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(71) Applicant: SANDOZ AG [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors: LENGAUER, Hannes; c/o Sandoz GmbH Biochemiestr. 10, 6250 Kundl (AT). PICHLER, Arthur; Biochemiestr. 10, 6250 Kundl (AT). SCHREINER, Erwin; c/o Sandoz GmbH Biochemiestrasse 10, 6250 Kundl (AT).

(74) Agent: KLUSCHANZOFF, Harald et al.; Industriestr. 25, 83607 Holzkirchen (DE).

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(57) Abstract: The present invention relates to crystalline solid forms of tenofovir alafenamide and methods for their preparation. Furthermore, the invention relates to the use of one or more of the crystalline solid forms of tenofovir alafenamide of the present invention for the preparation of pharmaceutical compositions as well as to pharmaceutical compositions comprising an effective amount of one or more of said forms. The pharmaceutical compositions of the present invention can be used as medicaments, in particular for the treatment and/or prophylaxis of viral infections such as HIV infections.



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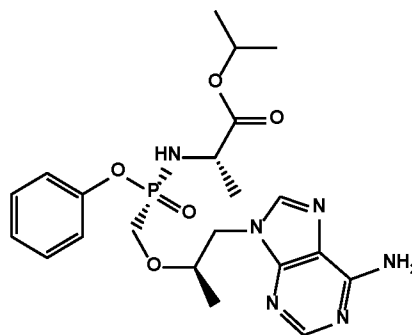
CRYSTALLINE SOLID FORMS OF TENOFOVIR ALAFENAMIDE

FIELD OF THE INVENTION

The present invention relates to crystalline solid forms of tenofovir alafenamide and methods for their preparation. Furthermore, the invention relates to the use of one or more of the crystalline solid forms of tenofovir alafenamide of the present invention for the preparation of pharmaceutical compositions as well as to pharmaceutical compositions comprising an effective amount of one or more of said forms. The pharmaceutical compositions of the present invention can be used as medicaments, in particular for the treatment and/or prophylaxis of viral infections such as HIV infections.

10 BACKGROUND OF THE INVENTION

Tenofovir alafenamide, a prodrug of tenofovir, is chemically designated as 9-[(*R*)-2-[[(*S*)-[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine and can be represented by the following chemical structure according to formula (I):



formula (I)

Tenofovir alafenamide is an antiviral compound useful for the treatment and/or prophylaxis of viral infections including infections caused by DNA viruses, RNA viruses, herpesviruses (e.g. CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g. HBV), papillomavirus, hantavirus, adenoviruses and HIV. Tenofovir alafenamide may be administered alone or in combination with other antiviral agents to patients in need.

WO 02/008241 A2 discloses tenofovir alafenamide and a tenofovir alafenamide monofumarate form as well as processes for their preparations. WO 2013/025788 A1 describes a crystalline hemifumarate form of tenofovir alafenamide. WO 2015/040640 discloses acid addition salts of

tenofovir alafenamide (from ferulic acid, phosphoric acid, succinic acid, citric acid, tartaric acid, lactic acid or methane sulfonic acid). WO 2015/176602 discloses a synthesis for preparing tenofovir alafenamide forms of phosphoric acid, succinic acid, citric acid, L-tartaric acid, D-tartaric acid, D,L-tartaric acid, L-malic acid, oxalic acid and sulfuric acid. WO 2016/192692 discloses solid forms of tenofovir alafenamide with hydrochloric, hydrobromic, sulfuric, phosphoric, maleic, citric, succinic, tartaric, gallic, benzenesulfonic, salicylic, 4-aminobenzoic acids.

Different solid state forms of an active pharmaceutical ingredient often possess different properties. Different properties of solid state forms can allow for improved formulations, for example, formulations with improved dissolution profile, or with improved stability and shelf-life. Also processing or handling of the active pharmaceutical ingredient during the formulation process may be improved. Thus, new solid state forms of an active pharmaceutical ingredient can have desirable processing properties. They can be easier to handle, better suited for storage, and/or allow for better purification, compared to previously known solid state forms.

Different properties of different salts and solid state forms and solvates in turn can allow improved formulations, for example, formulations with improved dissolution profile, or with improved stability and shelf-life. Also processing or handling of the active pharmaceutical ingredient during the formulation process may also be improved. Even bioavailability of the drug in the pharmaceutical dosage form may be improved.

Thus, there is still a strong need for the provision of further solid forms of tenofovir alafenamide. In particular, there is the need for the provision of new salts of tenofovir alafenamide. There is also the need for the provision of new cocrystals of tenofovir alafenamide.

SUMMARY OF THE INVENTION

It was an objective of the current invention to provide new means of improving the properties of tenofovir alafenamide, especially in regard to the treatment and/or prophylaxis of viral infections such as HIV infections, by providing new drugable forms of tenofovir alafenamide.

Especially desirable improvements/advantages of the new drugable form include:

- improvement of physicochemical properties in order to facilitate the formulation, the manufacture, or to enhance the absorption and/or the bioavailability:

- thus being more active when compared to the hemifumarate or monofumarate forms of tenofovir alafenamide; or
 - being easily obtainable, easy to manufacture or
 - allowing more flexibility in formulating, or facilitating its formulation,
 - 5 • being highly soluble, thus allowing better dissolution rates, especially if dissolving in an aqueous physiological surrounding, or
 - reducing hygroscopicity;
 - improving stability;
 - allowing new routes of administration;
 - 10 • allowing to combine tenofovir alafenamide with a chemically usually non-compatible active agent in the same formulation or even in immediate contact, without having to isolate tenofovir alafenamide;
 - or minimizing/reducing the side effects, especially the severe side effects, assigned to tenofovir alafenamide.
- 15 Most desirably the new drugable forms should combine more than one, or even most of these advantages.

The present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with maleic acid, herein also designated “tenofovir alafenamide maleate”.

20 In addition, the present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with malonic acid, herein also designated “tenofovir alafenamide malonate”.

Furthermore, the present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with 3,4-dihydroxybenzoic acid, herein also designated “tenofovir alafenamide protocatechuate”.

25 The invention further relates to a composition comprising one or more of the aforementioned crystalline form(s) of tenofovir alafenamide and processes for the preparation of the crystalline form(s) and the composition. In addition, the invention relates to the use of the crystalline form(s) of tenofovir alafenamide of the present invention for the preparation of a pharmaceutical composition and to a pharmaceutical composition comprising an effective amount of the crystalline form(s) of tenofovir alafenamide of the present invention.

Abbreviations

	PXRD	powder X-ray diffractogram
	XRPD	X-ray powder diffraction
	DSC	differential scanning calorimetry
5	TGA	thermogravimetric analysis
	GMS	gravimetric moisture sorption
	THF	tetrahydrofuran
	MTBE	methyl <i>tert</i> -butyl ether
	RH	relative humidity
10	MF	monofumarate
	HF	hemifumarate
	Mp	melting point

Definitions

The term “tenofovir alafenamide” as used herein refers to 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine according to formula (I) disclosed herein above. A process for the preparation is disclosed in WO 02/008241 A2. Tenofovir alafenamide (INN/USAN, formerly GS-7340) is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir. Developed by Gilead Sciences for use in the treatment of HIV infection and chronic hepatitis B, it is applied in the form of tenofovir alafenamide fumarate (TAF).

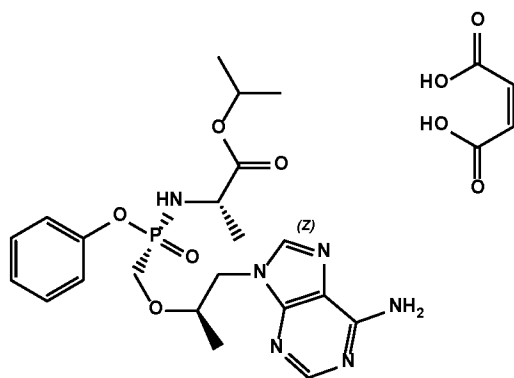
The term “tenofovir alafenamide hemifumarate” as used herein refers to the hemifumarate form of tenofovir alafenamide, having a chemical structure, wherein about two molecules of tenofovir alafenamide are associated with one molecule of fumaric acid. In one embodiment, the tenofovir alafenamide hemifumarate can be a crystalline salt, wherein protons have been transferred from at least some of the fumaric acid molecules to tenofovir alafenamide molecules. Since fumaric acid is a dicarboxylic acid, either one proton (i.e. hydrogen fumarate) or two protons (i.e. fumarate) can be transferred, dependent on the environment. In another embodiment, the tenofovir alafenamide hemifumarate can be a cocrystal, wherein substantially no protons have been transferred from fumaric acid molecules to tenofovir alafenamide molecules. Preferably, the term “tenofovir alafenamide hemifumarate” as used herein refers to a cocrystal.

The transfer of protons from one molecule to another in a crystal is dependent on the environment. Crystalline salts and cocrystals may be thought of as two ends of a proton transfer spectrum, where the salt has completed the proton transfer at one end and an absence of proton transfer exists for cocrystals at the other end.

- 5 The term “crystalline tenofovir alafenamide hemifumarate” as used herein refers to the crystalline form of tenofovir alafenamide hemifumarate disclosed in WO 2013/025788 A1. This form can be characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(6.9 \pm 0.2)^\circ$, $(8.6 \pm 0.2)^\circ$, $(10.0 \pm 0.2)^\circ$, $(11.0 \pm 0.2)^\circ$, $(12.2 \pm 0.2)^\circ$, $(15.9 \pm 0.2)^\circ$, $(16.3 \pm 0.2)^\circ$, $(20.2 \pm 0.2)^\circ$ and $(20.8 \pm 0.2)^\circ$, when measured at a temperature in the
10 range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

The term “tenofovir alafenamide monofumarate” as used herein refers to the monofumarate form of 9-[(R)-2-[[*(S)*-[[*(S)*-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine having a chemical structure comprising about one molecule of tenofovir alafenamide per molecule fumaric acid. Tenofovir alafenamide monofumarate has a
15 molar ratio of tenofovir alafenamide and fumaric acid typically and preferably in a range of from about 1.0: 0.7 to 1.3, more preferably in a range of from about 1.0: 0.8 to 1.2, most preferably in a range of from about 1.0: 0.9 to 1.1 and in particular the molar ratio is about 1.0: 1.0.

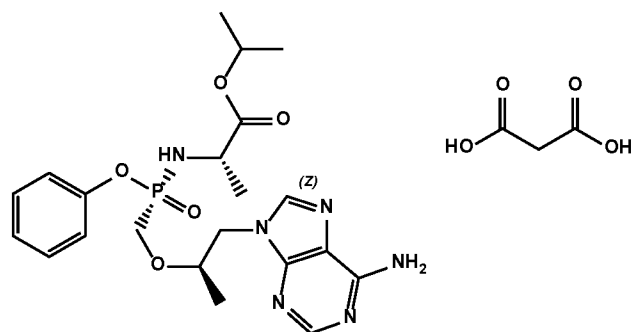
The term “crystalline form (salt/cocrystal) of tenofovir alafenamide with maleic acid” as used
20 herein refers to the maleate form of 9-[(R)-2-[[*(S)*-[[*(S)*-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine according to formula (II) disclosed herein having a chemical structure comprising about one molecule of tenofovir alafenamide per molecule maleic acid:



Formula (II)

In one embodiment, the tenofovir alafenamide maleate can be a crystalline salt, wherein protons have been transferred from at least some of the maleic acid molecules to tenofovir alafenamide molecules. Since maleic acid is a dicarboxylic acid, either one proton (i.e. hydrogen maleate) or two protons (i.e. maleate) can be transferred, dependent on the environment. In another embodiment, the tenofovir alafenamide maleate can be a cocrystal, wherein substantially no protons have been transferred from maleic acid molecules to tenofovir alafenamide molecules. Preferably, the term “tenofovir alafenamide maleate” as used herein refers to a cocrystal.

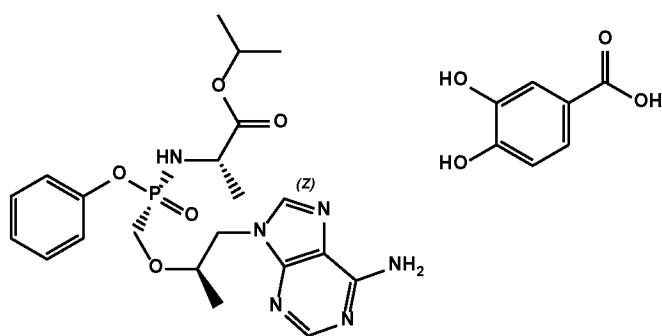
The term “crystalline form (salt/cocrystal) of tenofovir alafenamide with malonic acid” as used herein refers to the malonate form of 9-[(*R*)-2-[[(*S*)-[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine according to formula (III) disclosed herein having a chemical structure comprising about one molecule of tenofovir alafenamide per molecule malonic acid:



Formula (III)

In one embodiment, the tenofovir alafenamide malonate can be a crystalline salt, wherein protons have been transferred from at least some of the malonic acid molecules to tenofovir alafenamide molecules. Since malonic acid is a dicarboxylic acid, either one proton (i.e. hydrogen malonate) or two protons (i.e. malonate) can be transferred, dependent on the environment. In another embodiment, the tenofovir alafenamide malonate can be a cocrystal, wherein substantially no protons have been transferred from malonic acid molecules to tenofovir alafenamide molecules. Preferably, the term “tenofovir alafenamide malonate” as used herein refers to a cocrystal.

