(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 February 2017 (23.02.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/029408 A1

(51) **International Patent Classification**:
C07H 19/10 (2006.01) ***A61K 31/7072*** (2006.01)
C07D 207/16 (2006.01) ***A61P 31/14*** (2006.01)
C07H 1/00 (2006.01)

(21) **International Application Number**:
PCT/EP2016/069749

(22) **International Filing Date**:
19 August 2016 (19.08.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
15181861.4 20 August 2015 (20.08.2015) EP
16153230.4 28 January 2016 (28.01.2016) EP

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/029408 A1

(54) **Title**: SOLID STATE FORMS OF SOFOSBUVIR

(57) **Abstract**: Disclosed are solid state forms of sofosbuvir. The solid state forms may be co-crystals of sofosbuvir with at least one co-crystal former.

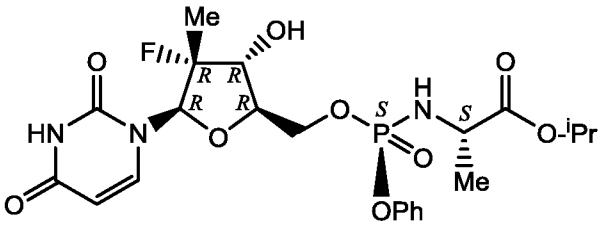
Solid State Forms of Sofosbuvir

Field of the Invention

The present invention encompasses solid state forms of sofosbuvir. The solid state forms may include sofosbuvir in the form of co-crystals.

Background of the Invention

Sofosbuvir, L-alanine, N-[[P(S),2'R]-2'-deoxy-2'-fluoro-2'-methyl-P-phenyl-5'-uridylyl]-, 1-methylethyl ester, or (2S)-isopropyl 2-(((((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-10 dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-amino)propanoate, having the following formula:



is an orally available, second generation uridine nucleoside analogue which inhibits the NS-5 protein of hepatitis C virus (HCV). Sofosbuvir and its isomer act as prodrugs and are converted through a series of in vivo transformations to an active triphosphate metabolite.

Sofosbuvir is described in US 7,964,580 and in US 8,334,270. Solid state forms of sofosbuvir are described in WO 2010/135569, US 2011/251152, WO2011/123645 and CN 104130302.

Polymorphism, the occurrence of different crystalline or solid state forms, is a property of some molecules and molecular complexes. A single molecule, such as sofosbuvir, may give rise to a variety of polymorphs having distinct crystal structures and physical properties such as melting point, thermal behaviours (e.g. as measured by capillary melting point, thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), X-ray diffraction (XRD) or powder X-ray diffraction (PXRD), infrared absorption and Raman fingerprint, and solid state (13C-) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound. Some of these techniques can be used to quantify the amount of one or more crystalline forms in a mixture. The differences in the

physical properties of different polymorphic forms result from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid.

A co-crystal is a molecular complex with a crystalline structure composed of at least two components (co-crystal formers), wherein the components may be atoms, ions or molecules. A co-crystal consists of two or more components that form a unique crystalline structure having unique properties. A co-crystal structure exhibits long-range order and the components interact via weak interaction (i.e. non-covalent interactions) such as hydrogen bonding, van der Waals forces and π-interactions. Co-crystals may optionally include one or more solvate molecules in the crystal lattice.

The discovery of new solid state forms, including co-crystals of sofosbuvir can provide new ways to improve the characteristics of sofosbuvir as an active pharmaceutical ingredient.

US 2011/251152 describes a number of crystalline forms of sofosbuvir, i.e. forms 1, 2, 3, 4, 5 and 6 which are characterised by X-ray powder diffraction (XRPD) peaks, as well as an amorphous form. According to this publication, crystalline forms 2, 3, 4 and 5 of sofosbuvir are said to be prepared by crystallisation from dichloromethane, chloroform, acetonitrile and anisole. However, following filtration and/or drying, these crystalline forms convert to Form 1. This publication further discloses that form 6 sofosbuvir can be prepared from Form 1 by various methods. The first method involves exposure of Form 1 to atmospheric humidity for several days, following by grinding and further storage of the ground material over a prolonged period (about 6-10 weeks). The second method involves suspending in water for a few hours optionally with heating. A third method comprises slurrying sofosbuvir in hot water, followed by a number of separate stages of cooling and holding at specific rates and temperatures.

CN 104130302 describes crystalline sofosbuvir form A characterised by XRD peaks at 8.19, 10.44, 12.22, 12.47, 13.51, 16.26, 16.84, 17.29, 18.06, 18.77, 19.47, 20.06, 20.91, 21.46, 23.50, 23.71, 24.43, 25.00, 25.51, 27.20, 28.15, 28.63, 29.08, 29.65, 31.35, 32.31, 32.81, 33.17, 35.19 and 37.95. Form A is described as a non-solvated, non-hydrated form. The Form A is prepared by dissolving sofosbuvir in a solvent and adding an antisolvent and allowing the mixture to stand in a sealed vessel for 15-24 hours under certain conditions. The solvent/antisolvent combinations include anhydrous ethanol and one of isopropyl ether, cyclohexane, n-pentane, or toluene or the solvent/anti-solvent may be acetone/n-pentane, acetone/petroleum ether or ethyl acetate/petroleum ether.

Different salts and solid state forms including co-crystals and solvated forms of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, changing the dissolution profile in a favourable direction, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also offer improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to assess variations in the properties and characteristics of a solid active pharmaceutical ingredient.

Discovering new solid state forms and solvates of a pharmaceutical product may yield materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New solid state forms of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher crystallinity or polymorphic stability which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life (chemical/physical stability). For example it has now been found that Form 6 of sofosbuvir has a high propensity to become electrostatically charged. Electrostatically charged active pharmaceutical ingredients may display poor flowability and/or a tendency to sticking, and thus ultimately may result in difficulties during the operations of the manufacturing process of a pharmaceutical composition based on such an electrostatically charged active pharmaceutical ingredient. Moreover poor content uniformity may be observed in the final dosage form when a dry process such as, for example, dry compression is used to make a pharmaceutical composition with an electrostatically charged active pharmaceutical ingredient. For at least these reasons, there is a need for additional solid state forms of sofosbuvir.

The present invention aims to provide new crystalline forms of sofosbuvir, as well as new processes for preparing crystalline forms of sofosbuvir.

Summary of the Invention

In one aspect, the present invention provides new crystalline forms of sofosbuvir characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

In another aspect, the present invention provides a crystalline form comprising sofosbuvir and at least one co-crystal former (i.e. a co-crystal of sofosbuvir with at least one co-crystal former).

The co-crystal former is preferably an amino acid, more preferably an α-amino acid, such as an α-amino acid selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine. Preferably the α-amino acid is selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine. In some embodiments of the present invention, the co-crystal of sofosbuvir is with an α-amino acid which is proline, or a substituted proline, particularly selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline. Preferably, in any embodiment of the present invention, the amino acid co-crystal former has L-configuration.

In an embodiment of the present invention, the crystalline form is a co-crystal of sofosbuvir with proline. In another embodiment of the present invention, the crystalline form is a co-crystal of sofosbuvir with L-proline. Particular, the co-crystal comprises sofosbuvir and L-proline in a molar ratio of 1:1.

In another aspect, the present invention provides a crystalline form of sofosbuvir which is substantially free of any other crystalline forms of sofosbuvir, preferably wherein the crystalline form of sofosbuvir is substantially free of sofosbuvir Form 1, and/or substantially free of sofosbuvir Form 6, and/or substantially free of Form 7.

A further aspect of the invention provides the use of a crystalline form of sofosbuvir of the present invention for the preparation of a pharmaceutical composition.

The present invention additionally provides a composition comprising a crystalline form of sofosbuvir according to the present invention, preferably wherein the composition is a pharmaceutical composition.

In a further aspect, the present invention provides pharmaceutical compositions comprising a crystalline form of sofosbuvir of the present invention and at least one pharmaceutically acceptable excipient.

In a yet further aspect, the present invention provides a crystalline form of sofosbuvir according to the invention for use as a medicament, preferably for the treatment of Hepatitis C.

Also provided is a process for the preparation of a crystalline form of sofosbuvir, wherein the process comprises combining sofosbuvir with at least one co-crystal former. In another aspect of the present invention, there is provided a co-crystal of sofosbuvir and a co-crystal former which is prepared by this process.

The present invention further encompasses a process for preparing the above mentioned pharmaceutical compositions. The process comprises combining a sofosbuvir solid state form according to the present invention with at least one pharmaceutically acceptable excipient.

Brief Description of the Drawings

Figure 1 shows X-Ray powder diffraction listings for Form 1 of sofosbuvir

Figure 2 shows an X-ray powder diffractogram of Form 1 of sofosbuvir

Figure 3 shows an X-ray powder diffractogram of Form 6 of sofosbuvir

Figure 4 shows X-Ray powder diffraction listings for Form 7 of sofosbuvir

Figure 5 shows an X-Ray powder diffractogram of Form 7 of sofosbuvir

Figure 6 shows X-ray powder diffraction peaks of sofosbuvir:L-proline (1:1) co-crystal

Figure 7 shows an X-ray powder diffractogram of sofosbuvir:L-proline (1:1) co-crystal

Figure 8 shows a Differential Scanning Calorimetry plot of sofosbuvir:L-proline (1:1) co-crystal

Figure 9 shows a ^{1}H-NMR-spectrum of sofosbuvir:L-proline (1:1) co-crystal

Figure 10 shows a solid state ^{13}C NMR spectra of (S)-proline (upper spectrum) and sofosbuvir-(S)-proline cocrystal

Figure 11 shows XRPD traces for sofosbuvir:proline cocrystal samples following storage under different conditions

Detailed Description of the Invention

As used herein, the term "co-crystal former" is defined as a component with which sofosbuvir is capable of forming co-crystals. As discussed above, typically co-crystal formers are capable of forming non-covalent interactions with the active agent (e.g. hydrogen bonding, van der Waals forces and π-interactions). Preferably, the co-crystal former is an amino acid. More preferably, the co-crystal former is an α-amino acid, such as α-amino acids selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine. Preferred α-amino acids are those selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine. Particularly preferred α-amino acid co-crystal formers are proline or substituted prolines, especially those selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline. Proline is an especially preferred co-crystal former. Preferably, the amino acid co-crystal formers are amino acids having L-configuration. In an especially preferred embodiment, the co-crystal former is L-proline, i.e. wherein the crystalline form is a co-crystal of sofosbuvir with L-proline.

As used herein, unless otherwise indicated, "substantially free" is meant that the solid state form of the present invention contains 20% (w/w) or less of polymorphs, or of a specified polymorph of sofosbuvir. According to some embodiments, the salts and solid state forms of sofosbuvir prepared by the processes of the present invention contain 10% (w/w) or less, 5% (w/w) or less, 2% (w/w) or less, 1% (w/w) or less, 0.5% (w/w) or less, or 0.2% (w/w) or less of other polymorphs, or of a specified polymorph of sofosbuvir. In other embodiments, solid state form of sofosbuvir of the present invention contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of any solid state forms or of a specified polymorph of

sofosbuvir. Preferably the solid state form of sofosbuvir of the present invention contains 20% (w/w) or less, or 10% (w/w) or less, or 5% (w/w) or less, or 2% (w/w) or less, or 1% (w/w) or less, or 0.5% (w/w) or less, or 0.2% (w/w) or less of other polymorphs (including other crystalline forms as well as amorphous form, solvated forms, or co-crystal forms), or of a specified polymorph of sofosbuvir.

