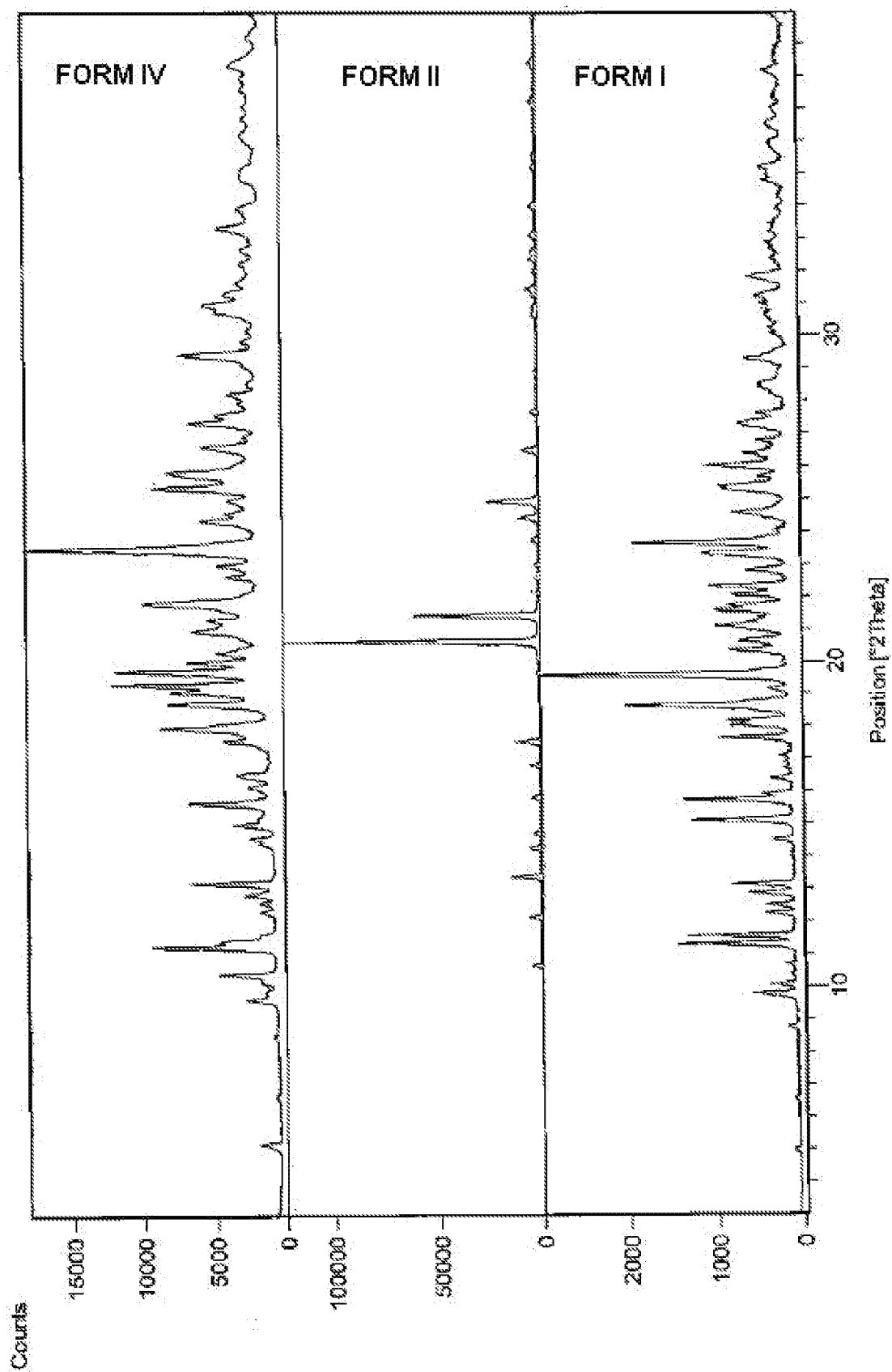
FIGURE 4: TGA OF CRYSTALLINE FORM IV LAMIVUDINE

FIGURE 5: COMPARATIVE XRPD OF CRYSTALLINE FORM IV, FORM I AND FORM II OF LAMIVUDINE



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/051493

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D411/04 A61K31/513 A61P31/12

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

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 practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 517 145 A (GLAXO GROUP LTD [GB]) 9 December 1992 (1992-12-09) cited in the application page 1 - page 2 figures 1-6 examples 1-4	1-10
X	R. K. HARRIS ET AL: "Polymorphism in a novel anti-viral agent: Lamivudine" JOURNAL OF CHEMICAL SOCIETY, PERKIN TRANS., vol. 2, 1997, pages 2653-2659, XP002432450 cited in the application tables 1,2 figures 2,3,7 ----- -/--	1-10

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

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20/08/2009

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INTERNATIONAL SEARCH REPORT

International application No

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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 2007/119248 A (LUPIN LTD [IN]; SINGH GIRIJ PAL [IN]; SRIVASTAVA DHANANJAI [IN]; SAINI) 25 October 2007 (2007-10-25) cited in the application examples 1-15 tables 1-3 figures 1-16 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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