The term “crystalline form (salt/cocrystal) of tenofovir alafenamide with 3,4-dihydroxybenzoic acid” as used herein refers to the protocatechuate form of 9-[(*R*)-2-[[(*S*)-[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl] methoxy]propyl]adenine according to formula (IV) disclosed herein having a chemical structure comprising about one molecule of tenofovir alafenamide per molecule 3,4-dihydroxybenzoic acid:



Formula (IV)

In one embodiment, the tenofovir alafenamide protocatechuate can be a crystalline salt, wherein protons have been transferred from at least some of the 3,4-dihydroxybenzoic acid molecules to tenofovir alafenamide molecules. In another embodiment, the tenofovir alafenamide protocatechuate can be a cocrystal, wherein substantially no protons have been transferred from 3,4-dihydroxybenzoic acid molecules to tenofovir alafenamide molecules. Preferably, the term “tenofovir alafenamide protocatechuate” as used herein refers to a cocrystal.

The term “drugable form (of tenofovir alafenamide)” as used herein is defined as any form (salt, amorphous, crystal, solution, dispersion, mixture etc.) that tenofovir alafenamide might take which still can be formulated into a pharmaceutical formulation usable as a medicament to treat a disease or a symptom.

As used herein, the term “measured at a temperature in the range of from 20 to 30 °C” refers to a measurement under standard conditions. Typically, standard conditions mean a temperature in the range of from 20 to 30 °C, i.e. at room temperature. Standard conditions can mean a temperature of about 22 °C. Standard conditions can also mean a temperature of about 25 °C. Typically, standard conditions can additionally mean a measurement under 20-80% relative humidity, preferably 30-70% relative humidity, more preferably 40-60% relative humidity and most preferably 50% relative humidity.

As used herein the term “room temperature” refers to a temperature in the range of from 20 to 30 °C.

The term “reflection” with regards to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as

solid material, which lacks long-range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately 100 to 1000 atoms, whereas short-range order is over a few atoms only (see “*Fundamentals of Powder Diffraction and Structural Characterization of Materials*” by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003, page 3).

The term “essentially the same” with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably in the range of $\pm 0.1^\circ$ 2-theta. Thus, a reflection that usually appears at 7.3° 2-Theta for example can appear between 7.1° and 7.5° 2-theta, preferably between 7.2° and 7.4° 2-Theta on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

As used herein, the term “substantially pure” with reference to a particular physical form means that the physical form includes at most 20%, preferably at most 10%, more preferably at most 5%, even more preferably at most 3% and most preferably at most 1% by weight of any other physical form of the compound.

The terms “physical form” and “solid form” are used interchangeably herein and refer to any crystalline and/or amorphous phase of a compound.

A crystalline solid form of tenofovir alafenamide may be referred to herein as being characterized by graphical data “as shown in” a figure. Such data include, for example, PXRDs, DSCs, TGAs and GMS isotherms. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample concentration, sample purity, sample history and sample preparation may lead to variations for such data when presented in graphical form, for example variations relating to the exact peak positions and intensities. However, a comparison of the graphical data in the figures herein with the graphical data generated for an unknown physical form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

The presence of more than one polymorph in a sample may be determined by techniques such as x-ray powder diffraction (PXRD) or solid state nuclear magnetic resonance spectroscopy. For example, the presence of extra peaks in the comparison of an experimentally measured PXRD pattern with a simulated PXRD pattern may indicate more than one polymorph in the sample. The simulated PXRD may be calculated from single crystal x-ray data. see Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns*," Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963) or TOPAS program (Total Pattern Analysis Solution, available through Bruker AXS Inc.).

As used herein, the term "mother liquor" refers to the solution remaining after crystallization of a solid.

The term "non-hygroscopic" as used herein refers to a compound which shows a water uptake of at most 0.5 weight%, based on the weight of the compound, when measured with gravimetric moisture sorption at a relative humidity in the range of from 0 to 95% and a temperature of 25.0 ± 0.1 °C.

The term "anhydrous" as used herein, refers to a solid, where no water is coordinated in or accommodated by the crystal structure. However, an anhydrate may still comprise residual water due to surface adsorption, solvent inclusions and/or absorption in disordered regions.

The term "solvate" as used herein, refers to a solid, where one or more organic solvent(s) is/are coordinated in or accommodated by the crystal structure.

The term "isostructural solvate" as used herein, refers to solvates having the same space group with only small distortions of the unit cell dimensions and the same type of molecular network of the host molecule. Isostructural solvates as defined herein, only differ in the type of organic solvent present as guest molecule.

The term "desolvating" as used herein, means the at least partial removal of organic solvent from the crystal structure of the host molecule.

"Reduced pressure" as used herein means a pressure in the range of from 10 mbar to 900 mbar.

As used herein, the term "about" means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range.

Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

BRIEF DESCRIPTION OF THE FIGURES

5 **Figure 1:** illustrates a representative PXRD of the crystalline form of tenofovir alafenamide maleate of the present invention. The x-axis shows the scattering angle in $^{\circ}2\text{-theta}$, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 2: illustrates a representative DSC curve of the crystalline form of tenofovir alafenamide maleate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the
10 y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 3: illustrates a representative TGA curve of the crystalline form of tenofovir alafenamide maleate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the mass (loss) of the sample in percent (%).

Figure 4: illustrates a representative FTIR spectrum of the crystalline form of tenofovir
15 alafenamide maleate.

Figure 5: illustrates a representative gravimetric moisture sorption of the crystalline form of tenofovir alafenamide maleate of the present invention.

Figure 6: illustrates a representative PXRD of the crystalline form of tenofovir alafenamide malonate of the present invention. The x-axis shows the scattering angle in $^{\circ}2\text{-theta}$, the y-axis
20 shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 7: illustrates a representative DSC curve of the crystalline form of tenofovir alafenamide malonate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 8: illustrates a representative TGA curve of the crystalline form of tenofovir alafenamide malonate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the mass (loss) of the sample in percent (%).
25

Figure 9: illustrates a representative FTIR spectrum of the crystalline form of tenofovir alafenamide malonate.

Figure 10: illustrates a representative gravimetric moisture sorption of the crystalline form of
30 tenofovir alafenamide malonate of the present invention.

Figure 11: illustrates a representative PXRD of the crystalline form of tenofovir alafenamide protocatchuate of the present invention. The x-axis shows the scattering angle in $^{\circ}2\text{-theta}$, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 12: illustrates a representative DSC curve of the crystalline form of tenofovir alafenamide protocatchuate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 13: illustrates a representative TGA curve of the crystalline form of tenofovir alafenamide protocatchuate of the present invention. The x-axis shows the temperature in degree Celsius ($^{\circ}\text{C}$), the y-axis shows the mass (loss) of the sample in percent (%).

Figure 14: illustrates a representative FTIR spectrum of the crystalline form of tenofovir alafenamide protocatchuate.

Figure 15: illustrates a representative gravimetric moisture sorption of the crystalline form of tenofovir alafenamide protocatchuate of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with maleic acid, herein also designated “tenofovir alafenamide maleate”.

In addition, the present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with malonic acid, herein also designated “tenofovir alafenamide malonate”.

Furthermore, the present invention provides a crystalline form (salt/cocrystal) of tenofovir alafenamide with 3,4-dihydroxybenzoic acid, herein also designated “tenofovir alafenamide protocatchuate”.

A process for the preparation of tenofovir alafenamide is described WO 02/08241 A2.

The crystalline forms of tenofovir alafenamide of the present invention may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise but are not limited to PXRD, Raman, DSC, TGA and GMS. The crystalline forms of the present invention may be characterized by one of the aforementioned analytical methods or by combining two or more of them. In particular, they may be characterized by any one of the following embodiments or by combining two or more of the following embodiments.

Tenofovir alafenamide maleate

In a first aspect the present invention relates to a crystalline form of tenofovir alafenamide maleate. Surprisingly it has been found that tenofovir alafenamide can form a crystalline salt or
5 cocrystal with maleic acid, which salt/cocrystal has properties that makes it useful for use in pharmaceutical formulations.

In an embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(4.6 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$ and $(12.6 \pm 0.2)^\circ$; or

10 $(4.6 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(6.7 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(16.9 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(18.0 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(6.7 \pm 0.2)^\circ$; $(7.8 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$ and $(18.0 \pm 0.2)^\circ$; or

$(4.6 \pm 0.2)^\circ$, $(6.7 \pm 0.2)^\circ$; $(7.8 \pm 0.2)^\circ$, $(12.6 \pm 0.2)^\circ$, $(16.9 \pm 0.2)^\circ$ and $(18.0 \pm 0.2)^\circ$;

15 when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm.

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by having a PXRD comprising at least 4, more preferably at least 5, even more preferably at least 6 or most preferably at least 7 reflections at 2-Theta angles
20 selected from Table 1 ($\pm 0.2^\circ$ 2-Theta), when measured at a temperature in the range of from 20 to 30 °C with Cu-K α _{1,2} radiation having a wavelength of 0.15419 nm:

Table 1 Tenofovir alafenamide maleate	
Pos. [2θ]	Rel. Int. [%]
4,6	28
6,7	16
7,8	65
11,1	9
12,6	63
13,4	8
15,2	3
15,6	9
16,7	11

16,9	21
17,3	12
18,0	100
18,5	52
19,2	8
19,5	18
20,2	4
20,5	4
21,1	44
21,5	6
22,1	7
22,9	4
24,0	13
25,4	9
25,7	23
26,3	4
27,0	3
27,4	8
27,9	4

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by having a PXRD essentially the same as shown in figure 1 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In a further preferred embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by showing an endotherm with an onset temperature in the range of from 121.0 to 121.5 °C, preferably of about 121 °C, more preferably of 121.1°, when measured with DSC at a heating rate of 10 K/min.

More preferably, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by having a heat of fusion of at least 102.0 J/g, preferably of at least 103.0 J/g, even more preferably of at least 104.0 J/g, such as of at least 104.4 J/g, when measured with DSC at a heating rate of 10 K/min. Most preferably, a crystalline form of tenofovir alafenamide maleate is characterized by a heat of fusion of 104.5 J/g, when measured with DSC at a heating rate of 10 K/min.

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by showing a mass loss of not more than 2.0 weight%, preferably not more than 1.5 weight%, more preferably not more than 1.0 weight% and most preferably not more than 0.5 weight%, such as not more than 0.3 weight%, based on the weight

of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130 °C and a heating rate of 10 K/min.

Preferably, the crystalline form of tenofovir alafenamide maleate of the present invention is anhydrous, more preferably it is non-hygroscopic.

- 5 In a further embodiment, the present invention relates to a crystalline form of tenofovir alafenamide maleate characterized by having a FTIR essentially the same as shown in figure 4 of the present invention, when measured at a temperature in the range of from 20 to 30 °C.

Also preferably, the crystalline form of tenofovir alafenamide maleate of the present invention is a cocrystal.

- 10 In one embodiment of the disclosure, the crystalline form of tenofovir alafenamide maleate is provided in substantially pure form. The crystalline form of tenofovir alafenamide maleate in substantially pure form may be employed in pharmaceutical compositions which may optionally include one or more other components selected, for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients active
15 chemical entities of different molecular structure.

- Preferably, the crystalline form of tenofovir alafenamide maleate has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5 %, and more preferably less than 2 % of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern. Most preferred is a crystalline
20 form having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern.

- In one embodiment, a composition is provided consisting essentially of the crystalline form of tenofovir alafenamide maleate of the present invention. The composition of this embodiment
25 may comprise at least 90 weight % of the crystalline form of tenofovir alafenamide maleate of the present invention, based on the weight of tenofovir alafenamide maleate in the composition.