According to some embodiments, the solid state forms of the present invention contains 20% (w/w) or less, 10% (w/w) or less, 5% (w/w) or less, 2% (w/w) or less, 1% (w/w) or less, 0.5% (w/w) or less, or 0.2% (w/w) or less of sofosbuvir forms 1 and/or 6 and/or 7. More preferably the solid state forms of the present invention are substantially free of sofosbuvir forms 1, 6 and 7, and preferably contains 20% (w/w) or less, 10% (w/w) or less, 5% (w/w) or less, 2% (w/w) or less, 1% (w/w) or less, 0.5% (w/w) or less, or 0.2% (w/w) or less of sofosbuvir forms 1, 6 and 7.

A solid state form, such as a crystalline form or amorphous form, may be referred to herein as being characterized by graphical data “as depicted in” or “substantially as depicted in” a figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called “fingerprint”) which cannot necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to certain factors such as, but not limited to, variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the figures herein with graphical data generated for an unknown solid state form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of a sofosbuvir referred to herein as being characterized by graphical data “as depicted in” or “as substantially depicted in” a figure will thus be understood to include any crystal forms of sofosbuvir characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the figure.

As used herein, the term "isolated" in reference to solid state forms of sofosbuvir of the present invention corresponds to a solid state form of sofosbuvir that is physically separated from the reaction mixture in which it is formed.

As used herein, unless otherwise indicated, the XRPD measurements are taken using copper Kα1/Kα2 radiation with a weighted median of the wavelengths of 1.54187 Å. Unless otherwise indicated, XRPD 2-theta values are reported with an error of ± 0.2 degrees 2-theta.

As used herein, the term “room temperature” (RT) refers to an ambient temperature of from about 18°C to about 30°C, about 18°C to about 28°C, about 18°C to about 25°C or about 20°C to about 25°C.

A thing, e.g., a reaction mixture, may be characterized herein as being at, or allowed to come to “room temperature” or “ambient temperature”, often abbreviated as “RT.” This means that the temperature of the thing is close to, or the same as, that of the space, e.g., the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C, or about 22°C to about 27°C, or about 25°C.

The amount of solvent employed in a chemical process, e.g., a reaction or a crystallization, may be referred to herein as a number of “volumes” or “vol” or “V.” For example, a material may be referred to as being suspended in 10 volumes (or 10 vol 10 or 10V) of a solvent. In this context, this expression would be understood to mean millilitres of the solvent per gram of the material being suspended, such that suspending a 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 millilitres of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding solvent X (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of solvent X was added.

A process or step may be referred to herein as being carried out "overnight." Unless otherwise indicated, this refers to a time interval, e.g., for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10-18 hours, typically about 16 hours. As used herein, unless indicated otherwise, the term “reduced pressure” refers to a pressure that is less than atmospheric pressure. For example, reduced pressure is about 10 mbar to about 50 mbar.

As used herein, unless indicated otherwise, the term “under vacuum” refers to a pressure of about 0.2 mbar to about 10 mbar, about 0.2 to about 5 mbar, about 0.5 to about 4 mbar, about 1 mbar to about 3 mbar, and preferably about 2 mbar.

Unless otherwise indicated, as used herein, crystalline form 1 of sofosbuvir refers to a crystalline form of sofosbuvir which may be characterized by XRPD peaks or the X-ray powder diffractogram disclosed in US 2011/0251152 or WO2011/123645. Thus, as used herein, Form 1 sofosbuvir may be characterised by XRPD peaks at approximately 5.0, 7.3, 9.4, 18.1 ± 0.2 degrees 2-theta. Form 1 may be further characterised by additional XRPD peaks at approximately 8.8, 10.0, 11.4, 15.0 and 22.3 degrees 2-theta ± 0.2 degrees 2-theta. Form I may also be characterised by the XRPD listings in the first column of the table in Figure 1, optionally with the relative intensity values in the second column of the table in Figure 1. Form I may alternatively be characterised by the X-ray powder diffractogram substantially as depicted in Figure 2.

Unless otherwise indicated, as used herein, crystalline Form 6 of sofosbuvir refers to a crystalline form of sofosbuvir which may be characterised by an X-ray powder diffraction pattern having peaks as disclosed in US 2011/0251152 or WO2011/123645, namely XRPD peaks at 6.08, 8.2, 10.38, 10.85, 12.17, 12.7, 13.73, 14.1, 15.91, 16.83, 17.17, 17.66, 17.95, 18.79, 19.1, 19.41, 19.8, 20.11, 20.82, 21.81, 22.03, 23.03, 23.26, 23.64, 23.89 and 24.73 degrees 2-theta (± 0.2 degrees 2-theta). Alternatively, Form 6 of sofosbuvir may be characterised by an X-ray powder diffractogram substantially as depicted in Figure 3.

Unless otherwise indicated, as used herein, crystalline Form 7 of sofosbuvir refers to a crystalline form of sofosbuvir which may be characterised by XPRD peaks at approximately: 12.4, 13.5, 16.2, 25.3, and 27.2 ± 0.2 degrees 2-theta. Form 7 may further be characterised by additional XRPD peaks at approximately 8.1, 10.4, 17.2, 19.4, and 20.9 ± 0.2 degrees 2-theta (± 0.2 degrees 2-theta). Alternatively, Form 7 may be further characterised by the XRPD peak listing in the first column of the table in Figure 4, optionally with the intensity values in the second column of the table in Figure 4. Alternatively, Form 7 of sofosbuvir may be characterised by an X-ray powder diffractogram substantially as depicted in Figure 5.

The present invention provides crystalline form of sofosbuvir characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta. Alternatively, crystalline form of sofosbuvir according to the present invention may alternatively be characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta, and optionally further characterised by an X-ray powder diffraction pattern having peaks at about: 7.3, 9.5, 10.7, 12.5 and 14.7 ± 0.2 degrees

two theta. Crystalline form of sofosbuvir according to the present invention may be alternatively characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and optionally further characterised by one or more peaks at about 17.2, 17.4, 18.0, 18.3, 18.7, 19.2, 19.7, 19.9, 20.2, 20.9, 21.5, 22.1, 24.1, 24.5, 25.8, 27.0, 27.8, 28.7, 29.1, 29.7, 30.1, 31.5, 32.5, 33.3, 33.7, 34.2 and 35.0 ± 0.2 degrees two theta.

Crystalline form of sofosbuvir according to the present invention may be characterised by an X-ray powder diffraction pattern having the peaks set out in the first column in the table in Figure 6, optionally with the corresponding intensity values in the second column in the table in Figure 6.

Crystalline form of sofosbuvir according to the present invention may be characterised by an X-ray powder diffraction pattern substantially as depicted in Figure 7.

In a preferred embodiment of the present invention, the crystalline form of sofosbuvir is a co-crystal of sofosbuvir with at least one co-crystal former. The co-crystal former is a compound or molecule which is capable of forming a co-crystal with sofosbuvir. A preferred co-crystal former is an amino acid, particularly α-amino acid, i.e. the crystalline form is a co-crystal of sofosbuvir with an amino acid, preferably an α-amino acid). Preferred α-amino acids are selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine. More preferred α-amino acids are selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine. The amino acids preferably have L-configuration.

Particularly, the crystalline form of sofosbuvir according to the present invention is a co-crystal of sofosbuvir and an α-amino acid selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline.

In an especially preferred embodiment, the present invention provides a crystalline form of sofosbuvir which is a co-crystal of sofosbuvir with proline, and most preferably L-proline.

Preferred are crystalline forms of sofosbuvir which comprise sofosbuvir and the co-crystal former in a 1:1 molar ratio.

Another aspect of the present invention provides a crystalline form comprising sofosbuvir and at least one co-crystal former as described above.

A preferred embodiment provides a co-crystal comprising sofosbuvir and L-proline, wherein the molar ratio of sofosbuvir to proline is 1:1. The crystalline form of sofosbuvir may be characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta. Alternatively, this crystalline form of sofosbuvir according to the present invention may be characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta, and optionally further characterised by an X-ray powder diffraction pattern having peaks at about: 7.3, 9.5, 10.7, 12.5 and 14.7 ± 0.2 degrees two theta. The crystalline form of sofosbuvir may alternatively be characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and optionally further characterised by one or more peaks at about 17.2, 17.4, 18.0, 18.3, 18.7, 19.2, 19.7, 19.9, 20.2, 20.9, 21.5, 22.1, 24.1, 24.5, 25.8, 27.0, 27.8, 28.7, 29.1, 29.7, 30.1, 31.5, 32.5, 33.3, 33.7, 34.2 and 35.0 ± 0.2 degrees two theta, or may be characterised by an X-ray powder diffraction pattern having the peaks set out in the first column in the table in Figure 6, optionally with the corresponding intensity values in the second column in the table in Figure 6. The crystalline form of sofosbuvir according to the present invention may alternatively be characterised by an X-ray powder diffraction pattern substantially as depicted in Figure 7.

Crystalline form of sofosbuvir according to any aspect of the present invention may be characterised by having a high melting point. In particular, a melting point of about 170 to about 180ºC, preferably about 172-176ºC, and more preferably about 174ºC as measured by differential scanning calorimetry.

Crystalline form of sofosbuvir according to any aspect of the present invention may be characterised by a DSC plot having a major endothermic peak having an onset at about 173.1ºC, and a minor endothermic peak having an onset at about 180.2ºC.

Crystalline form of sofosbuvir according to any aspect of the present invention may be characterised by a dissolution after 15 minutes at 37°C of any one of (A), (B) or (C):

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2,

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, or

(C) at least about 4.0 mg/ml, and preferably at least about 4.5 mg/ml, and more preferably at least about 4.8 mg/ml, in 50 mM potassium dihydrogen phosphate at pH 6.8.

Crystalline form of sofosbuvir according any aspect of the present invention may be characterised by having a dissolution profile after 15 minutes at 37°C of:

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2, and

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5

Alternatively, the crystalline form of sofosbuvir according to any aspect of the present invention may be characterised by having a dissolution profile after 15 minutes at 37°C of:

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2,

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, and

(C) at least about 4.0 mg/ml, and preferably at least about 4.5 mg/ml, and more preferably at least about 4.8 mg/ml in 50 mM potassium dihydrogen phosphate at pH 6.8.

Crystalline form of sofosbuvir according to any aspect of the present invention may alternatively be characterised by having a dissolution after 15 minutes at 37°C of any one of (A), (B) or (C):

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2,

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, or

(C) about 4.0 to about 5.5 mg/ml, and preferably about 4.5 to about 5.3 mg/ml, and more preferably about 4.8 to about 5.3 mg/ml, in 50 mM potassium dihydrogen phosphate at pH 6.8.

Alternatively, the crystalline form of sofosbuvir according to any aspect of the present invention may be characterised by having a dissolution profile after 15 minutes at 37°C of:

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2, and

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5.

The crystalline form of of sofosbuvir according to any aspect of the invention may alternatively be characterised by having a dissolution profile after 15 minutes at 37°C of:

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2,

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, and

(C) about 4.0 to about 5.5 mg/ml, and preferably about 4.5 to about 5.3 mg/ml, and more preferably about 4.8 to about 5.3 mg/ml, in 50 mM potassium dihydrogen phosphate at pH 6.8.

The dissolution is preferably measured following stirring at 250 rpm at 37°C in the specified buffer solution (e.g. as illustrated in Example 4 herein).

Preferably crystalline forms of sofosbuvir according to any aspect and embodiment of the present invention are substantially free of any other crystalline forms of sofosbuvir, particularly wherein the crystalline form is substantially free of sofosbuvir Form 1, or wherein the crystalline form is substantially free of sofosbuvir Form 6, or wherein the crystalline form is substantially free of Form 7. More preferably, crystalline forms according to any aspect or embodiment of the present invention are substantially free of sofosbuvir Forms 1, 6 and 7.

The crystalline forms of sofosbuvir, such as a co-crystal of sofosbuvir and L-proline, can be used for the preparation of a pharmaceutical composition.

The invention further provides compositions comprising a crystalline form of sofosbuvir of the invention, preferably wherein the composition is a pharmaceutical composition., and more preferably wherein the crystalline form is a co-crystal of sofosbuvir and L-proline,

The pharmaceutical compositions of the present invention are preferably solid, and preferably comprise a crystalline form of sofosbuvir, such as a co-crystal of sofosbuvir and L-proline, and at least one pharmaceutically acceptable excipient.

The crystalline forms of sofosbuvir of the present invention, particularly e.g. a co-crystal of sofosbuvir and L-proline, are particularly suitable for use as medicaments, such as for the treatment of Hepatitis C.

The present invention further provides a process for preparing a crystalline form of sofosbuvir comprising combining sofosbuvir with a co-crystal former.

In one embodiment, the process comprises:

(a) combining sofosbuvir with a co-crystal former in a solvent or a mixture of solvents (preferably wherein the solvent comprises an organic solvent) to form a mixture,

(b) optionally isolating the crystalline form of sofosbuvir, and

(c) optionally drying the crystalline form of sofosbuvir.

Suitable organic solvents include: aliphatic ethers, cyclic ethers, ketones, alcohols and esters, such as C_{4-8} dialkyl ether, C_{1-3} alkyl-substituted C_{4-8} cyclic ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-4} alkyl ester of C_{1-6} alcohol, preferably C_{4-6} alkyl ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-3} alkyl ester of C_{1-6} alcohol, and more preferably C_{1-6} alcohol or a C_{1-4} alkyl ester of C_{1-6} alcohol.

Particularly preferred organic solvent include one or more of: methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, ethyl acetate, n-propylacetate, n-butylacetate and iso-butylacetate, with methanol, ethanol, n-propanol, isopropanol, ethyl acetate, and n-propylacetate being more preferred

Most preferably, the organic solvent is selected from the group consisting of methanol, ethanol, isopropanol and ethyl acetate or the organic solvent is selected from one of: ethanol, isopropanol, ethyl acetate, or wherein the solvent is a mixture of methanol and isopropanol.

In the above process, step (a) may comprises mixing, in any order, sofosbuvir and the co-crystal former with the solvent or solvents (particularly ethanol, isopropanol or ethyl acetate).

Step (a) may further comprise allowing the mixture to stand, optionally with stirring, for a period of time sufficient to form the crystalline form of sofosbuvir. A suitable time period is about 15 minutes to about 10 hours, or about 15 minutes to about 8 hours, or about 15 minutes to about 5 hours, or about 15 minutes to about 3 hours, or about 15 minutes to about 2 hours, or about 30 minutes to about 2 hours, or about 30 minutes to about 1.5 hours.

Step (a) may result in the formation of a suspension or a solution, depending on solvent and temperature.

Alternatively, step (a) may comprise combining a solution or suspension of sofosbuvir in a first solvent, with a solution of the co-crystal former in a second solvent which may be the same or different as the first solvent. Preferably, the first solvent is isopropanol, and the second solvent is methanol. Step (a) can comprise addition of the solution of the co-crystal former and second solvent to the solution or suspension of sofosbuvir in the first solvent, preferably wherein the addition is dropwise. The mixture may be allowed to stand, optionally with stirring, for a period of time sufficient to form the crystalline form of sofosbuvir. A suitable time period is about 15 minutes to about 10 hours, or about 15 minutes to about 8 hours, or about 15 minutes to about 5 hours, or about 15 minutes to about 3 hours, or about 15 minutes to about 2 hours, or about 30 minutes to about 2 hours, or about 30 minutes to about 1.5 hours.

Preferably in the processes of the present invention, step (a) is carried out at ambient temperature or at a temperature of about 10°C to about 50°C, or about 15°C to about 40°C, or about 18°C to about 30°C, or about 18°C to about 25°C.

The sofosbuvir and co-crystal former are preferably combined in a molar ratio of sofosbuvir : co-crystal former of about 1:1 to about 1: 1.5, or about 1:1 to about 1:1.2, or about 1:1 to about 1.15, or about 1:1 to about 1:1.1, or about 1:1. Preferably the co-crystal former is added in a slight excess (e.g. about 1.1) relative to sofosbuvir in order to ensure complete conversion of the sofosbuvir starting material to form a co-crystal.

The solvent can be added in a wt/vol ratio of sofosbuvir and co-crystal former to solvent is about 0.1 g per ml to about 10 g per ml, or about 0.1 g per ml to about 5 g per ml, or about 0.1 g per ml to about 2 g per ml, or about 0.1 g per ml to about 1 g per ml, or about 0.1 g per ml to about 0.5 g per ml.

The sofosbuvir starting material in step (a) can be in any suitable crystalline form, but is preferably selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7. Crystalline Form 1 is particularly preferred. It will, however, be appreciated

that if the solvent(s) employed in step (a) can dissolve the sofosbuvir starting material, the solid state form of the sofosbuvir starting material is immaterial. In such a case, any solid state form of sofosbuvir can be used. In other embodiments, when the sofosbuvir is not completely soluble in the solvent(s) employed in step (a), it is preferred that the solid state form of the sofosbuvir is selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7, and preferably crystalline Form 1.

After reaction, the crystalline form of sofosbuvir (co-crystals) may be isolated by filtration, and optionally dried, preferably under reduced pressure. The drying may be carried at an ambient temperature, or may be at a temperature of about 18°C to about 30°C, about 20°C to about 25°C, or at room temperature.

In an alternative embodiment, crystalline sofosbuvir of the present invention may be prepared by combining sofosbuvir with a co-crystal former to form a mixture, and grinding the mixture, optionally in the presence of a wetting agent. The starting material can be selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7, preferably crystalline Form 1.

The grinding may be conducted in a ball mill, optionally in the presence of a wetting agent.

The wetting agent can comprise an organic solvent, such as aliphatic ethers, cyclic ethers, ketones, alcohols and esters, preferably C_{4-8} dialkyl ether, C_{1-3} alkyl-substituted C_{4-8} cyclic ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-4} alkyl ester of C_{1-6} alcohol, more preferably C_{4-6} alkyl ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-3} alkyl ester of C_{1-6} alcohol.

The wetting agent may particularly comprise a C_{1-6} alcohol or a C_{1-4} alkyl ester of C_{1-6} alcohol, such as one or more of the group consisting of: methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, ethyl acetate, n-propylacetate, n-butylacetate and iso-butylacetate, particularly methanol, ethanol, n-propanol, isopropanol, ethyl acetate, and n-propylacetate.

The wetting agent preferably comprises at least one C_{1-6} aliphatic alcohol, preferably methanol, ethanol, n-propanol and isopropanol.

The sofosbuvir starting material for the grinding process may be selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7 of sofosbuvir. Preferably the starting material is sofosbuvir Form 1. Suitable co-crystal formers include amino acids, particularly α-amino acids, and more particularly an amino acid selected from the group

consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine. Of these, alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine, are particularly preferred. Most preferred are α-amino acids selected from proline and substituted prolines, particularly those selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline. The amino acids preferably have L-configuration, and is preferably L-proline.

The present invention further provides crystalline form of sofosbuvir crystalline prepared by the above described processes.

The process may further comprise combining the crystalline form of sofosbuvir with one or more pharmaceutically acceptable excipients to form a pharmaceutical composition thereof.

Depending on which other solid state forms comparison is made with, the crystalline forms of sofosbuvir according to the present invention, including those prepared according to any embodiment of the present invention, may have advantageous properties selected from at least one of the following: chemical purity, flowability, solubility, dissolution rate, morphology or crystal habit, stability, such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion and/or storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density. Particularly, the crystalline forms of sofosbuvir of the present invention have good solubility, dissolution and/or polymorphic stability characteristics.

The present invention furthermore relates to pharmaceutical preparations comprising a co-crystal of sofosbuvir according to the present invention. The pharmaceutical preparation of the present invention is preferably an oral solid preparation, such as a capsule or tablet.

The pharmaceutical preparation can additionally contain one or more pharmaceutically acceptable excipients, such as fillers, binder, glidants, disintegrants, flow regulating agents and release agents. Suitable excipients are for example disclosed in “Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete”, published by H.P. Fielder, 4th Edition and

"Handbook of Pharmaceutical Excipients", 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

Suitable fillers are for example: mannitol, microcrystalline cellulose, lactose and calcium hydrogen phosphate. Fillers can be present in an amount of 0-80% by weight, preferably in an amount of 10-60% by weight of the total weight of the composition.

Suitable binders are for example: microcrystalline cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, sugars like lactose, dextran, cornstarch. Binders can be present in an amount of 0-80% by weight, preferably in an amount of 10-60% by weight of the total weight of the composition.

Suitable glidants are for example: alkaline earth metal salts of fatty acids, like stearic acid. The glidant can be present for example in an amount of 0-2% by weight, preferably in an amount of 0.5-1.5% by weight of the total weight of the composition.

Suitable disintegrants are for example: croscarmellose sodium, sodium carboxymethyl starch, crosslinked polyvinylpyrrolidone (crospovidone), sodium carboxymethylglycolate (such as Explotab) and sodium bicarbonate. The disintegrant can be present in an amount of 0-20% by weight, preferably in an amount of 1-15% by weight of the total weight of the composition.

A suitable flow regulating agent is for example colloidal silica. The flow regulating agent can be present in an amount of 0-8% by weight, preferably in an amount of 0.1-3% by weight of the total weight of the composition.

A suitable release agent is for example talcum. The release agent can be present in an amount of 0-5% by weight, preferably in an amount of 0.5-3% by weight of the total weight of the composition.

The solid preparation, preferably a tablet or a capsule can be coated, preferably film coated.

Suitable coating agents are for example: cellulose derivatives, polyvinyl alcohol, poly(meth)acrylate, polyvinyl pyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers such as carrageenan.

The pharmaceutical preparation and/or the coating may additionally contain a colorant. Suitable colorants are compatible with the ingredients of the pharmaceutical composition. Suitable colorants are for example titanium dioxide (E171) or yellow iron oxide (E172).