Embodiments:

Some aspects, advantageous features and preferred embodiments of the present invention are summarized in the following items:

1. Crystalline tenofovir alafenamide maleate.
2. The crystalline tenofovir alafenamide maleate according to item 1, which is a cocrystal.
3. The crystalline tenofovir alafenamide maleate according to any one of items 1 or 2 in substantially pure form.
- 5 4. The crystalline tenofovir alafenamide maleate according to any one of aspects 1 to 3 having a molar ratio of tenofovir alafenamide : maleic acid in a range of from 1.0 : 0.7 to 1.0 : 1.3.
5. The crystalline tenofovir alafenamide maleate according to item 4, having a molar ratio of tenofovir alafenamide : maleic acid in a range of from 1.0 : 0.8 to 1.0 : 1.2.
6. The crystalline tenofovir alafenamide maleate according to item 5 having a molar ratio of
10 tenofovir alafenamide : maleic acid of about 1.0 : 1.0.
7. The crystalline tenofovir alafenamide maleate according to any one of items 1 to 6, characterized by a x-ray powder diffraction pattern comprising **four** or more 2 θ values selected from the group consisting of the values listed in Table 1 ($\pm 0.2^\circ$ 2-Theta) when measured at a temperature of about 22°C using Cu K α radiation.
- 15 8. The crystalline tenofovir alafenamide maleate according to item 7, characterized by a XRPD comprising characteristic peaks at 2-Theta angles of $(4.6 \pm 0.2)^\circ$, $(6.7 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$ and $(12.6 \pm 0.2)^\circ$.
9. The crystalline tenofovir alafenamide maleate according to any one of items 7 or 8, wherein the XRPD further comprises at least one additional peak at 2-Theta angles of $(16.9 \pm 0.2)^\circ$ or
20 $(18.0 \pm 0.2)^\circ$.
10. The crystalline tenofovir alafenamide maleate according to any one of items 7 or 8, wherein the XRPD comprises peaks at all positions identified in Table 1 ($\pm 0.2^\circ$ 2-Theta).
11. The crystalline tenofovir alafenamide maleate according to item 10, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in
25 FIG. 1.
12. The crystalline tenofovir alafenamide maleate according to any one of items 1 to 11 further characterized by showing an endotherm with an onset temperature in the range of from 121.0

to 121.5 °C, preferably of about 121 °C, more preferably of 121.1°, when measured with DSC at a heating rate of 10 K/min.

13. The crystalline tenofovir alafenamide maleate according to any one of items 1 to 11 further characterized by having a heat of fusion of at least 102.0 J/g, preferably of at least 103.0 J/g, even more preferably of at least 104.0 J/g, such as of at least 104.4 J/g, when measured with DSC at a heating rate of 10 K/min.

14. The crystalline tenofovir alafenamide maleate according to any one of items 1 to 13 further characterized by showing a mass loss of not more than 2.0 weight%, preferably not more than 1.5 weight%, more preferably not more than 1.0 weight% and most preferably not more than 0.5 weight%, such as not more than 0.3 weight%, based on the weight of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130 °C and a heating rate of 10 K/min.

15. The crystalline tenofovir alafenamide maleate according to any one of items 1 to 14 further characterized by having a FTIR essentially the same as shown in figure 4 of the present invention, when measured at a temperature in the range of from 20 to 30 °C.

16. A composition comprising at least 90 weight % of crystalline tenofovir alafenamide maleate according to any one of items 1 to 15, based the weight of the composition.

17. The composition of item 16 consisting essentially of the crystalline form of any one of items 4 to 15.

18. Use of the crystalline tenofovir alafenamide maleate according to any one of items 1 to 5 or of the composition according to any one of items 16 to 17 for the preparation of a pharmaceutical composition.

19. Use of the crystalline tenofovir alafenamide maleate according to any one of items 1 to 15 or of the composition according to any one of items 16 to 17 for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of viral infections such as HIV or HBV infections.

20. A pharmaceutical composition comprising crystalline tenofovir alafenamide maleate according to any one of claims 1 to 15 or a composition according to any one of claims 16 or 17, and a pharmaceutically acceptable carrier or diluent.

21. The pharmaceutical composition of item 20 which is an oral solid dosage form.
22. The pharmaceutical composition of item 21 which is a tablet.
23. The pharmaceutical composition according to any one of items 21 or 22, further comprising at least one water-soluble filler; at least one water-insoluble filler; at least one binder; and at least one lubricant.
24. A method of treating and/or preventing viral infections in a human comprising administering to the human a therapeutically-effective amount of crystalline tenofovir alafenamide maleate according to any one of items 1 to 15.
25. A process of making crystalline tenofovir alafenamide maleate according to any one of items 1 to 15 comprising the step of
- allowing tenofovir alafenamide maleate to crystallize from a solvent comprising a nitrile.
26. The process of claim 25, wherein the nitrile has a solubility in water at 20°C of at least 100g/l.
27. The process of any one of items 25 or 26, wherein the nitrile is acetonitrile.
28. The process of any one of items 25 to 27, wherein tenofovir alafenamide maleate is allowed to crystallize at a temperature of from 0°C to 40°C.

Tenofovir alafenamide malonate

In a second aspect the present invention relates to a crystalline form of tenofovir alafenamide malonate. Surprisingly it has been found that tenofovir alafenamide can form a crystalline salt or cocrystal with malonic acid, which salt/cocrystal has properties that makes it useful for use in pharmaceutical formulations.

In an embodiment, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by having a PXRD comprising reflections at 2-Theta angles of:

- (4.0 ± 0.2)°, (6.8 ± 0.2)° and (8.7 ± 0.2)°; or
(4.0 ± 0.2)°, (6.8 ± 0.2)°, (8.7 ± 0.2)° and (9.0 ± 0.2)°; or
(4.0 ± 0.2)°, (6.8 ± 0.2)°, (8.7 ± 0.2)°, (9.0 ± 0.2)° and (18.4 ± 0.2)°;

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by having a PXRD comprising at least 4, more preferably at least 5, even more preferably at least 6 or most preferably at least 7 reflections at 2-Theta angles selected from Table 2 ($\pm 0.2^\circ$ 2-Theta), when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm:

Table 2 : Tenofovir alafenamide malonate	
Pos. [°2 θ]	Rel. Int. [%]
4,0	100
6,8	25
8,7	28
9,0	15
11,8	5
13,0	4
15,1	6
15,4	9
17,5	7
18,1	4
18,4	17
18,6	10
19,0	5
19,6	18
20,3	17
20,5	4
20,7	5
21,4	16
21,7	4
22,1	15
23,2	6
23,9	2
24,4	9
25,8	9
26,8	7
27,2	3
30,0	4

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by having a PXRD essentially the same as shown in figure 6 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In a further preferred embodiment, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by showing an endotherm with an onset temperature in the range of from 132.0 to 132.5 °C, preferably of about 132 °C, more preferably of 132.2°, when measured with DSC at a heating rate of 10 K/min.

- 5 More preferably, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by having a heat of fusion of at least 83.0 J/g, preferably of at least 84.0 J/g, even more preferably of at least 85.0 J/g, such as of at least 85.6 J/g, when measured with DSC at a heating rate of 10 K/min. Most preferably, a crystalline form of tenofovir alafenamide maleate is characterized by a heat of fusion of 85.7 J/g, when measured with DSC at a heating
10 rate of 10 K/min.

- In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide malonate characterized by showing a mass loss of not more than 2.0 weight%, preferably not more than 1.5 weight%, more preferably not more than 1.0 weight% and most preferably not more than 0.5 weight%, such as not more than 0.3 weight%, based on the weight
15 of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130 °C and a heating rate of 10 K/min.

Preferably, the crystalline form of tenofovir alafenamide malonate of the present invention is anhydrous, more preferably it is non-hygroscopic.

- In a further embodiment, the present invention relates to a crystalline form of tenofovir
20 alafenamide malonate characterized by having a FTIR essentially the same as shown in figure 9 of the present invention, when measured at a temperature in the range of from 20 to 30 °C.

Also preferably, the crystalline form of tenofovir alafenamide malonate of the present invention is a cocrystal.

- In one embodiment of the disclosure, the crystalline form of tenofovir alafenamide malonate is
25 provided in substantially pure form. The crystalline form of tenofovir alafenamide malonate in substantially pure form may be employed in pharmaceutical compositions which may optionally include one or more other components selected, for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients active chemical entities of different molecular structure.

Preferably, the crystalline form of tenofovir alafenamide malonate has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5 %, and more preferably less than 2 % of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern. Most preferred is a crystalline form having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern.

In one embodiment, a composition is provided consisting essentially of the crystalline form of tenofovir alafenamide malonate of the present invention. The composition of this embodiment may comprise at least 90 weight % of the crystalline form of tenofovir alafenamide malonate of the present invention, based on the weight of tenofovir alafenamide malonate in the composition.

Embodiments:

Some aspects, advantageous features and preferred embodiments of the present invention are summarized in the following items:

1. Crystalline tenofovir alafenamide malonate.
2. The crystalline tenofovir alafenamide malonate according to item 1, which is a cocrystal.
3. The crystalline tenofovir alafenamide malonate according to any one of items 1 or 2 in substantially pure form.
4. The crystalline tenofovir alafenamide malonate according to any one of aspects 1 to 3 having a molar ratio of tenofovir alafenamide : malonic acid in a range of from 1.0 : 0.7 to 1.0 : 1.3.
5. The crystalline tenofovir alafenamide malonate according to item 4, having a molar ratio of tenofovir alafenamide : malonic acid in a range of from 1.0 : 0.8 to 1.0 : 1.2.
6. The crystalline tenofovir alafenamide malonate according to item 5 having a molar ratio of tenofovir alafenamide : malonic acid of about 1.0 : 1.0.
7. The crystalline tenofovir alafenamide malonate according to any one of items 1 to 6, characterized by a x-ray powder diffraction pattern comprising **four** or more 2 θ values selected

from the group consisting of the values listed in Table 2 ($\pm 0.2^\circ$ 2-Theta) when measured at a temperature of about 22°C using Cu K α radiation.

8. The crystalline tenofovir alafenamide malonate according to item 7, characterized by a XRPD comprising characteristic peaks at 2-Theta angles of $(4.0 \pm 0.2)^\circ$, $(6.8 \pm 0.2)^\circ$, $(8.7 \pm 0.2)^\circ$ and $(9.0 \pm 0.2)^\circ$.
9. The crystalline tenofovir alafenamide malonate according to any one of items 7 or 8, wherein the XRPD further comprises at least one additional peak at the 2-Theta angle of $(18.4 \pm 0.2)^\circ$.
10. The crystalline tenofovir alafenamide malonate according to any one of items 7 or 8, wherein the XRPD comprises peaks at all positions identified in Table 2 ($\pm 0.2^\circ$ 2-Theta).
- 10 11. The crystalline tenofovir alafenamide malonate according to item 10, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 6.
12. The crystalline tenofovir alafenamide malonate according to any one of items 1 to 11 further characterized by showing an endotherm with an onset temperature in the range of from 132.0 to 132.5°C , preferably of about 132°C , more preferably of 132.2° , when measured with DSC at a heating rate of 10 K/min .
- 15 13. The crystalline tenofovir alafenamide malonate according to any one of items 1 to 11 further characterized by having a heat of fusion of at least 83.0 J/g , preferably of at least 84.0 J/g , even more preferably of at least 85.0 J/g , such as of at least 85.6 J/g , when measured with DSC at a heating rate of 10 K/min .
- 20 14. The crystalline tenofovir alafenamide malonate according to any one of items 1 to 13 further characterized by showing a mass loss of not more than $2.0\text{ weight\%}$, preferably not more than $1.5\text{ weight\%}$, more preferably not more than $1.0\text{ weight\%}$ and most preferably not more than $0.5\text{ weight\%}$, such as not more than $0.3\text{ weight\%}$, based on the weight of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130°C and a heating rate of 10 K/min .
- 25 15. The crystalline tenofovir alafenamide malonate according to any one of items 1 to 14 further characterized by having a FTIR essentially the same as shown in figure 9 of the present invention, when measured at a temperature in the range of from 20 to 30°C .

16. A composition comprising at least 90 weight % of crystalline tenofovir alafenamide malonate according to any one of items 1 to 15, based the weight of the composition.
17. The composition of item 16 consisting essentially of the crystalline form of any one of items 4 to 15.
- 5 18. Use of the crystalline tenofovir alafenamide malonate according to any one of items 1 to 5 or of the composition according to any one of items 16 to 17 for the preparation of a pharmaceutical composition.
19. Use of the crystalline tenofovir alafenamide malonate according to any one of items 1 to 15 or of the composition according to any one of items 16 to 17 for the preparation of a
10 pharmaceutical composition for the treatment and/or prophylaxis of viral infections such as HIV or HBV infections.
20. A pharmaceutical composition comprising crystalline tenofovir alafenamide malonate according to any one of claims 1 to 15 or a composition according to any one of claims 16 or 17, and a pharmaceutically acceptable carrier or diluent.
- 15 21. The pharmaceutical composition of item 20 which is an oral solid dosage form.
22. The pharmaceutical composition of item 21 which is a tablet.
23. The pharmaceutical composition according to any one of items 21 or 22, further comprising at least one water-soluble filler; at least one water-insoluble filler; at least one binder; and at least one lubricant.
- 20 24. A method of treating and/or preventing viral infections in a human comprising administering to the human a therapeutically-effective amount of crystalline tenofovir alafenamide malonate according to any one of items 1 to 15.
25. A process of making crystalline tenofovir alafenamide malonate according to any one of items 1 to 15 comprising the step of
25 - allowing tenofovir alafenamide malonate to crystallize from a solvent comprising a nitrile.
26. The process of claim 25, wherein the nitrile has a solubility in water at 20°C of at least 100g/l.

27. The process of any one of items 25 or 26, wherein the nitrile is acetonitrile.

28. The process of any one of items 25 to 27, wherein tenofovir alafenamide malonate is allowed to crystallize at a temperature of from 0°C to 40°C.

5 Tenofovir alafenamide protocatchuate

In a third aspect the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate. Surprisingly it has been found that tenofovir alafenamide can form a crystalline salt or cocrystal with 3,4-dihydroxybenzoic acid, which salt/cocrystal has properties that makes it useful for use in pharmaceutical formulations.

10 In an embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by having a PXRD comprising reflections at 2-Theta angles of:

$(3.0 \pm 0.2)^\circ$, $(8.9 \pm 0.2)^\circ$ and $(12.2 \pm 0.2)^\circ$; or

$(3.0 \pm 0.2)^\circ$, $(8.9 \pm 0.2)^\circ$, $(12.2 \pm 0.2)^\circ$ and $(10.3 \pm 0.2)^\circ$; or

$(3.0 \pm 0.2)^\circ$, $(8.9 \pm 0.2)^\circ$, $(12.2 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$ and $(17.6 \pm 0.2)^\circ$;

15 when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by having a PXRD comprising at least 4, more preferably at least 5, even more preferably at least 6 or most preferably at least 7 reflections at
20 2-Theta angles selected from Table 3 ($\pm 0.2^\circ$ 2-Theta), when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm:

Table 3: Tenofovir alafenamide protocatchuate	
Pos. [$^\circ 2\theta$]	Rel. Int. [%]
3,0	27
6,1	7
8,9	51
10,3	17
12,2	100
14,7	13
17,3	32
17,6	57

18,4	11
19,3	50
19,6	46
20,4	18
21,3	10
23,2	9
24,6	80
25,3	72
26,2	12
27,5	16
29,2	11
31,0	8

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by having a PXRD essentially the same as shown in figure 11 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In a further preferred embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by showing an endotherm with an onset temperature in the range of from 124.5 to 125.0 °C, preferably of about 125 °C, more preferably of 124.8°, when measured with DSC at a heating rate of 10 K/min.

More preferably, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by having a heat of fusion of at least 91.0 J/g, preferably of at least 92.0 J/g, even more preferably of at least 93.0 J/g, such as of at least 93.6 J/g, when measured with DSC at a heating rate of 10 K/min. Most preferably, a crystalline form of tenofovir alafenamide protocatchuate is characterized by a heat of fusion of 93.7 J/g, when measured with DSC at a heating rate of 10 K/min.

In another embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by showing a mass loss of not more than 2.0 weight%, preferably not more than 1.5 weight%, more preferably not more than 1.0 weight% and most preferably not more than 0.5 weight%, such as not more than 0.3 weight%, based on the weight of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130 °C and a heating rate of 10 K/min.

Preferably, the crystalline form of tenofovir alafenamide protocatchuate of the present invention is anhydrous, more preferably it is non-hygroscopic.

In a further embodiment, the present invention relates to a crystalline form of tenofovir alafenamide protocatchuate characterized by having a FTIR essentially the same as shown in figure 14 of the present invention, when measured at a temperature in the range of from 20 to 30 °C.

- 5 Also preferably, the crystalline form of tenofovir alafenamide protocatchuate of the present invention is a cocrystal.

In one embodiment of the disclosure, the crystalline form of tenofovir alafenamide protocatchuate is provided in substantially pure form. The crystalline form of tenofovir alafenamide protocatchuate in substantially pure form may be employed in pharmaceutical
10 compositions which may optionally include one or more other components selected, for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients active chemical entities of different molecular structure.

Preferably, the crystalline form of tenofovir alafenamide protocatchuate has substantially pure phase homogeneity as indicated by less than 10%, preferably less than 5 %, and more preferably
15 less than 2 % of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern. Most preferred is a crystalline form having substantially pure phase homogeneity with less than 1% of the total peak area in the experimentally measured XRPD pattern arising from the extra peaks that are absent from the simulated XRPD pattern.

20 In one embodiment, a composition is provided consisting essentially of the crystalline form of tenofovir alafenamide protocatchuate of the present invention. The composition of this embodiment may comprise at least 90 weight % of the crystalline form of tenofovir alafenamide protocatchuate of the present invention, based on the weight of tenofovir alafenamide protocatchuate in the composition.

25 Embodiments:

Some aspects, advantageous features and preferred embodiments of the present invention are summarized in the following items:

1. Crystalline tenofovir alafenamide protocatchuate.

2. The crystalline tenofovir alafenamide protocatchuate according to item 1, which is a cocrystal.
3. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 or 2 in substantially pure form.
- 5 4. The crystalline tenofovir alafenamide protocatchuate according to any one of aspects 1 to 3 having a molar ratio of tenofovir alafenamide : 3,4-dihydroxybenzoic acid in a range of from 1.0 : 0.7 to 1.0 : 1.3.
5. The crystalline tenofovir alafenamide protocatchuate according to item 4, having a molar ratio of tenofovir alafenamide : 3,4-dihydroxybenzoic acid in a range of from 1.0 : 0.8 to 1.0 :
10 1.2.
6. The crystalline tenofovir alafenamide protocatchuate according to item 5 having a molar ratio of tenofovir alafenamide : 3,4-dihydroxybenzoic acid of about 1.0 : 1.0.
7. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 6, characterized by a x-ray powder diffraction pattern comprising **four** or more 2θ values selected
15 from the group consisting of the values listed in Table 3 ($\pm 0.2^\circ$ 2-Theta) when measured at a temperature of about 22°C using Cu $K\alpha$ radiation.
8. The crystalline tenofovir alafenamide protocatchuate according to item 7, characterized by a XRPD comprising characteristic peaks at 2-Theta angles of $(3.0 \pm 0.2)^\circ$, $(8.9 \pm 0.2)^\circ$, $(10.3 \pm 0.2)^\circ$ and $(12.2 \pm 0.2)^\circ$.
- 20 9. The crystalline tenofovir alafenamide protocatchuate according to any one of items 7 or 8, wherein the XRPD further comprises at least one additional peak at the 2-Theta angle of $(17.6 \pm 0.2)^\circ$.
10. The crystalline tenofovir alafenamide protocatchuate according to any one of items 7 or 8, wherein the XRPD comprises peaks at all positions identified in Table 3 ($\pm 0.2^\circ$ 2-Theta).
- 25 11. The crystalline tenofovir alafenamide protocatchuate according to item 10, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 11.

12. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 11 further characterized by showing an endotherm with an onset temperature in the range of from 124.5 to 125.0 °C, preferably of about 125 °C, more preferably of 124.8°, when measured with DSC at a heating rate of 10 K/min.
- 5 13. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 11 further characterized by having a heat of fusion of at least 91.0 J/g, preferably of at least 92.0 J/g, even more preferably of at least 93.0 J/g, such as of at least 93.6 J/g, when measured with DSC at a heating rate of 10 K/min.
- 10 14. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 13 further characterized by showing a mass loss of not more than 2.0 weight%, preferably not more than 1.5 weight%, more preferably not more than 1.0 weight% and most preferably not more than 0.5 weight%, such as not more than 0.3 weight%, based on the weight of the crystalline form, when measured with TGA at a temperature in the range of from 25 to 130 °C and a heating rate of 10 K/min.
- 15 15. The crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 14 further characterized by having a FTIR essentially the same as shown in figure 14 of the present invention, when measured at a temperature in the range of from 20 to 30 °C.
16. A composition comprising at least 90 weight % of crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 15, based the weight of the composition.
- 20 17. The composition of item 16 consisting essentially of the crystalline form of any one of items 4 to 15.
18. Use of the crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 5 or of the composition according to any one of items 16 to 17 for the preparation of a pharmaceutical composition.
- 25 19. Use of the crystalline tenofovir alafenamide protocatchuate according to any one of items 1 to 15 or of the composition according to any one of items 16 to 17 for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of viral infections such as HIV or HBV infections.

20. A pharmaceutical composition comprising crystalline tenofovir alafenamide protococatechuate according to any one of claims 1 to 15 or a composition according to any one of claims 16 or 17, and a pharmaceutically acceptable carrier or diluent.
21. The pharmaceutical composition of item 20 which is an oral solid dosage form.
- 5 22. The pharmaceutical composition of item 21 which is a tablet.
23. The pharmaceutical composition according to any one of items 21 or 22, further comprising at least one water-soluble filler; at least one water-insoluble filler; at least one binder; and at least one lubricant.
24. A method of treating and/or preventing viral infections in a human comprising
10 administering to the human a therapeutically-effective amount of crystalline tenofovir alafenamide protococatechuate according to any one of items 1 to 15.
25. A process of making crystalline tenofovir alafenamide protococatechuate according to any one of items 1 to 15 comprising the step of
- allowing tenofovir alafenamide protococatechuate to crystallize from a solvent comprising a
15 nitrile.
26. The process of claim 25, wherein the nitrile has a solubility in water at 20°C of at least 100g/l.
27. The process of any one of items 25 or 26, wherein the nitrile is acetonitrile.
28. The process of any one of items 25 to 27, wherein tenofovir alafenamide protococatechuate is
20 allowed to crystallize at a temperature of from 0°C to 40°C.

Preparation of Crystalline Materials

Crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt,
25 solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the

solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture.

5 Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents may be employed, for
10 example, the compound may be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An antisolvent is a solvent in which the compound has low solubility.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding
15 may be employed to control growth of a particular polymorph or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, 1971,26, 369-377. In general, seeds of small size are
20 needed to control effectively the growth of crystals in the batch. Seed of small size may be generated by sieving, milling, or micronizing of large crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change in crystallinity from the desired crystal form (i.e., change to amorphous or to another polymorph).

25 A cooled crystallization mixture may be filtered under vacuum, and the isolated solids may be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids may be analyzed by a suitable spectroscopic or analytical technique, such as solid state nuclear magnetic resonance, differential scanning calorimetry, x-ray powder diffraction, or the like, to assure formation of
30 the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight % isolated yield, preferably greater than

90 weight % isolated yield, based on the weight of the compound originally employed in the crystallization procedure. The product may be comilled or passed through a mesh screen to delump the product, if necessary.

Preferred processes for the preparation of the crystalline solid forms of tenofovir alafenamide of the invention are provided in the examples and in the embodiment sections, respectively.

The crystalline solid forms of tenofovir alafenamide according to the present invention may be prepared *in situ* by reacting tenofovir alafenamide free base with either maleic acid, malonic acid or 3,4-dihydroxybenzoic acid in the presence of a solvent comprising a nitrile, preferably acetonitrile. Tenofovir alafenamide free base can be prepared according to the procedure disclosed in WO 02/08241 A2 (compound IV with development code GS-7340 corresponds to tenofovir alafenamide free base).

The solid starting material may be slurried in a solvent comprising acetonitrile. Most preferably acetonitrile is the only solvent present in the slurry. The tenofovir alafenamide concentration of the suspension is preferably in the range of from about 10 to 200 g/L, more preferably from about 25 to 150 g/L and most preferably from about 25 to 100 g/L, for example the concentration is about 50 g/L. Preferably, slurrying is performed at room temperature but depending on the applied concentration may also be conducted at elevated temperature. Slurrying encompasses any kind of movement of the solid material suspended in the solvent caused by, but not limited to e.g. agitation, stirring, mixing, shaking, vibration, sonication, wet milling and the like.

Once, the crystalline solid form of tenofovir alafenamide is obtained in essentially pure form, at least a part of the crystals are separated from their mother liquor. Preferably, the crystals are separated from their mother liquor by any conventional method such as filtration, centrifugation, solvent evaporation or decantation, more preferably by filtration or centrifugation and most preferably by filtration. Optionally, in a further step the isolated crystals are washed with a suitable solvent, for example acetonitrile. The obtained crystals may optionally be dried.

Compositions and medical use

In a further aspect the present invention relates to the use of the crystalline form(s) of tenofovir alafenamide of the present invention for the preparation of a pharmaceutical composition.

5 The pharmaceutical composition of the present invention can be prepared by wet or dry processing methods. In certain embodiments the pharmaceutical composition is prepared by wet processing methods, such as, but not limited to, wet granulation methods. Suitable wet granulation methods comprise high-shear granulation or fluid-bed granulation. In another embodiment the pharmaceutical composition is prepared by dry processing methods, such as, but not limited to, direct compression or dry granulation methods. An example of dry
10 granulation is roller compaction. The pharmaceutical composition obtained by dry or wet processing methods may be compressed into tablets, encapsulated or metered into sachets.