The pharmaceutical preparation of the present invention can be prepared by methods well known to a person skilled in the art.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way.

Examples

Reference examples:

Reference Example A. Sofosbuvir Form 1 starting material

Form I sofosbuvir was prepared by crystallisation of sofosbuvir from dichloromethane according to the method described in B. S. Ross, P. G. Reddy, H.-R. Zhang, S. Rachakonda, M. J. Sofia, J. Org. Chem. 2011, 76, 8311 (page 8311). Crystalline form 1 of sofosbuvir is disclosed in US 2011/0251152 or WO2011/123645. The Form 1 sofosbuvir is characterised by XRPD peaks at approximately 5.0, 7.3, 9.4, 18.1 ± 0.2 degrees 2-theta. Form 1 may be further characterised by additional XRPD peaks at approximately 8.8, 10.0, 11.4, 15.0 and 22.3 degrees 2-theta ± 0.2 degrees 2-theta.

Reference Example B. Sofosbuvir Form 7 (seed crystals)

(i) Small amounts of Form 7 sofosbuvir, which were used as seed crystals, were prepared in the following way: Form 1 of sofosbuvir (200 mg) was stored as a powder in an

open glass vial at 40ºC / 75% relative humidity. After storage for 8 weeks at 40ºC / 75% relative humidity, Form 7 was obtained as a colourless solid in quantitative yield.

(ii) Form 7 was prepared by heating Form 1 of sofosbuvir (1.04 g) in deionized water (40 mL) at 50°C for 2 hours with stirring. Partial dissolution occurred and the remaining solid changed into a sticky mass. No crystallization was observed. Approximately 10 mg of Form 7 [obtained from (i)] was added and the mixture was cooled to room temperature. Crystallization of Form 7 occurred during storage overnight. A small amount of sticky mass remaining on the stirring bar, which was removed mechanically. Crystalline Form 7 was isolated by filtration and dried in an evacuated desiccator over silica gel.

Reference Example C. Sofosbuvir Form 7

Water-saturated methyl tert-butyl ether (MTBE) was prepared by vigorous stirring (500 rpm) of MTBE with deionized water in a volume ratio of 10 : 1 for 30 minutes at room temperature and subsequent phase separation to remove the aqueous layer. The organic phase was prepared freshly before use. Alternatively, the organic phase may be stored in a sealed container at ambient temperature.

Sofosbuvir (50 g) was dissolved almost completely in water-saturated MTBE (800 ml) (prepared as described above) at room temperature. The solution was filtered through a folded filter. Seed crystals of sofosbuvir Form 7 (150 mg) were added and the solution was stored for two days in a closed flask at room temperature without stirring. The formed crystals (Form 7) were isolated by filtration, washed with a small amount of MTBE, and dried at room temperature under vacuum (2 mbar) overnight. The yield was 23.9 g. The mother liquor was concentrated to a volume of 350 ml on a rotary evaporator and then stored for two days in a closed flask at room temperature without stirring. During this time, the initially separated oil crystallised. The formed solid (Form 7) was then isolated by filtration, washed with a small amount of MTBE, and dried at room temperature under vacuum (2 mbar) overnight. The weight of the solid (Form 7) was 15.7 g. Hence the combined yield of Form 7 was 39.7 g (79%).

Reference Example D. Sofosbuvir Form 6, small scale)

Sofosbuvir (2 g) was dissolved almost completely in water-saturated MTBE (30 ml) (prepared as described above) at room temperature. The solution was filtered through a folded filter and was magnetically stirred (400 rpm) for 12 h in a closed flask at room temperature. The

formed crystals (consisting of Form 6) were isolated by filtration, washed with a small amount of MTBE, and dried at room temperature under vacuum (2 mbar) overnight. The yield was 1.2 g (60%).

Reference Example E. Sofosbuvir Form 6

Sofosbuvir (40 g) was dissolved almost completely in water-saturated MTBE (600 ml) at room temperature. The solution was filtered through a folded filter. Seed crystals of sofosbuvir Form 6 (100 mg, obtained from Example 2) were added and the solution was mechanically stirred (300 rpm) for 12 h in a closed flask at room temperature. The formed crystals (Form 6) were isolated by filtration, washed with a small amount of MTBE, and dried at room temperature under vacuum (2 mbar) overnight. The yield was 29.6 g (74%).

EXAMPLE 1: Preparation of a sofosbuvir co-crystal by solvent-drop grinding

A. A mixture of sofosbuvir form 1 (127.6 mg) (Reference Example A) and co-crystal former, L-proline (29.3 mg) [corresponding to a molar ratio of about 1:1 (1:1.05)], was subjected to grinding in a ball mill (Mikro-dismembrator II/ B Braun 853162/4). The mixture was subjected to 15 min of grinding with a 50% of power, 3 (3mm) porcelain balls and 50 µL of methanol as wetting agent.

XRPD analysis confirmed the presence of a crystalline form of sofosbuvir comprising a co-crystal of sofosbuvir with L-proline.

B. Example 1A was repeated with sofosbuvir Form 6 (124.3 mg) (Reference Example D or Reference Example E) and L-proline (27.4 mg). XRPD analysis again confirmed the presence of a crystalline form of sofosbuvir comprising a co-crystal of sofosbuvir with L-proline.

C. Example 1A was repeated with sofosbuvir Form 7 (126.4 mg) (Reference Example B or Reference Example C) and L-proline (26.7 mg). XRPD analysis again confirmed the presence of a crystalline form of sofosbuvir comprising a co-crystal of sofosbuvir with L-proline.

The crystalline form of sofosbuvir from Examples 1A, 1B and 1C are identical.

EXAMPLE 2: Preparation of a sofosbuvir co-crystal by crystallisation

A. Form 1 of sofosbuvir (329 mg; 0.62 mmol) (Example 1) and L-proline (71 mg; 0.62 mmol) were suspended in 1 mL of ethanol, 2-propanol or ethyl acetate at room temperature (RT). After 1 hour sofosbuvir:L-proline (1:1) co-crystal crystallized in a quantitative yield. The product was dried in an evacuated dessicator at room temperature (RT) for 2 hours.

B. Form 1 of Sofosbuvir (1.00 g; 1.9 mmol) (Example 1) was dissolved in 5 mL of 2-propanol at RT. Separately L-proline (0.24 g; 2.1 mmol) was dissolved in 4 mL of methanol at RT. L-proline solution was added dropwise to the sofosbuvir solution. After 1 hour it crystallized as a colourless solid. Sofosbuvir:L-proline (1:1) co-crystal was isolated by filtration and dried in an evacuated dessiccator at RT for 2 hours. Yield: 47%.

EXAMPLE 3: Analytical Methods

A. ^{1}H-NMR Spectroscopy

Instrument: Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz. As solvent, MeOH-d4 was used.

B. X-ray powder diffraction (XRPD)

Samples were measured on a D8 Advance powder X-ray diffractometer (Bruker AXS, Karlsruhe, Germany) in a rotating PMMA sample holder (diameter: 25 mm; depth: 1 mm) in reflection mode (Bragg-Brentano geometry). Conditions of the measurements are summarized in the table below. Raw data were analyzed with the program EVA (Bruker AXS, Karlsruhe, Germany).

Radiation	Cu Kα_1/α_2 (weighted median of the wavelengths of 1.54187 Å)
source	34 kV / 40 mA
detector	Vantec-1 (electronic window: 3°)
Kβ filter	Ni (diffracted beam)
measuring circle diameter	435 mm

detector window slit	12 mm
anti-scatter slit (diffracted beam)	8 mm
divergence slit	v6.00 (variable)
Soller slit (incident /diffracted beam)	2.5°
2θ range	2° ≤ 2θ ≤ 55°
step size	0.016
step time	0.2 s

C. Differential Scanning Calorimetry (DSC)

The samples were placed in sealed aluminum crucibles (40 µL) with perforated lids (one hole in the centre, made by puncturing with a cannula of 0.6 mm diameter). The measured DSC curves are displayed as a function of the program temperature (proportional to the measurement time). Characteristic temperature values of DSC signals (onset / endset temperature, peak maximum) are determined from the sample temperature, which may deviate from the program temperature. Signals with positive area correspond to endothermic events. Conditions of the measurements are summarized in the table below.

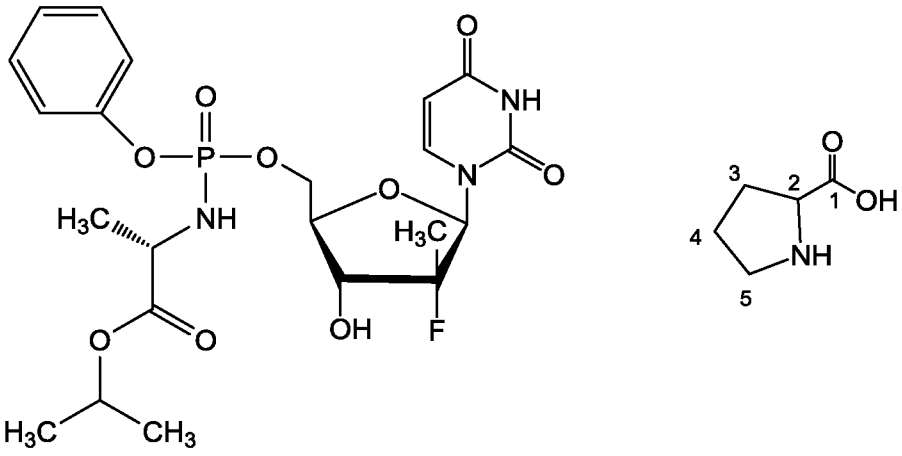
Instrument:	Mettler-Toledo DSC 822E (Mettler-Toledo GmbH, Gießen, Germany)
Aluminium crucible:	40 µL (with perforated lid)
Lid:	perforated
Temperature range:	25°C to 350°C
Heating rate:	10°C/min
Nitrogen flush:	50 mL/min
Software:	STARe Version 11.0
Interpretation:	Endothermic mode

D. Solid State ^{13}C NMR

All ^{13}C CP/MAS (cross polarization.magic angle spinning with dipolar decoupling) NMR spectra were measured at 125 MHz using Bruker Avance III HD 500 WB/US NMR spectrometer (Karlsruhe, Germany, 2013) at magic angle spinning (MAS) frequency $\omega_r/2\pi$ = 11 kHz. In all cases finely powdered samples were placed into 4mm ZrO_2 rotors and standard "cp" pulse-program was used. During acquisition of the data a high-power dipolar decoupling SPINAL-64

was applied. The applied nutation frequency of $B_1(^1H)$ field was $\omega_1/2\pi$ = 89.3 kHz. The nutation frequency of $B_1(^{13}C)$ and $B_1(^1H)$ fields during cross-polarization was $\omega_1/2\pi$ = 62.5 kHz. Repetition delay for the measurement of ^{13}C CP/MAS NMR spectra of **(*S*)-proline** and **Sofosbuvir-(*S*)-proline cocrystal** was 240 and 12 s, and the number of scans was 32 and 1024, respectively. The ^{13}C scale was calibrated with glycine as external standard (176.03 ppm – low-field carbonyl signal).