In a further aspect, the present invention relates to a pharmaceutical composition comprising an effective amount of the crystalline form(s) of tenofovir alafenamide of the present invention, one or more pharmaceutically acceptable excipient(s) and optionally one or more additional
15 active pharmaceutical ingredient(s). The one or more pharmaceutically acceptable excipient(s) which is comprised in the pharmaceutical composition of the present invention is/are preferably selected from the group of carriers, fillers, diluents, lubricants, sweeteners, stabilizing agents, solubilizing agents, antioxidants and preservatives, flavouring agents, binders, colorants, osmotic agents, buffers, surfactants, disintegrants, granulating agents, coating materials and
20 combinations thereof.

In a preferred embodiment, the pharmaceutically acceptable excipient(s) is/are selected from the group consisting of croscarmellose sodium, hydroxypropyl cellulose, lactose (as monohydrate), magnesium stearate, microcrystalline cellulose, silicon dioxide and sodium lauryl sulfate. In a preferred embodiment, all these pharmaceutically acceptable excipients are
25 comprised by the pharmaceutical composition of the present invention. In one embodiment, the pharmaceutical composition contains one or more additional active pharmaceutical ingredient(s) selected from the group consisting of elvitegravir, cobicistat, emtricitabine, darunavir and rilpivirine.

In a further aspect, the present invention relates to the pharmaceutical composition as described
30 above for use as a medicament.

In yet another aspect, the present invention relates to the pharmaceutical composition as described above for use in the treatment or prophylaxis of viral infections caused by DNA viruses, RNA viruses, herpesviruses (e.g. CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g. HBV), papillomavirus, hantavirus, adenoviruses and HIV.

- 5 In a particular embodiment, the present invention relates to the crystalline form(s) of tenofovir alafenamide or pharmaceutical compositions as described above for use in the treatment or prophylaxis of HIV-1 infections. The present invention also relates to a method of treatment and/or prophylaxis of HIV-1 infections in humans, comprising administration of an effective amount of the crystalline form(s) of tenofovir alafenamide or pharmaceutical compositions as
10 described above to a human in need thereof.

- In a further particular embodiment, the present invention relates to the crystalline form(s) of tenofovir alafenamide or pharmaceutical compositions as described above for use in the treatment or prophylaxis of Hepatitis B (HBV) infections. The present invention also relates to a method of treatment and/or prophylaxis of HBV infections in humans, comprising
15 administration of an effective amount of the crystalline form(s) of tenofovir alafenamide or pharmaceutical compositions as described above to a human in need thereof.

EXAMPLES

Powder X-ray diffraction:

- 20 PXRD was performed with a PANalytical X'Pert PRO diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-K α 1,2 radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. Diffractograms were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a stepsize of 0.013°
2-theta with 40s per step (255 channels) in the angular range of 2° to 40° 2-theta at ambient
25 conditions. A typical precision of the 2-theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-theta. Thus, the diffraction peak of the crystalline solid forms of tenofovir alafenamide that appears for example at 7.3° 2-Theta can appear in the range of from 7.1 to 7.5°
2-theta, preferably in the range of from 7.2 to 7.4° 2-Theta on most X-ray diffractometers under standard conditions.

Differential scanning calorimetry:

Differential scanning calorimetry was performed on a Mettler Polymer DSC R instrument. The sample was heated in a 40 microL aluminum pan with pierced aluminum lid from 25 to 200 °C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas.

5 Thermogravimetric analysis:

TGA was performed on a Mettler TGA/DSC 1 instrument. The sample was weighed into a 100 microL aluminum pan closed with an aluminum lid. The lid was automatically pierced at the beginning of the measurement. The sample was heated from 25 to 200 °C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas.

10 Gravimetric moisture sorption:

Moisture sorption isotherms were recorded with an SPSx-1 μ moisture sorption analyzer (ProUmid, Ulm). The measurement cycle was started at ambient relative humidity (r.h.) of 25%. Relative humidity was then decreased to 5% r.h. in 5% steps, followed by a further decrease to 3% r.h. and to 0% r.h.. Afterwards r.h. was increased from 0% to 95% r.h. in a sorption cycle and decreased to 0 % in a desorption cycle in 5% steps. Finally r.h. was increased to 30% r.h. in 5% steps.

The time per step was set to a minimum of 2 hours and a maximum of 6 hours. If an equilibrium condition with a constant mass of $\pm 0.01\%$ within 1 hour was reached before the maximum time for all examined samples the sequential humidity step was applied before the maximum time of 6 hours. If no equilibrium was achieved the consecutive humidity step was applied after the maximum time of 6 hours. The temperature was 25 ± 0.1 °C.

Fourier transform infrared spectrometry:

Fourier transform infrared spectroscopy (FTIR) was performed on an MKII Golden Gate™ Single Reflection Diamond ATR (attenuated total reflection) cell with a Bruker Tensor 27 FTIR spectrometer with 4 cm⁻¹ resolution at ambient conditions. To record a spectrum a spatula tip of a sample was applied to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum. A typical precision of the wavenumber values is in the range of about ± 2 cm⁻¹.

Example 1: Preparation of crystalline tenofovir alafenamide maleate

500mg tenofovir alafenamide free base were mixed at room temperature with 10ml of acetonitrile. 128mg of maleic acid (1,05eq) were added and the mixture was heated to reflux until a solution was observed. The hot solution was filtered and allowed to cool to room temperature and further stored at 2-8°C in a fridge. The precipitate was filtered and dried under vacuum to yield 250mg of tenofovir alafenamide maleic acid form.

The final product was investigated by powder X-ray diffraction (Figure 1) and the results are summarized in Table 1 disclosed herein above. The isolated crystals of tenofovir alafenamide maleate were investigated in more detail by means of DSC, TGA, GMS and FTIR. The results are below discussed in more detail.

The DSC curve of tenofovir alafenamide maleate shows a single melting endotherm with an onset temperature of 121.1 °C and a heat of fusion of 104.5 J/g. The DSC curve is displayed in Figure 2 herein. Thermogravimetric analysis revealed a mass loss of about 0.3 weight% from the beginning of the measurement up to a temperature of about 130 °C. The TGA curve is displayed in Figure 3 herein. From the thermal analysis it can be concluded that this crystalline form is an anhydrous and non-solvated form of tenofovir alafenamide maleate. The corresponding GMS isotherm is displayed in Figure 5. The final product was also investigated by fourier transform infrared spectroscopy (Figure 4) and the results are summarized in Table 4:

Table 4
Wavenumber (cm ⁻¹)
3201
3090
2983
2938
1741
1703
1681
1615
1557
1471
1408
1362
1258
1200
1148
1133

1110
1062
1029
993
917
904
881
864
819
802
757
719
690
654
641

Example 2: Preparation of crystalline tenofovir alafenamide malonate

500mg tenofovir alafenamide free base were mixed at room temperature with 10ml of acetonitrile. 115mg of malonic acid (1,05eq) were added and the mixture was heated to reflux until a solution was observed. The hot solution was filtered and allowed to cool to room temperature and further stored at 2-8°C in a fridge. The precipitate was filtered and dried under vacuum to yield 330mg of tenofovir alafenamide malonic acid form.

The final product was investigated by powder X-ray diffraction (Figure 6) and the results are summarized in Table 2 disclosed herein above. The isolated crystals of tenofovir alafenamide maleate were investigated in more detail by means of DSC, TGA, GMS and FTIR. The results are below discussed in more detail.

The DSC curve of tenofovir alafenamide malonate shows a single melting endotherm with an onset temperature of 132.2 °C and a heat of fusion of 85.7 J/g. The DSC curve is displayed in Figure 7 herein. Thermogravimetric analysis revealed a mass loss of about 0.3 weight% from the beginning of the measurement up to a temperature of about 130 °C. The TGA curve is displayed in Figure 8 herein. From the thermal analysis it can be concluded that this crystalline form is an anhydrous and non-solvated form of tenofovir alafenamide malonate. The corresponding GMS isotherm is displayed in Figure 10. The final product was also investigated by fourier transform infrared spectroscopy (Figure 9) and the results are summarized in Table

5:

Table 5
Wavenumber [cm ⁻¹]
3329
3163
2979
2934
1732
1698
1595
1493
1441
1409
1372
1317
1267
1203
1152
1101
1025
998
919
894
733
686
647

Example 3: Preparation of crystalline tenofovir alafenamide protocatchuate

500mg tenofovir alafenamide free base were mixed at room temperature with 10ml of acetonitrile. 170mg of 3,4-dihydroxybenoic acid (1,05eq) were added and the mixture was heated to reflux until a solution was observed. The hot solution was filtered and allowed to cool to room temperature and further stored at 2-8°C in a fridge. The precipitate was filtered and dried under vacuum to yield 480mg of tenofovir alafenamide 3,4-dihydroxybenoic acid form.

The final product was investigated by powder X-ray diffraction (Figure 11) and the results are summarized in Table 3 disclosed herein above. The isolated crystals of tenofovir alafenamide protocatchuate were investigated in more detail by means of DSC, TGA, GMS and FTIR. The results are below discussed in more detail.

The DSC curve of tenofovir alafenamide protocatchuate shows a single melting endotherm with an onset temperature of 132.2 °C and a heat of fusion of 85.7 J/g. The DSC curve is displayed in Figure 12 herein. Thermogravimetric analysis revealed a mass loss of about 0.3 weight% from the beginning of the measurement up to a temperature of about 130 °C. The TGA

curve is displayed in Figure 13 herein. From the thermal analysis it can be concluded that this crystalline form is an anhydrous and non-solvated form of tenofovir alafenamide protocatchuate. The corresponding GMS isotherm is displayed in Figure 15. The final product was also investigated by fourier transform infrared spectroscopy (Figure 14) and the results are summarized in Table 6:

Table 6
Wavenumber [cm ⁻¹]
3381
3351
3201
2976
2937
2890
1720
1663
1601
1487
1434
1372
1334
1287
1254
1223
1210
1186
1091
1027
1010
979
940
919
892
874
832
814
782
755
721
688
640

CLAIMS

1. A crystalline form of tenofovir alafenamide maleate, characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(4.6 \pm 0.2)^\circ$, $(7.8 \pm 0.2)^\circ$ and $(12.6 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.
5
2. The crystalline form of claim 1, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 1.
3. A crystalline form of tenofovir alafenamide malonate, characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(4.0 \pm 0.2)^\circ$, $(6.8 \pm 0.2)^\circ$ and $(8.7 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.
10
4. The crystalline form of claim 3, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 6.
5. A crystalline form of tenofovir alafenamide protocatechuate, characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(3.0 \pm 0.2)^\circ$, $(8.9 \pm 0.2)^\circ$ and $(12.2 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.
15
6. The crystalline form of claim 5, having a X-ray diffraction spectrum substantially the same as the X-ray powder diffraction spectrum shown in FIG. 11.
7. A pharmaceutical composition comprising an effective amount of the crystalline form as defined in any one of claims 1 to 6 and one or more pharmaceutically acceptable excipient(s).
20
8. The pharmaceutical composition of claim 7 for use as a medicament.
9. The pharmaceutical composition of claim 7 for use in the treatment and/or prophylaxis of viral infections, optionally viral infections caused by DNA viruses, RNA viruses, herpesviruses, retroviruses, hepadnaviruses, papillomavirus, hantavirus, adenoviruses and HIV.
25