The NMR spectrometer was completely calibrated and all experimental parameters were carefully optimized prior the investigation. Magic angle was set using KBr during standard optimization procedure and homogeneity of magnetic field was optimized using adamantane sample (resulting line-width at half-height $\Delta\nu_{1/2}$ was less than 3.5 Hz at 250 ms of acquisition time). Taking into account frictional heating of the samples during fast rotation all NMR experiments were performed at 305 K (precise temperature calibration was performed).



The SS ^{13}C NMR spectra are shown in Figure 10.

E. Analytical Results

Identification of Sofosbuvir:L-Proline (1:1)

(I) ^{1}H-NMR Spectroscopy

The ^{1}H-NMR spectrum is shown in Figure 9. The signals are summarized below (*= signals of L-proline):

δ ppm 1.21 (d, J=6.26 Hz, 6 H) 1.31 - 1.38 (m, 6 H) 1.95 - 2.00 (m, 2 H*) 2.08 - 2.14 (m, 1 H*) 2.26 - 2.32 (m, 1 H*) 3.20 - 3.24 (m, 1 H*) 3.35 - 3.40 (m, 1 H*) 3.89 - 3.98 (m, 2 H, 1 H*) 4.08 - 4.12 (m, 1 H) 4.38 (ddd, J=11.83, 6.16, 3.52 Hz, 1 H) 4.49 - 4.54 (m, 1 H) 4.93 - 4.99 (m, 1 H) 5.62 (d, J=8.21 Hz, 1 H) 6.14 (br s, 1 H) 7.18 - 7.22 (m, 1 H) 7.24 - 7.28 (m, 2 H) 7.35 - 7.39 (m, 2 H) 7.62 (d, J=8.21 Hz, 1 H)

The integration values of the signal at 1.97 ppm, corresponding to 2H of L-proline, and the signal at 1.21 ppm, corresponding to 6H (isopropyl) of sofosbuvir, were 2 and 6 respectively, demonstrating a 1:1 molar ratio of sofosbuvir : L-proline.

(II) X-Ray Powder Diffraction

The x-ray powder diffractogram of sofosbuir:L-proline (1:1) co-crystal is shown in Figure 7, a peak list is given in Figure 6.

The crystalline form may be characterised by peaks at, for example, 5.8°, 9.0°, 11.7°, 13.8°, and 16.8° (2-theta) ± 0.2° (2-theta), and optionally peaks at 7.3°, 9.5°, 10.7°, 12.5°, and 14.7° (2-theta) ± 0.2° (2-theta).

(III) Differential Scanning Calorimetry

The Differential Scanning Calorimetry (DSC) of sofosbuir:L-proline (1:1) co-crystal is shown in Figure 8. DSC showed a higher melting point (174 °C) than other stable known forms from sofosbuvir (Form 1: 99 °C; Form 6: 125 °C and Form 7: 130 °C).

(VI) Solid-State ^{13}C NMR Spectra

(a) Pure (S)-Proline

Pure (S)-proline sample is characterized by the ^{13}C CP/MAS NMR spectrum in which each carbon atom is reflected by the narrow symmetrical line with the linewidth less than 40 Hz (Figure 10, upper spectrum). Optimization of the repetition delay for the measurement of ^{13}C CP/MAS NMR spectrum resulted in the value of 240 s indicating rigidity of the molecular segments of (S)-proline compound. The integral intensity of the signals and their count indicates that the crystal unit consists of a single symmetry independent molecule of (S)-proline. No phase impurities were detected.

(b) Sofosbuvir-(S)-Proline cocrystal

In the ^{13}C CP/MAS NMR spectrum of sofosbuvir-(S)-proline cocrystal sample prepared according to the examples (Figure 10, lower spectrum), all expected carbon resonances were detected. In majority the detected signals are narrow, basically symmetrical single lines indicating uniform molecular arrangment of the system. Splitting of the CF signal at 101 ppm results from ^{19}F-^{13}C spin-spin coupling (200 Hz), whereas broadening of the signals at 131 and 120 ppm reflects residual dyamics (flips) of phenyl ring.

Comparison of the spectra of both systems reveled considerable diferencies in ^{13}C CP/MAS NMR resonance frequencies of (S)-proline molecules. These differences, that reach up to 2.7 ppm for C3 (*S*-Proline) carbon atom, indicate that proline molecule in the sofosbuvir-(S)-proline system takes different arrangement than in the basic crystal form. Moreover, as followed form the optimization procedure of the repetition delay, $T_1(^1H)$ spin-lattice relaxation time of proline molecule is considerably shorter in the sofosbuvir-(*S*)-proline system. This phenomenon can be explained by the close direct contact between the molecules of proline and sofosbuvir. If the molecules of both constituents are intimately mixed together and sufficiently close the ^1H-^1H dipolar interactions are active and allow fast ^1H magnetization transfer and exchange. This process results in equilibration of ^1H magnetization behavior. Consequently, phenyl flips or other segmental motions of sofosbuvir become dominant relaxation mechanism also for ^1H spins of proline molecules.

Altogether, these findings indicate formation of cocrystalline structure in the sofosbuvir-(*S*)-proline sample. As indicated by the signal intensities and number of resonance frequencies the basic crystal unit consists of a single symmetry independent molecule of proline and a single symmetry independent molecule of sofosbuvir. The molecular ratio of sofosbuvir : (S)-proline in this sample is 1:1.

EXAMPLE 4: Solubility/dissolution study

A. Test Solutions

Approx. 100 - 150 mg test substance was weighed into a glass vial, followed by addition of 4 mL the appropriate test medium. The test media were:

A. 0.01 M HCl(pH ≈ 2.2),
B. 20 mM sodium acetate / acetic acid (pH 4.5)
C 50 mM KH_2PO_4 (pH 6.8)
D solution of FaSSIF powder in buffer

The FaSSIF powder was obtained from Biorelevant (UK). The FaSSIF powder [i.e. a Fasted State Simulated Intestinal Fluid contains a complex of bile salt (sodium taurocholate) and phospholipid (lecithin) in a 4:1 molar ratio and physiologically relevant surfactants present in GI fluids]. The composition is as follows: – sodium taurochlorate, 3.0 mM; lecithin, 0.75 mM; sodium chloride 105.9 mM, sodium hydroxide 8.7 mM, monobasic sodium phosphate, 28.4 mM; pH 6.5; having pH 6.5, osmolarity 270 ± 10 mOsmol/kg and buffer capacity approx. 10 mEq/L/pH). The FASSIF solution was prepared as follows:

(i) Preparation of buffer:

The following were dissolved in 0.900 L of purified water: NaOH pellets (0.420 g), NaH_2PO_4 anhydrous (3.438 g) and NaCl (6.186 g). The pH was adjusted to 6.5 with either 1 N NaOH or 1 N HCl. The mixture was made up to 1.000 L with purified water at room temperature.

(ii) Preparation of FASSIF solution

To 0.5 L of the buffer from step (i) was added the FaSSIF powder (2.240 g). The mixture was stirred until the powder completely dissolved. The mixture was made up to 1.000 L with the buffer from step (i), at room temperature.

B. Solubility/Dissolution Study and Results

A stirring bar was added, the vial was fixed in a block heater at 37°C and the suspension was stirred with 250 rpm. After 15 min samples were withdrawn and filtered through a 0.2 µm PTFE filter. 100 µL of the clear filtrate were diluted with 900 µL acetonitrile / water mixture (1:1) and 1 µL thereof was analyzed by UHPLC/UV:

Instrument:	Agilent 1290	
Wavelength:	260 nm	
Column:	Phenomenex Kinetex XB - C18, 1.7 µm, 50 x 3 mm	
Column temp.:	40.0 °C	
Flow [mL / min]:	0.4	
Injection volume:	1 µL	
Solvent A:	water + 0.2% Formic acid + 0.1% HFBA (heptafluorobutyric acid)	
Solvent B:	acetonitrile	
Gradient:	time [min]	Solvent B [%]
	0.00	30.0
	7.00	70.0
	7.10	30.0
	10.00	30.0

The results are given in the following table (nd = not determined):

	Dissolution after 15 minutes (mg/ml ± 0.2 mg/ml)		
Test medium	Sofosbuvir:proline cocrystal	Form 6 sofosbuvir	Form 7 sofosbuvir
0,01M HCl	6.1	2.4	3.2
20mM NaOAc	6.2	2.3	3.1
50mM KH_2PO_4 pH 6.8	5.1	2.3	3.2
FaSSIF	4.9	2.2	nd

The above results show that cocrystals of the present invention have a superior dissolution at physiologically relevant conditions, when compared with prior art crystalline forms of sofosbuvir.

EXAMPLE 5: Stability study

300 mg aliquots of sofosbuvir:proline cocrystals were placed in screw cap glass vials which were stored with tightly closed cap and with open cap, respectively, in climate chambers at 25℃ / 60% RH, 30℃ / 65% RH, and 40℃ / 75% RH for 12 weeks. The samples were then analyzed by X-ray powder diffraction.

As shown in Figure 11, no changes were observed, irrespective of the storage conditions.

Various aspects and embodiments of the present invention are described in the following numbered paragraphs:

1. Crystalline form of sofosbuvir characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

2. Crystalline form of sofosbuvir according to Paragraph 1 characterised by an X-ray powder diffraction pattern having peaks at about 5.8 and 9.0 ± 0.2 degrees two theta.

3. Crystalline form of sofosbuvir according to Paragraph 2 characterised by an X-ray powder diffraction pattern having peaks at about 5.8 and 9.0 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

4. Crystalline form of sofosbuvir according to Paragraph 3 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 11.7 ± 0.2 degrees two theta.

5. Crystalline form of sofosbuvir according to Paragraph 3 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 13.8 ± 0.2 degrees two theta.

6. Crystalline form of sofosbuvir according to Paragraph 3 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 16.8 ± 0.2 degrees two theta.

7. Crystalline form of sofosbuvir according to Paragraph 1 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 11.7 ± 0.2 degrees two theta.

8. Crystalline form of sofosbuvir according to Paragraph 7 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 11.7 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 9.0, 13.8 and 16.8 ± 0.2 degrees two theta.

9. Crystalline form of sofosbuvir according to Paragraph 8 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 11.7 and 13.8 ± 0.2 degrees two theta.

10. Crystalline form of sofosbuvir according to Paragraph 8 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 11.7 and 16.8 ± 0.2 degrees two theta.

11. Crystalline form of sofosbuvir according to Paragraph 1 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 13.8 ± 0.2 degrees two theta.

12. Crystalline form of sofosbuvir according to Paragraph 11 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 13.8 ± 0.2 degrees two theta,

and one or more peaks selected from the group consisting of: about 9.0, 11.7 and 16.8 ± 0.2 degrees two theta.

13. Crystalline form of sofosbuvir according to Paragraph 12 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 13.8 and 16.8 ± 0.2 degrees two theta.

14. Crystalline form of sofosbuvir according to Paragraph 1 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 16.8 ± 0.2 degrees two theta.

15. Crystalline form of sofosbuvir according to Paragraph 14 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 16.8 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 9.0, 11.7 and 13.8 ± 0.2 degrees two theta.

16. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, characterised by an X-ray powder diffraction pattern having peaks at about 5.8, 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

17. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, further characterised by an X-ray powder diffraction pattern having one or more peaks selected from the group consisting of: about 7.3, 9.5, 10.7, 12.5 and 14.7 ± 0.2 degrees two theta.

18. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, further characterised by an X-ray powder diffraction pattern having a peak at 7.3 ± 0.2 degrees two theta.

19. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18, further characterised by an X-ray powder diffraction pattern having a peak at 9.5 ± 0.2 degrees two theta.

20. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19, further characterised by an X-ray powder diffraction pattern having a peak at 10.7 ± 0.2 degrees two theta.

21. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, further characterised by an X-ray powder diffraction pattern having a peak at 12.5 ± 0.2 degrees two theta.

22. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21, further characterised by an X-ray powder diffraction pattern having a peak at 14.7 ± 0.2 degrees two theta.

23. Crystalline form of sofosbuvir according to Paragraph 17, characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta.

24. Crystalline form of sofosbuvir according to Paragraph 23, characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and further characterised by one or more peaks at about 17.2, 17.4, 18.0, 18.3, 18.7, 19.2, 19.7, 19.9, 20.2, 20.9, 21.5, 22.1, 24.1, 24.5, 25.8, 27.0, 27.8, 28.7, 29.1, 29.7, 30.1, 31.5, 32.5, 33.3, 33.7, 34.2 and 35.0 ± 0.2 degrees two theta.

25. Crystalline form of sofosbuvir according to Paragraph 24, characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and further characterised by one or more peaks at about 17.4, 18.3, 19.9, 24.1 and 31.5 ± 0.2 degrees two theta.

26. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25, which is further characterised by an X-ray powder diffraction pattern having the peaks set out in Figure 6, first column, optionally with the corresponding intensity values in Figure 6, second column.

27. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or 26, which is further characterised by an X-ray powder diffraction pattern substantially as depicted in Figure 7.

28. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27, which is a co-crystal with at least one co-crystal former.

29. Crystalline form of sofosbuvir according to Paragraph 28, wherein the co-crystal former is at least one amino acid.

30. Crystalline form of sofosbuvir according to Paragraph 29, wherein the co-crystal former is at least one α-amino acid.

31. Crystalline form of sofosbuvir according to Paragraph 30, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine.

32. Crystalline form of sofosbuvir according to Paragraph 30, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine.

33. Crystalline form of sofosbuvir according to Paragraph 30, wherein the α-amino acid is selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline.

34. Crystalline form of sofosbuvir according to any of Paragraphs 29, 30, 31, 32 or 33, wherein the amino acid has L-configuration.

35. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 which is a co-crystal with proline.

36. Crystalline form of sofosbuvir according to Paragraph 35 which is a co-crystal with L-proline.

37. Crystalline form of sofosbuvir according to any of Paragraphs 28, 29, 30, 31, 32, 33, 34, 35 or 36, which comprises sofosbuvir and the co-crystal former in a 1:1 molar ratio.

38. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36 or 37, further characterised by having a melting point of about 170 to about 180ºC, preferably about 172-176ºC, and more preferably about 174ºC as measured by differential scanning calorimetry.

39. Crystalline form of sofosbuvir according to any of Paragraphs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37 or 38, further characterised by having a major endothermic peak having an onset at about 173.1ºC, and a minor endothermic peak having an onset at about 180.2ºC,

and/or wherein the crystalline form is further characterised by a DSC plot substantially as depicted in Figure 8.

40. Crystalline form of sofosbuvir which is a co-crystal with at least one co-crystal former.

41. Crystalline form of sofosbuvir according to Paragraph 40, wherein the co-crystal former is at least one amino acid.

42. Crystalline form of sofosbuvir according to Paragraph 40, wherein the co-crystal former is at least one α-amino acid.

43. Crystalline form of sofosbuvir according to Paragraph 42, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine.

44. Crystalline form of sofosbuvir according to Paragraph 42, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine.

45. Crystalline form of sofosbuvir according to Paragraph 42, wherein the α-amino acid is selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline.

46. Crystalline form of sofosbuvir according to any of Paragraphs 41, 42, 43, 44 or 45, wherein the amino acid has L-configuration.

47. Crystalline form of sofosbuvir which is a co-crystal with proline.

48. Crystalline form of sofosbuvir according to Paragraph 47 which is a co-crystal with L-proline.

49. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47 or 48, which comprises sofosbuvir and a co-crystal former in a 1:1 molar ratio.

50. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49, which is characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

51. Crystalline form of sofosbuvir according to Paragraph 50 characterised by an X-ray powder diffraction pattern having peaks at about 5.8 and 9.0 ± 0.2 degrees two theta.

52. Crystalline form of sofosbuvir according to Paragraph 51 characterised by an X-ray powder diffraction pattern having peaks at about 5.8 and 9.0 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

53. Crystalline form of sofosbuvir according to Paragraph 52 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 11.7 ± 0.2 degrees two theta.

54. Crystalline form of sofosbuvir according to Paragraph 52 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 13.8 ± 0.2 degrees two theta.

55. Crystalline form of sofosbuvir according to Paragraph 52 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 9.0 and 16.8 ± 0.2 degrees two theta.

56. Crystalline form of sofosbuvir according to Paragraph 50 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 11.7 ± 0.2 degrees two theta.

57. Crystalline form of sofosbuvir according to Paragraph 56 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 11.7 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 9.0, 13.8 and 16.8 ± 0.2 degrees two theta.

58. Crystalline form of sofosbuvir according to Paragraph 57 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 11.7 and 13.8 ± 0.2 degrees two theta.

59. Crystalline form of sofosbuvir according to Paragraph 57 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 11.7 and 16.8 ± 0.2 degrees two theta.

60. Crystalline form of sofosbuvir according to Paragraph 50 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 13.8 ± 0.2 degrees two theta.

61. Crystalline form of sofosbuvir according to Paragraph 60 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 13.8 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 9.0, 11.7 and 16.8 ± 0.2 degrees two theta.

62. Crystalline form of sofosbuvir according to Paragraph 61 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8, 13.8 and 16.8 ± 0.2 degrees two theta.

63. Crystalline form of sofosbuvir according to Paragraph 50 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 16.8 ± 0.2 degrees two theta.

64. Crystalline form of sofosbuvir according to Paragraph 63 characterised by an X-ray powder diffraction pattern having peaks at about: 5.8 and 16.8 ± 0.2 degrees two theta, and one or more peaks selected from the group consisting of: about 9.0, 11.7 and 13.8 ± 0.2 degrees two theta.

65. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 characterised by an X-ray powder diffraction pattern having peaks at about 5.8, 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

66. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64 or 65, further characterised by an X-ray powder diffraction pattern having one or more peaks selected from the group consisting of: about 7.3, 9.5, 10.7, 12.5 and 14.7 ± 0.2 degrees two theta.

67. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65 or 66, further characterised by an X-ray powder diffraction pattern having a peak at 7.3 ± 0.2 degrees two theta.

68. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66 or 67, further characterised by an X-ray powder diffraction pattern having a peak at 9.5 ± 0.2 degrees two theta.

69. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67 or 68, further characterised by an X-ray powder diffraction pattern having a peak at 10.7 ± 0.2 degrees two theta.

70. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68 or 69, further characterised by an X-ray powder diffraction pattern having a peak at 12.5 ± 0.2 degrees two theta.

71. Crystalline form of sofosbuvir according to any of Paragraphs 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70, further characterised by an X-ray powder diffraction pattern having a peak at 14.7 ± 0.2 degrees two theta.

72. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49, characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta.

73. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49, characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and further characterised by one or more peaks at about 17.2, 17.4, 18.0, 18.3, 18.7, 19.2, 19.7, 19.9, 20.2, 20.9, 21.5, 22.1, 24.1, 24.5, 25.8, 27.0, 27.8, 28.7, 29.1, 29.7, 30.1, 31.5, 32.5, 33.3, 33.7, 34.2 and 35.0 ± 0.2 degrees two theta.

74. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 characterised by an X-ray powder diffraction pattern having peaks at: about 5.8, 7.3, 9.0, 9.5, 10.7, 11.7, 12.5, 13.8, 14.7 and 16.8 ± 0.2 degrees two theta, and further characterised by one or more peaks at about 17.4, 18.3, 19.9, 24.1 and 31.5 ± 0.2 degrees two theta.

75. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73 or 74 characterised by having a melting point of about 170 to about 180ºC, preferably about 172-176ºC, and more preferably about 174ºC as measured by differential scanning calorimetry.

76. Crystalline form of sofosbuvir according to any of Paragraphs 40, 41, 42, 43, 44, 45, 46, 47 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75, characterised by having a major endothermic peak having an onset at about 173.1ºC, and a minor endothermic peak having an onset at about 180.2ºC.

77. Crystalline form of sofosbuvir according to any of Paragraphs 1-39, or Paragraphs 40-76, having a dissolution after 15 minutes at 37℃ of any one of (A), (B) or (C):

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2,

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, or

(C) at least about 4.0 mg/ml, and preferably at least about 4.5 mg/ml, and more preferably at least about 4.8 mg/ml in 50 mM potassium dihydrogen phosphate at pH 6.8.

78. Crystalline form of sofosbuvir according to Paragraph 77, having a dissolution profile after 15 minutes at 37°C of:

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2, and

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5.

79. Crystalline form of sofosbuvir according to any of Paragraphs 77 or 78, having a dissolution profile after 15 minutes at 37°C of:

(A) at least about 5.5 mg/ml, and preferably at least about 6.0 mg/ml, in 0.01 M HCl at pH 2.2,

(B) at least about 5.8 mg/ml, and preferably at least about 6.0 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, and

(C) at least about 4.0 mg/ml, and preferably at least about 4.5 mg/ml, and more preferably at least about 4.8 mg/ml in 50 mM potassium dihydrogen phosphate at pH 6.8.

80. Crystalline form of sofosbuvir according to any of Paragraphs 1-39, or Paragraphs 40-76 having a dissolution after 15 minutes at 37°C of any one of (A), (B) or (C):

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2,

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, or

(C) about 4.0 to about 5.5 mg/ml, and preferably about 4.5 to about 5.3 mg/ml, and more preferably about 4.8 to about 5.3 mg/ml in 50 mM potassium dihydrogen phosphate at pH 6.8.

81. Crystalline form of sofosbuvir according to Paragraph 80, having a dissolution profile after 15 minutes at 37°C of:

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2, and

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5.

82. Crystalline form of sofosbuvir according to Paragraph 81, having a dissolution profile after 15 minutes at 37°C of:

(A) about 5.5 to about 6.5 mg/ml, and preferably about 5.8 to about 6.2 mg/ml, in 0.01 M HCl at pH 2.2,

(B) about 5.8 to about 6.5 mg/ml, and preferably about 6.0 to about 6.3 mg/ml, in 20 mM sodium acetate / acetic acid at pH 4.5, and

(C) about 4.0 to about 5.5 mg/ml, and preferably about 4.5 to about 5.3 mg/ml, and more preferably about 4.8 to about 5.3 mg/ml, in 50 mM potassium dihydrogen phosphate at pH 6.8.

83. Crystalline form of sofosbuvir according to any of Paragraphs 1-76, or Paragraphs 77-82 which is solvated.

84. Crystalline form of sofosbuvir according to any of Paragraphs 1-76, or Paragraphs 77-83 which is non-solvated.

85. Crystalline form of sofosbuvir according to any preceding paragraph, which is substantially free of any other crystalline forms of sofosbuvir, preferably wherein the crystalline form is substantially free of sofosbuvir Form 1, or wherein the crystalline form is substantially free of sofosbuvir Form 6, or wherein the crystalline form is substantially free of Form 7, and more preferably, wherein the crystalline form is substantially free of sofosbuvir Forms 1, 6 and 7.

86. Crystalline form of sofosbuvir according to any of Paragraphs 1-85, wherein the sofosbuvir is in the form of pharmaceutically acceptable addition salt.

87. Crystalline form of sofosbuvir according to Paragraph 86, wherein the pharmaceutically acceptable addition salt is an acid addition salt, preferably with an inorganic acid (preferably hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid) or with an organic acid (preferably glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, fumaric acid, tartaric acid, citric acid, and mandelic acid).

88. Use of a crystalline form of sofosbuvir as defined in any of Paragraphs 1-87 for the preparation of a pharmaceutical composition.

89. A composition comprising a crystalline form of sofosbuvir as defined in any preceding paragraph, preferably wherein the composition is a pharmaceutical composition.

90. A pharmaceutical composition according to Paragraph 89 comprising a crystalline form of sofosbuvir as defined in any preceding paragraph, and at least one pharmaceutically acceptable excipient.

91. A pharmaceutical composition according to Paragraph 90 the form of a solid.

92. Crystalline form of sofosbuvir as defined in any of Paragraphs 1-87 for use as a medicament.

93. Crystalline form of sofosbuvir as defined in any of Paragraphs 1-87 for use in the treatment of Hepatitis C.

94. A method of treating a subject suffering from Hepatitis C, comprising administering a therapeutically effective amount of the crystalline form of sofosbuvir as defined in any of Paragraphs 1-87, or a pharmaceutical composition thereof as defined Paragraph 89, 90 or 91.

95. A process for preparing a crystalline form of sofosbuvir comprising combining sofosbuvir with a co-crystal former.

96. A process according to Paragraph 95 comprising:

(a) combining sofosbuvir with a co-crystal former in a solvent or a mixture of solvents to form a mixture,

(b) optionally isolating the crystalline form of sofosbuvir, and

(c) optionally drying the crystalline form of sofosbuvir.

97. A process according to Paragraph 96, wherein the solvent comprises an organic solvent.

98. A process according to Paragraph 97, wherein the organic solvent is selected from the group consisting of: aliphatic ethers, cyclic ethers, ketones, alcohols and esters.

99. A process according to Paragraph 98, wherein the organic solvent is selected from the group consisting of: C_{4-8} dialkyl ether, C_{1-3} alkyl-substituted C_{4-8} cyclic ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-4} alkyl ester of C_{1-6} alcohol.

100. A process according to Paragraph 99, wherein the organic solvent is selected from the group consisting of: C_{4-6} alkyl ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-3} alkyl ester of C_{1-6} alcohol.

101. A process according to Paragraph 100, wherein the organic solvent is a C_{1-6} alcohol or a C_{1-4} alkyl ester of C_{1-6} alcohol.

102. A process according to Paragraph 101, wherein the organic solvent is selected from one or more of the group consisting of: methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, ethyl acetate, n-propylacetate, n-butylacetate and iso-butylacetate.

103. A process according to Paragraph 102, wherein the organic solvent is selected from one or more of the group consisting of methanol, ethanol, n-propanol, isopropanol, ethyl acetate, and n-propylacetate.

104. A process according to Paragraph 103, wherein the organic solvent is selected from the group consisting of methanol, ethanol, isopropanol and ethyl acetate.

105. A process according to Paragraph 96, wherein the solvent is selected from one of: ethanol, isopropanol, ethyl acetate, or wherein the solvent is a mixture of methanol and isopropanol.

106. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104 or 105, wherein step (a) comprises mixing, in any order, sofosbuvir and a co-crystal former with the solvent or solvents.

107. A process according to Paragraph 106, wherein the solvent is selected from one of ethanol, isopropanol or ethyl acetate.

108. A process according to Paragraph 106 or Paragraph 107, wherein step (a) further comprises allowing the mixture to stand, optionally with stirring, for a period of time sufficient to form the crystalline form of sofosbuvir.

109. A process according to any of Paragraphs 106, 107 or 108, wherein the mixture in step (a) is allowed to stand for about 15 minutes to about 10 hours, or about 15 minutes to about 8 hours, or about 15 minutes to about 5 hours, or about 15 minutes to about 3 hours, or about 15 minutes to about 2 hours, or about 30 minutes to about 2 hours, or about 30 minutes to about 1.5 hours.

110. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104 or 105, wherein step (a) comprises combining a solution or suspension of sofosbuvir in a first solvent, with a solution of the co-crystal former in a second solvent which may be the same or different as the first solvent.

111. A process according to Paragraph 110, wherein the first solvent is isopropanol, and the second solvent is methanol.

112. A process according to Paragraph 110 or Paragraph 111, wherein step (a) comprises addition of the solution of the co-crystal former and second solvent to the solution or suspension of sofosbuvir in the first solvent, preferably wherein the addition is dropwise.

113. A process according to any of Paragraphs 110, 111 or 112, wherein step (a) further comprises allowing the mixture to stand, optionally with stirring, for a period of time sufficient to form the crystalline form of sofosbuvir.

114. A process according to Paragraph 113, wherein the mixture in step (a) is allowed to stand for about 15 minutes to about 10 hours, or about 15 minutes to about 8 hours, or about 15 minutes to about 5 hours, or about 15 minutes to about 3 hours, or about 15 minutes to about 2 hours, or about 30 minutes to about 2 hours, or about 30 minutes to about 1.5 hours.

115. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113 or 114, wherein step (a) is carried out at ambient temperature.

116. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113 or 114, wherein step (a) is carried out at a temperature of about 10°C to about 50°C, or about 15°C to about 40°C, or about 18°C to about 30°C, or about 18°C to about 25°C.

117. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 or 116, wherein the sofosbuvir and co-

crystal former are combined in a molar ratio of sofosbuvir : co-crystal former of about 1:1 to about 1: 1.5, or about 1:1 to about 1:1.2, or about 1:1 to about 1.15, or about 1:1 to about 1:1.1, or about 1:1.

118. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116 or 117, wherein the wt/vol ratio of sofosbuvir and co-crystal former to solvent is about 0.1 g per ml to about 10 g per ml, or about 0.1 g per ml to about 5 g per ml, or about 0.1 g per ml to about 2 g per ml, or about 0.1 g per ml to about 1 g per ml, or about 0.1 g per ml to about 0.5 g per ml.

119. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117 or 118, wherein when the sofosbuvir is not completely soluble in the solvent(s), the sofosbuvir starting material in step (a) is selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7.

120. A process according to Paragraph 119, wherein the sofosbuvir starting material in step (a) is crystalline Form 1.

121. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119 or 120, wherein the crystalline form of sofosbuvir is isolated by filtration, or by evaporation.

122. A process according to any of Paragraphs 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120 or 121, wherein after isolating the sofosbuvir crystalline form, the product is dried, preferably under reduced pressure.

123. A process according to Paragraph 122, wherein the product is dried at ambient temperature.

124. A process according to Paragraph 122, wherein the product is dried at a temperature of about 18℃ to about 30℃, about 20℃ to about 25℃, or at room temperature.

125. A process according to Paragraph 95, comprising combining sofosbuvir with a co-crystal former to form a mixture, and grinding the mixture, optionally in the presence of a wetting agent, preferably wherein the grinding is in a ball mill.

126. A process according to Paragraph 125 wherein the sofosbuvir starting material is selected from the group consisting of crystalline Form 1, crystalline Form 6 or crystalline Form 7.

127. A process according to Paragraph 126, wherein the sofosbuvir starting material is crystalline Form 1.

128. A process according to any of Paragraphs 125, 126 or 127, wherein the grinding is in the presence of a wetting agent.

129. A process according to Paragraph 128, wherein the wetting agent comprises an organic solvent.

130. A process according to Paragraph 129, wherein the organic solvent is selected from the group consisting of: aliphatic ethers, cyclic ethers, ketones, alcohols and esters.

131. A process according to Paragraph 130, wherein the organic solvent is selected from the group consisting of: C_{4-8} dialkyl ether, C_{1-3} alkyl-substituted C_{4-8} cyclic ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-4} alkyl ester of C_{1-6} alcohol.

132. A process according to Paragraph 131, wherein the organic solvent is selected from the group consisting of: C_{4-6} alkyl ether, C_{3-6} ketone, C_{1-6} aliphatic alcohol and C_{1-3} alkyl ester of C_{1-6} alcohol.

133. A process according to Paragraph 132, wherein the organic solvent is a C_{1-6} alcohol or a C_{1-4} alkyl ester of C_{1-6} alcohol.

134. A process according to Paragraph 133, wherein the organic solvent is selected from one or more of the group consisting of: methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, ethyl acetate, n-propylacetate, n-butylacetate and iso-butylacetate.

135. A process according to Paragraph 134, wherein the organic solvent is selected from one or more of the group consisting of methanol, ethanol, n-propanol, isopropanol, ethyl acetate, and n-propylacetate.

136. A process according to Paragraph 135, wherein the organic solvent comprises at least one C_{1-6} aliphatic alcohol.

137. A process according to Paragraph 136, wherein the organic solvent is selected from the group consisting of methanol, ethanol, n-propanol and isopropanol.

138. A process according to any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122,

123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136 or 137, wherein the co-crystal former is an amino acid.

139. A process according to Paragraph 138, wherein the co-crystal former is an α-amino acid.

140. A process according to Paragraph 139, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine.

141. A process according to Paragraph 140, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine.

142. A process according to Paragraph 141, wherein the α-amino acid is selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline.

143. A process according to any of Paragraphs 138, 139, 140, 141 or 142, wherein the amino acid has L-configuration.

144. A process according to any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142 or 143, wherein the co-crystal former is proline.

145. A process according to Paragraph 144, wherein the co-crystal former is L-proline.

146. A process according to any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, or 145, wherein the crystalline form of sofosbuvir is as defined in any of Paragraphs 1 to 87.

147. Crystalline form of sofosbuvir crystalline prepared by the process of any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145 or 146.

148. A process according to any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145 or 146, further comprising combining the crystalline form of sofosbuvir with one or more pharmaceutically acceptable excipients to form a pharmaceutical composition thereof.

149. A pharmaceutical composition comprising the crystalline form of sofosbuvir prepared by the process of any of Paragraphs 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145 or 146.

150. A crystalline form of sofosbuvir according to any of Paragraphs 1-87 or Paragraph 147, with the proviso that the crystalline form is not: a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.2, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta, or a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about: 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.24, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta..

151. A crystalline form of sofosbuvir according to any of Paragraphs 1-87 or Paragraph 147, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about: 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.2, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 ± 0.2 degrees two theta, and further having peaks at about: 7.2, 8.9, 9.7, 13.9, 14.6, 16.6, 18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and 38.0 degrees 2-theta ± 0.2 degrees two theta.