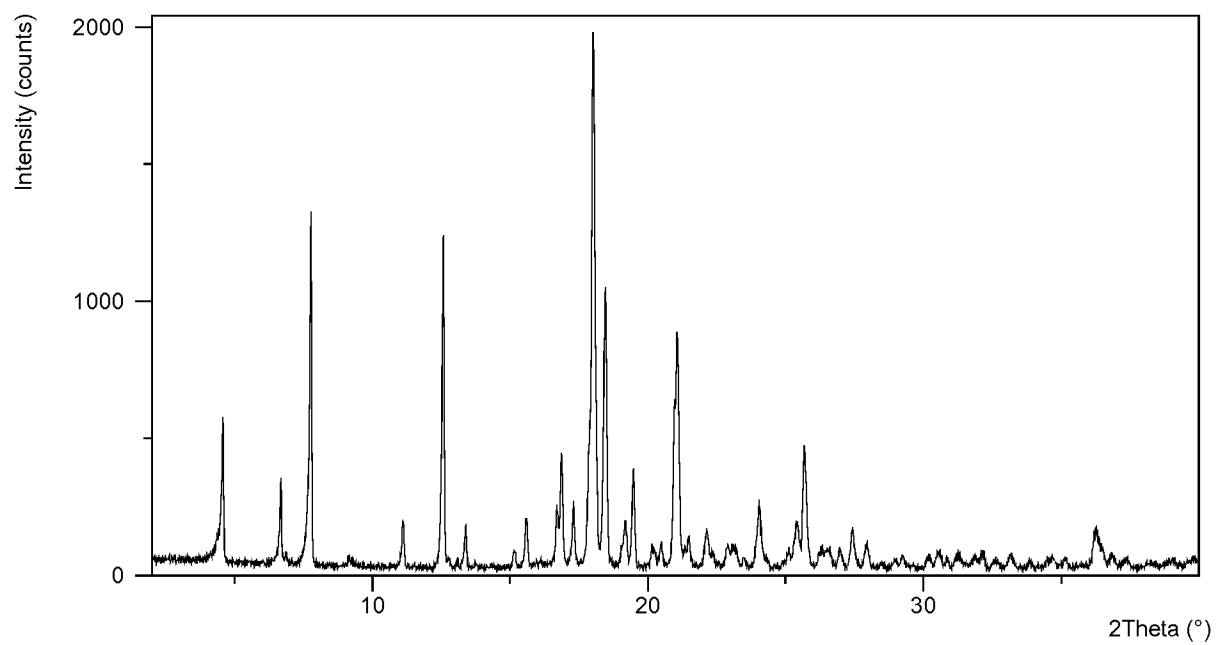
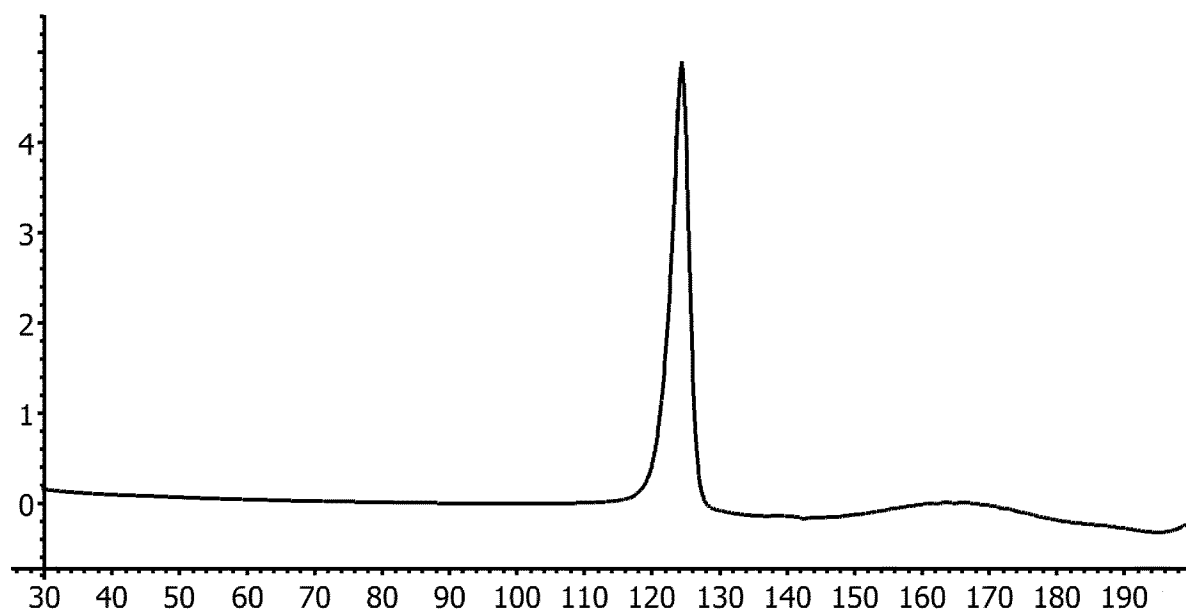
Figure 1:**Figure 2:**

Figure 3:

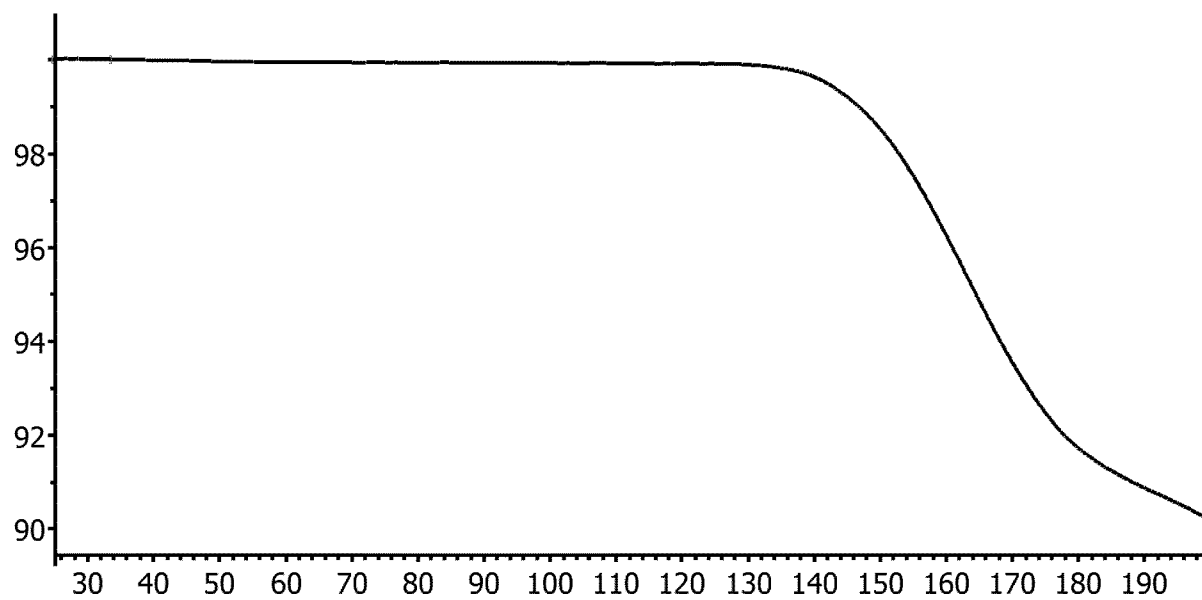


Figure 4:

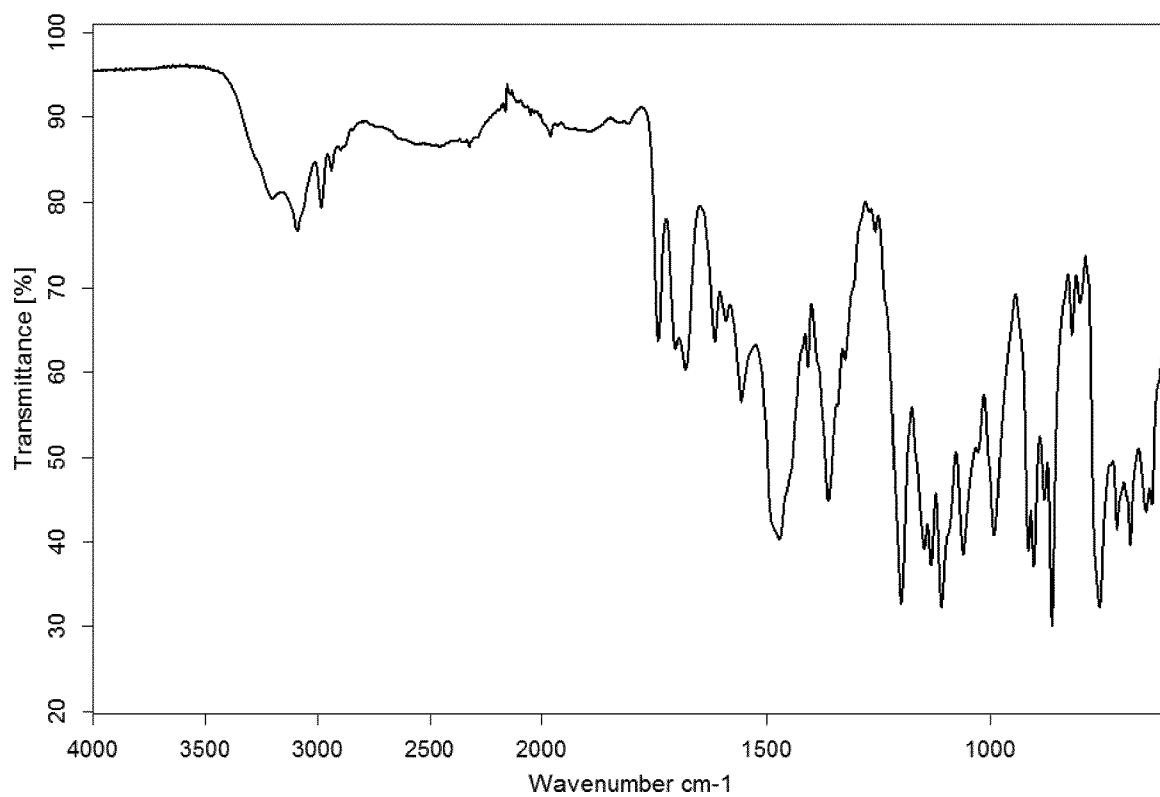


Figure 5:

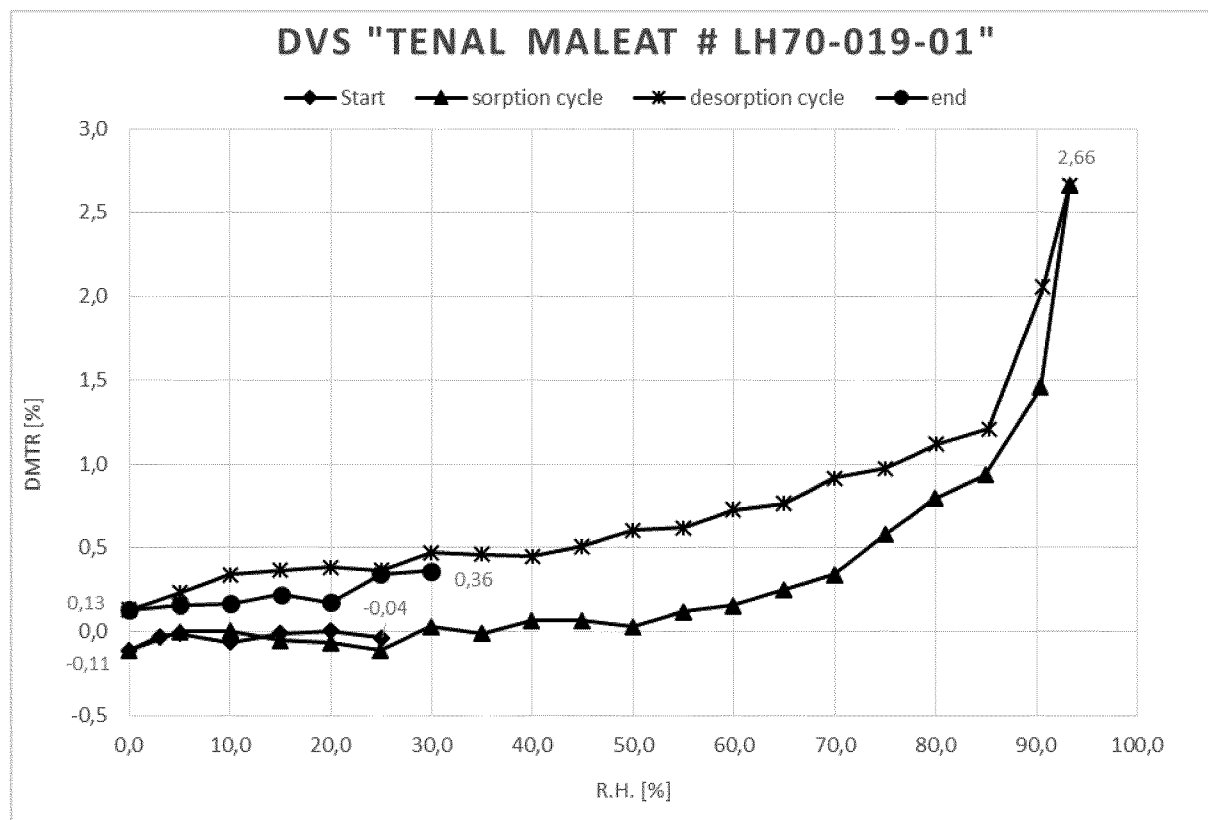


Figure 6:

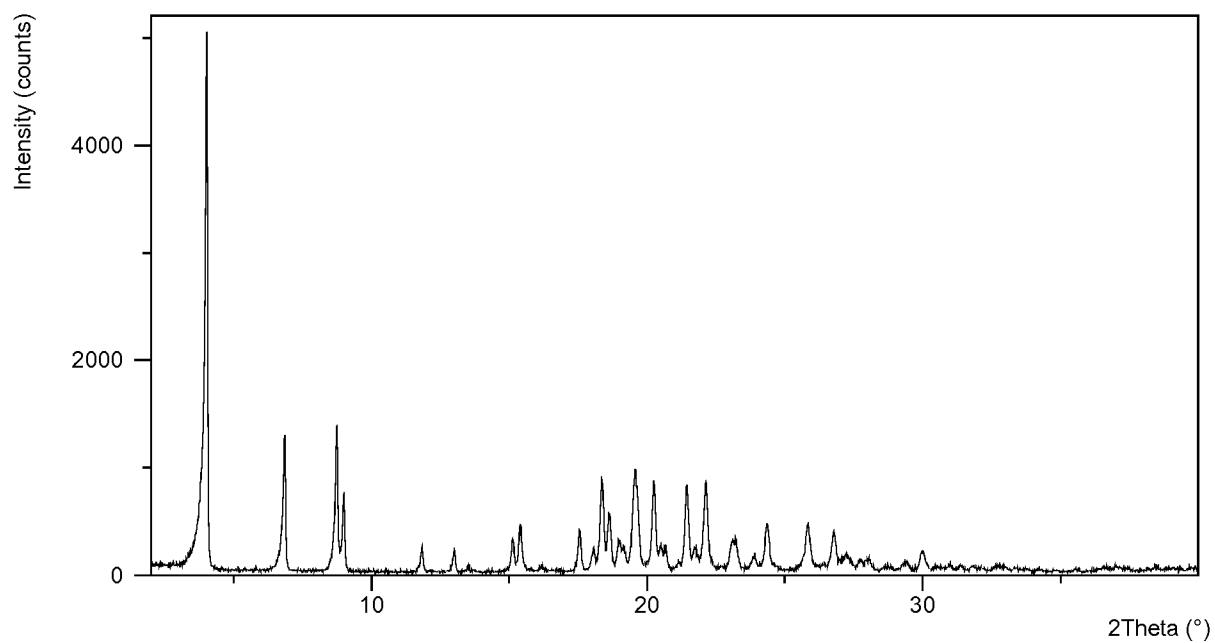


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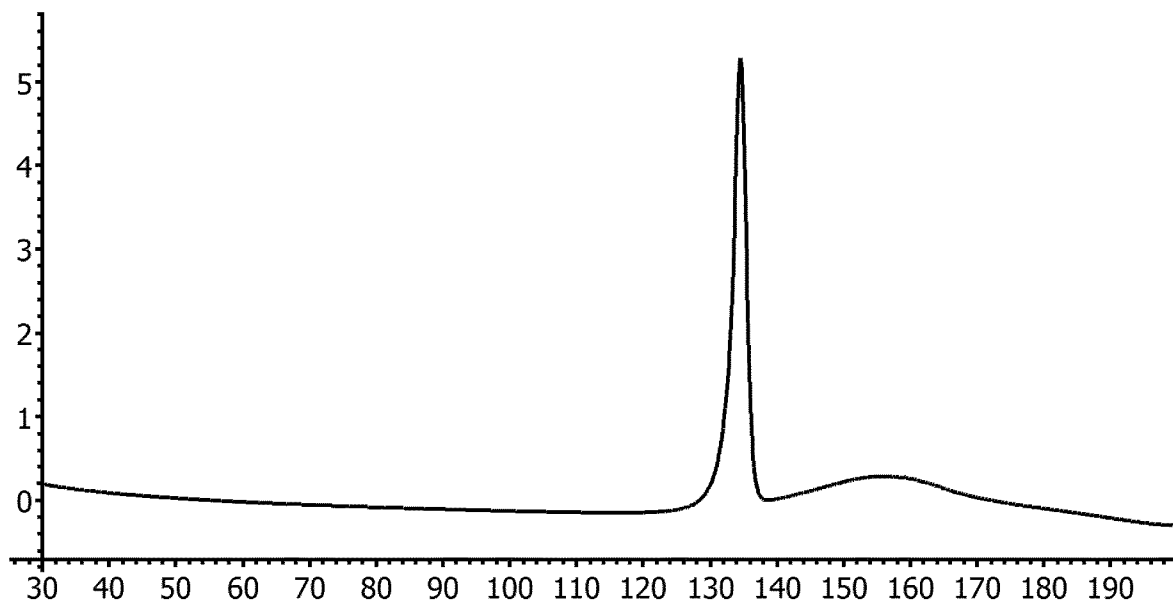


Figure 8:

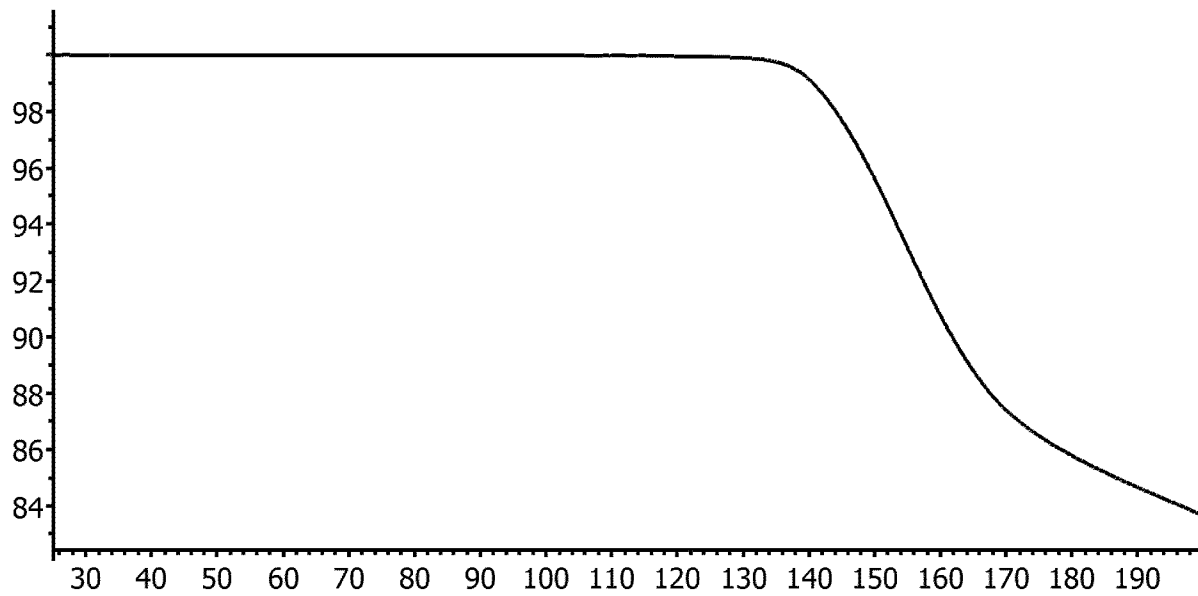


Figure 9:

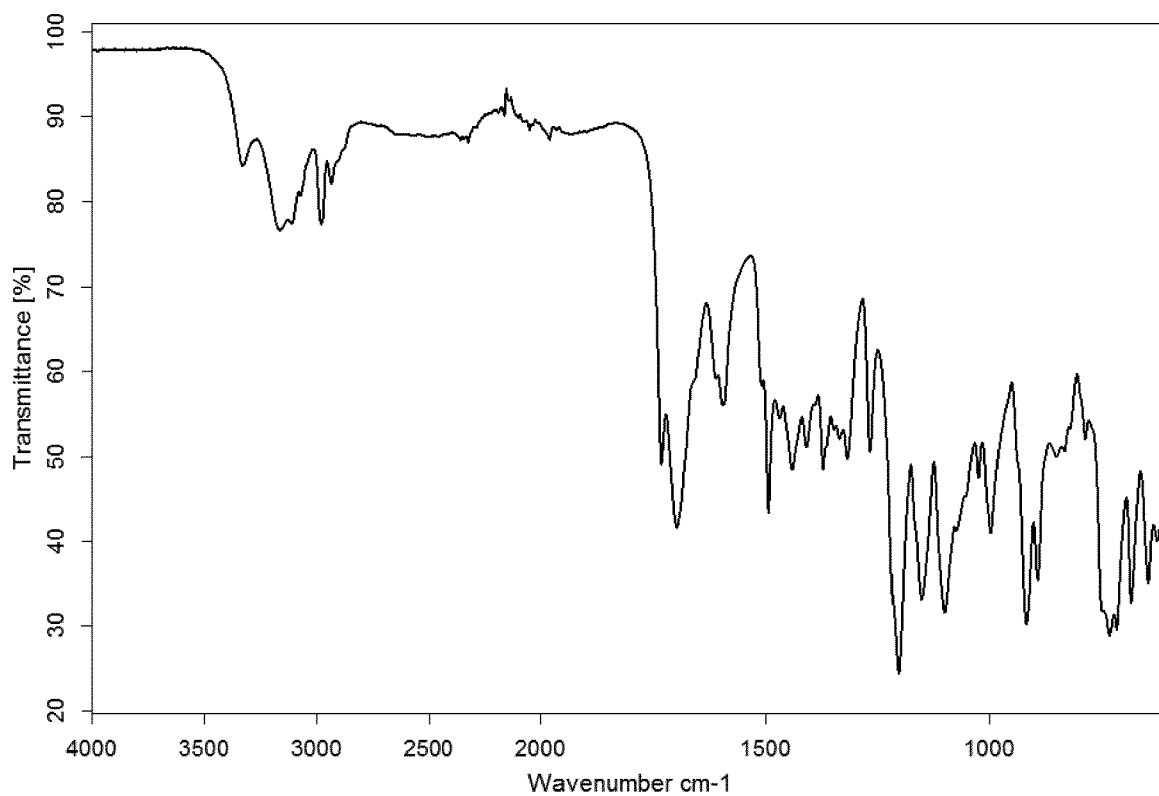


Figure 10:

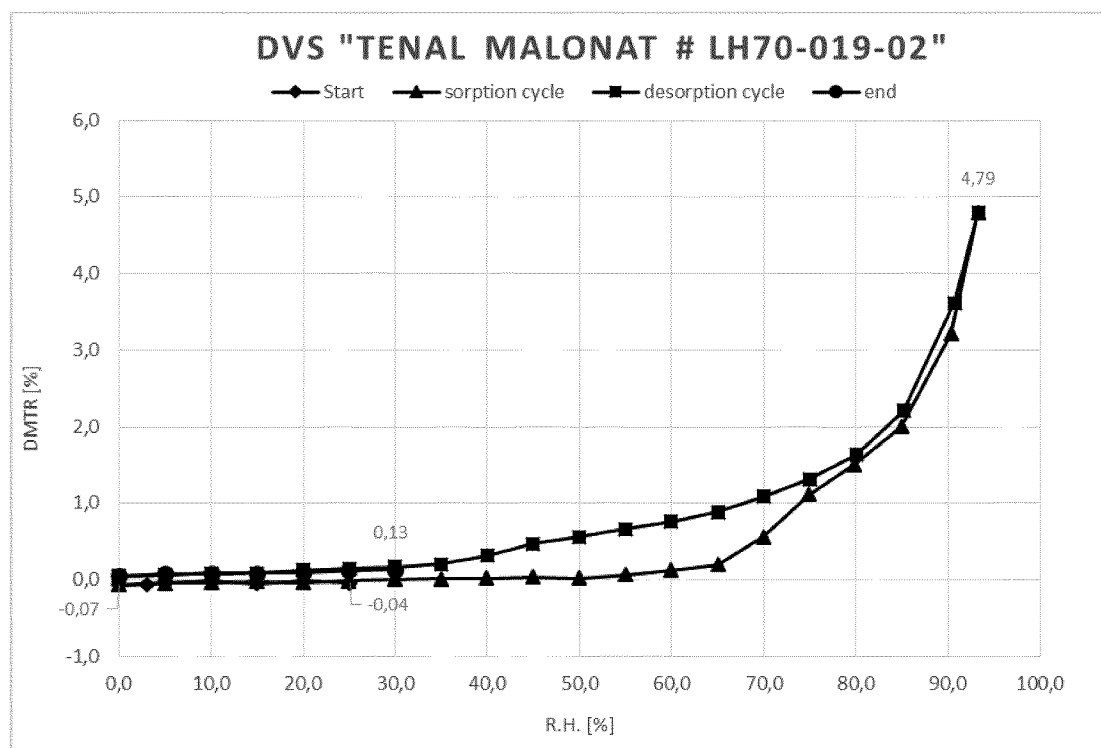


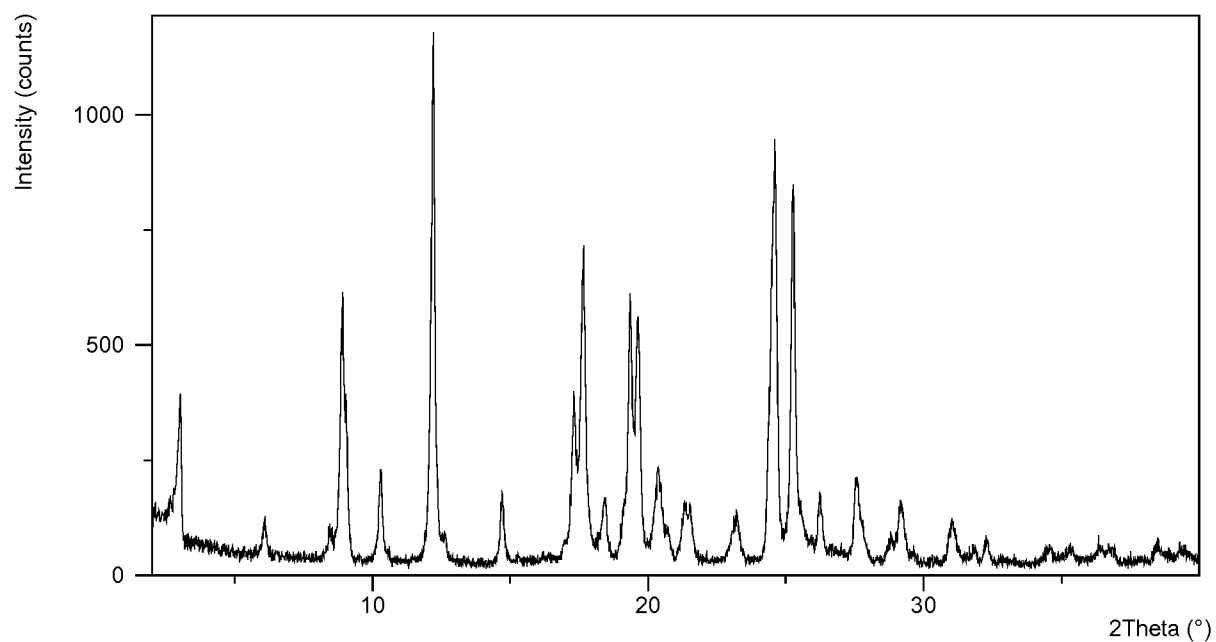
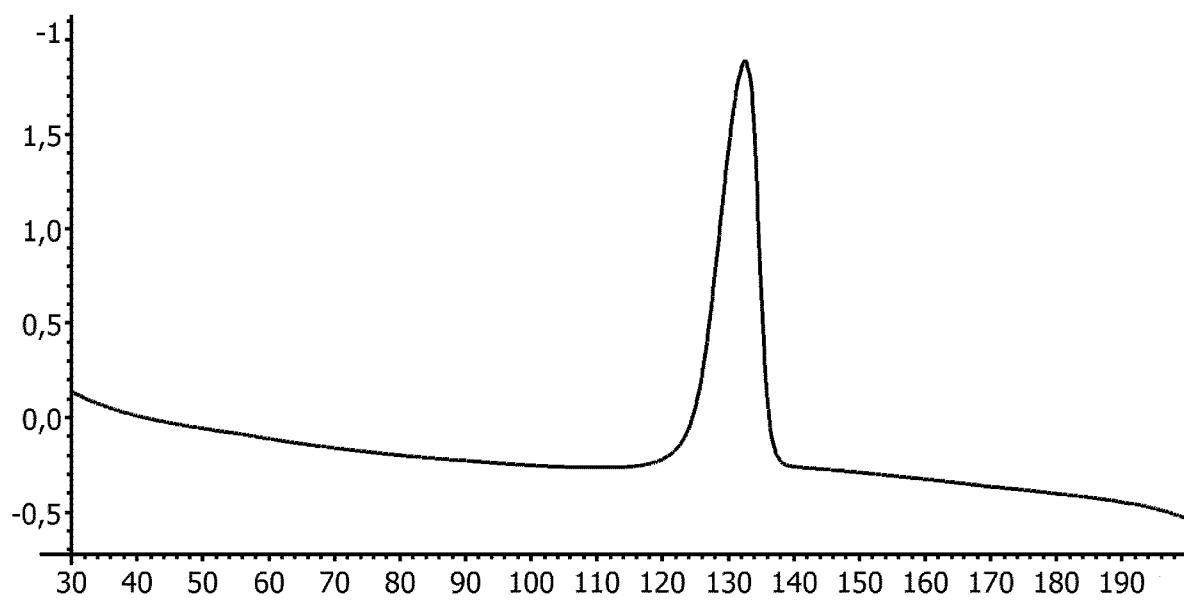
Figure 11:**Figure 12:**

Figure 13:

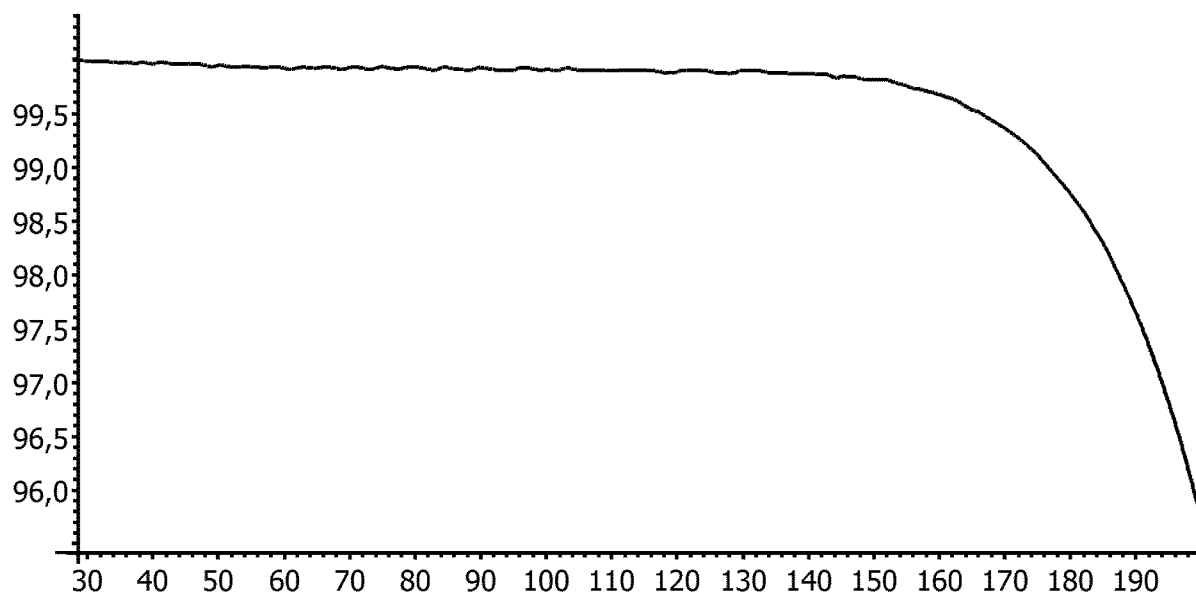


Figure 14:

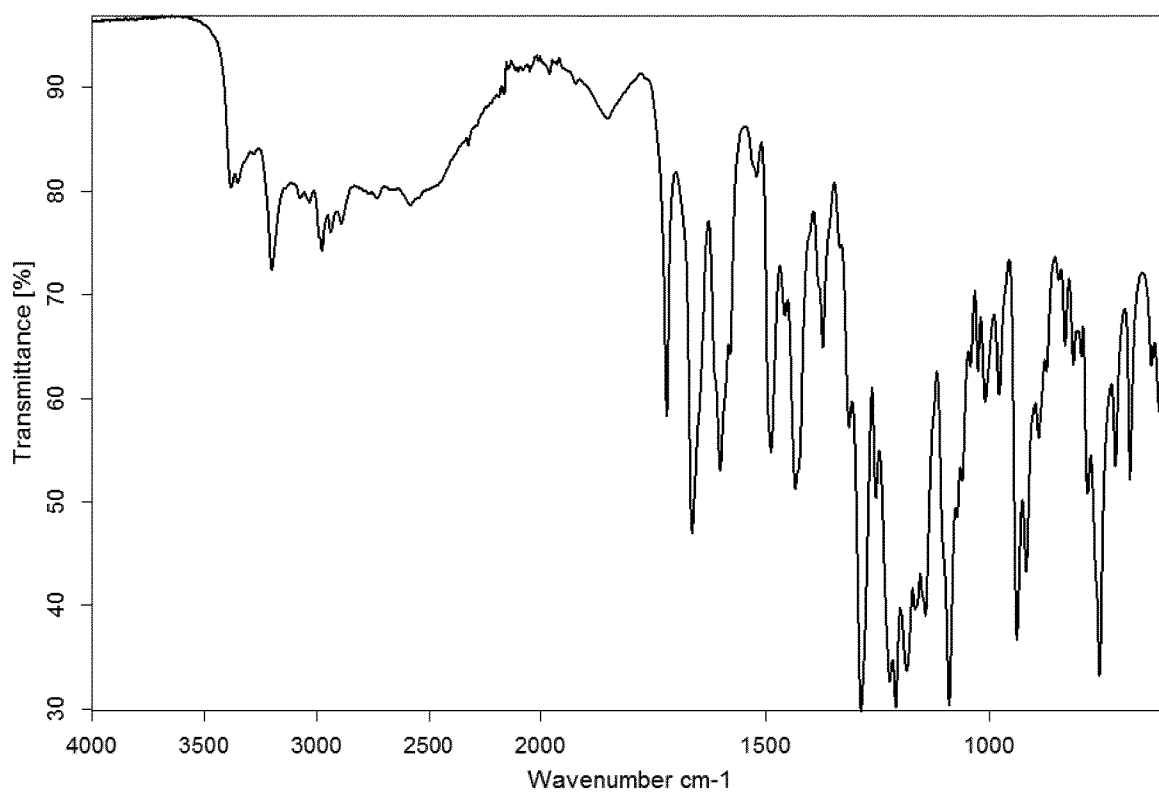
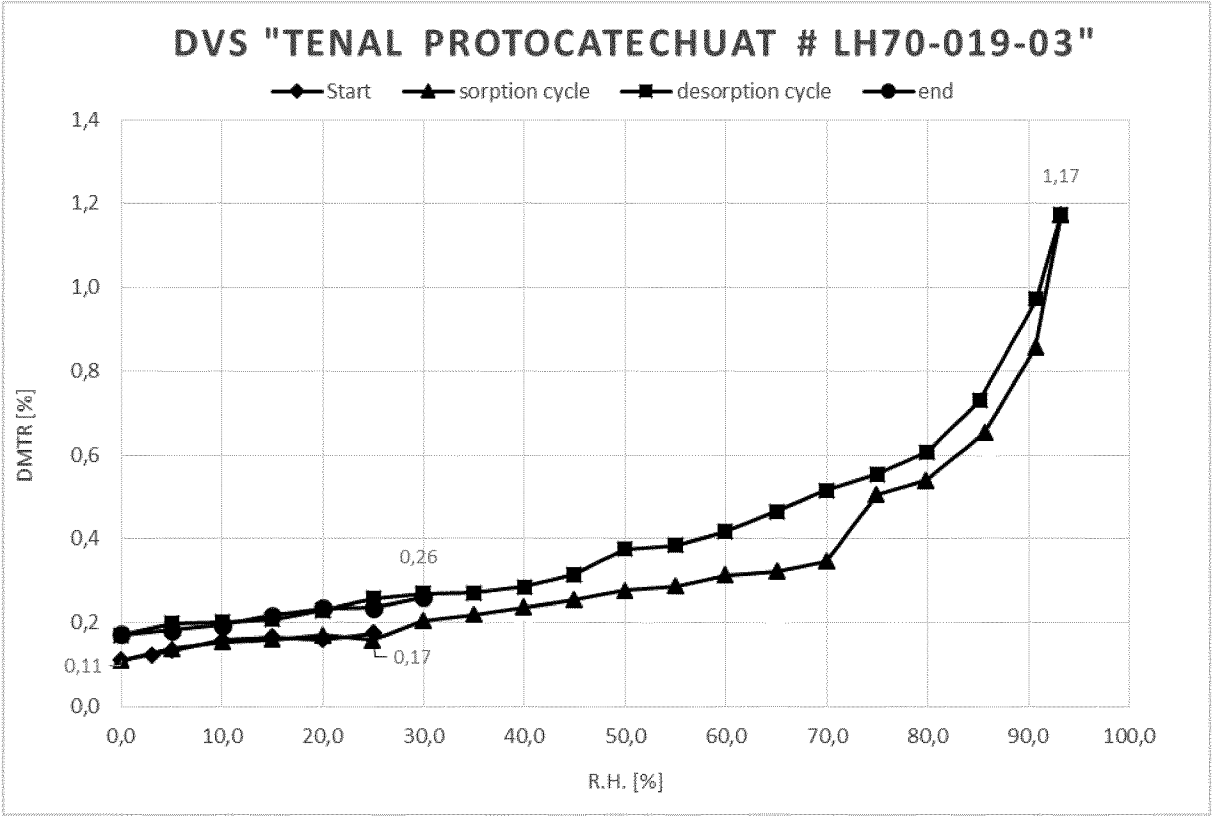


Figure 15:



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/083690A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F9/6561 A61K31/675
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)
C07F A61K

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, CHEM ABS 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	WO 2016/205141 A1 (GILEAD SCIENCES INC [US]) 22 December 2016 (2016-12-22) example 7 page 33 and example 4 page 29 -----	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

13 February 2018

Date of mailing of the international search report

22/02/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bourghida, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/083690

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016205141 A1	22-12-2016	AU 2016277859 A1	14-12-2017
		CA 2987085 A1	22-12-2016
		US 2016368938 A1	22-12-2016
		WO 2016205141 A1	22-12-2016