152. A crystalline form of sofosbuvir according to any of Paragraphs 1-87 or Paragraph 147, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.24, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta and further peaks at about: 7.2, 8.9, 9.7, 13.7, 14.6, 16.6,

18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and 38.0 degrees 2-theta ± 0.2 degrees two theta.

153. A crystalline form of sofosbuvir according to any of Paragraphs 1-87 or Paragraph 147, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern as defined in any of Claims 150-152 and further having a differential scanning calorimetry (DSC) having an endothermic event at about 177.2°C and an exothermic event at 244.3°C.

154. Use of a crystalline form of sofosbuvir as defined in any of Paragraphs 150-153, for the preparation of a pharmaceutical composition.

155. A composition comprising a crystalline form of sofosbuvir as defined in any of Paragraphs 150-153, preferably wherein the composition is a pharmaceutical composition.

156. A pharmaceutical composition according to Paragraph 155 comprising a crystalline form of sofosbuvir as defined in any of Paragraphs 150-153, and at least one pharmaceutically acceptable excipient.

157. A pharmaceutical composition according to Paragraph 156 in the form of a solid.

158. Crystalline form of sofosbuvir as defined in any of Paragraphs 150-153 for use as a medicament.

159. Crystalline form of sofosbuvir as defined in any of Paragraphs 150-153 for use in the treatment of Hepatitis C.

160. A method of treating a subject suffering from Hepatitis C, comprising administering a therapeutically effective amount of the crystalline form of sofosbuvir as defined in any of Paragraphs 150-153, or a pharmaceutical composition thereof as defined in any of Paragraphs 155, 156 or 157.

CLAIMS

1. Crystalline form of sofosbuvir, which is a co-crystal with at least one co-crystal former.

2. Crystalline form of sofosbuvir according to Claim 1, wherein the co-crystal former is at least one amino acid, preferably wherein the co-crystal former is at least one α-amino acid, and more preferably wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, arginine, asparagine, aspartic acid, benzyl proline, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan, tyrosine and valine.

3. Crystalline form of sofosbuvir according to Claim 2, wherein the α-amino acid is selected from the group consisting of: alanine, amino proline, benzyl proline, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, lysine, methionine, methyl proline, phenyl alanine, proline, serine, threonine, tryptophan and tyrosine, preferably wherein the α-amino acid is selected from the group consisting of: amino proline, benzyl proline, hydroxyproline, methyl proline, and proline.

4. Crystalline form of sofosbuvir according to any of Claims 1-3, wherein the amino acid has L-configuration.

5. Crystalline form of sofosbuvir according to any of Claims 1-4 which is a co-crystal with proline.

6. Crystalline form of sofosbuvir according to Claim 5 which is a co-crystal with L-proline.

7. Crystalline form of sofosbuvir according to any of Claims 1-6, which comprises sofosbuvir and the co-crystal former in a 1:1 molar ratio.

8. Crystalline form of sofosbuvir according to any of Claims 1-7, further characterised by having a melting point of about 170 to about 180ºC, preferably about 172-176ºC, and more preferably about 174ºC as measured by differential scanning calorimetry.

9. Crystalline form of sofosbuvir according to any of Claims 1-8, which is characterised by an X-ray powder diffraction pattern having a peak at about 5.8 ± 0.2 degrees two theta, and at least one peak selected from the group consisting of: about 9.0, 11.7, 13.8 and 16.8 ± 0.2 degrees two theta.

10. A crystalline form of sofosbuvir according to any of Claims 1-9, with the proviso that the crystalline form is not: a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.2, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta or a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about: 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.24, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta.

11. A crystalline form of sofosbuvir according to any of Claims 1-9, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about: 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.2, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 ± 0.2 degrees two theta, and further having peaks at about: 7.2, 8.9, 9.7, 13.9, 14.6, 16.6, 18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and 38.0 degrees 2-theta ± 0.2 degrees two theta.

12. A crystalline form of sofosbuvir according to any of Claims 1-9, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern having peaks at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.24, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9 degrees 2-theta ± 0.2 degrees two theta and further peaks at about: 7.2, 8.9, 9.7, 13.7, 14.6, 16.6, 18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and 38.0 degrees 2-theta ± 0.2 degrees two theta.

13. A crystalline form of sofosbuvir according to any of Claims 1-9, with the proviso that the crystalline form is not a co-crystal of sofosbuvir and L-proline having a powder X-ray diffraction pattern as defined in any of Claims 10-12 and further having a differential scanning calorimetry (DSC) having an endothermic event at about 177.2°C and an exothermic event at 244.3°C.

14. A composition comprising a crystalline form of sofosbuvir as defined in any of Claims 1-9 or Claims 10-13, preferably wherein the composition is a pharmaceutical composition.

15. A pharmaceutical composition according to Claim 14 comprising a crystalline form of sofosbuvir as defined in any of Claims 1-9 or Claims 10-13, and at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutical composition is in solid form.

16. Crystalline form of sofosbuvir as defined in any of Claims 1-9 or Claims 10-13, or a composition according to Claim 14 or Claim 15, for use as a medicament, preferably for the treatment of Hepatitis C.

17. A process for preparing a crystalline form of sofosbuvir comprising combining sofosbuvir with a co-crystal former.

18. A process according to Claim 17 comprising:

(a) combining sofosbuvir with a co-crystal former in a solvent or a mixture of solvents to form a mixture,

(b) optionally isolating the crystalline form of sofosbuvir, and

(c) optionally drying the crystalline form of sofosbuvir.

19. A process according to Claim 18 comprising combining sofosbuvir with a co-crystal former to form a mixture, and grinding the mixture, optionally in the presence of a wetting agent, preferably wherein the grinding is in a ball mill.

20. A process according to any of Claims 17-19, wherein the co-crystal former is L-proline.

21. A process according to any of Claims 17, 18, 19 or 20, further comprising combining the crystalline form of sofosbuvir with one or more pharmaceutically acceptable excipients to form a pharmaceutical composition thereof.

22. A method of treating a subject suffering from Hepatitis C, comprising administering a therapeutically effective amount of the crystalline form of sofosbuvir as defined in any of Claims 1-9 or Claims 10-13, or a pharmaceutical composition thereof as defined in Claim 14 or Claim 15.

Figure 1 – X-Ray Powder diffraction listings for Form 1 of sofosbuvir

Angle [° 2-theta ± 0.2° 2-theta]	Relative Intensity
4.1	1%
4.8	8%
5.0	100%
7.3	60%
7.8	2%
8.2	5%
8.8	5%
9.4	15%
10.0	8%
11.4	3%
11.6	1%
12.4	1%
13.2	2%
14.2	4%
14.7	1%
15.0	4%
15.1	1%
16.1	5%
16.4	10%
16.5	10%
16.8	1%
17.3	14%
17.6	6%
18.1	24%
18.4	6%
18.7	10%
18.9	5%
19.3	7%
19.5	2%
20.2	6%
20.5	10%
20.7	3%
21.2	1%
21.8	5%
22.0	11%
22.3	9%
22.8	2%
23.2	5%
23.3	6%
23.5	5%
23.7	6%
24.0	3%
24.7	3%
25.0	12%
25.5	2%
26.5	4%
27.1	4%
27.1	4%
27.2	3%
27.4	2%
28.1	3%
28.5	1%
28.9	2%
29.3	1%
30.0	2%
30.5	1%
31.0	2%
31.5	2%

Figure 2: X-ray powder diffractogram of Form 1 of sofosbuvir

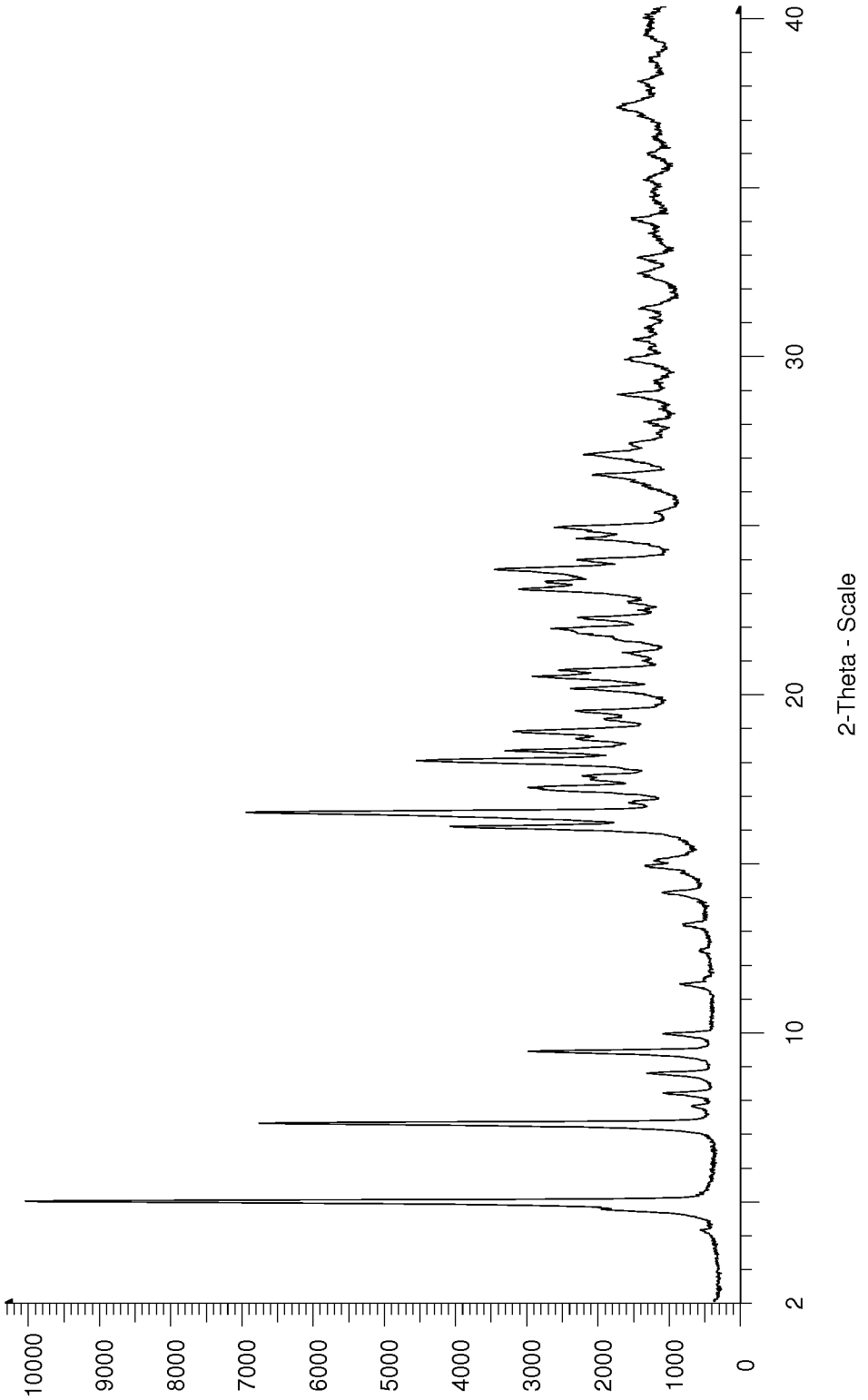


Figure 3: X-ray powder diffractogram of Form 6 of sofosbuvir

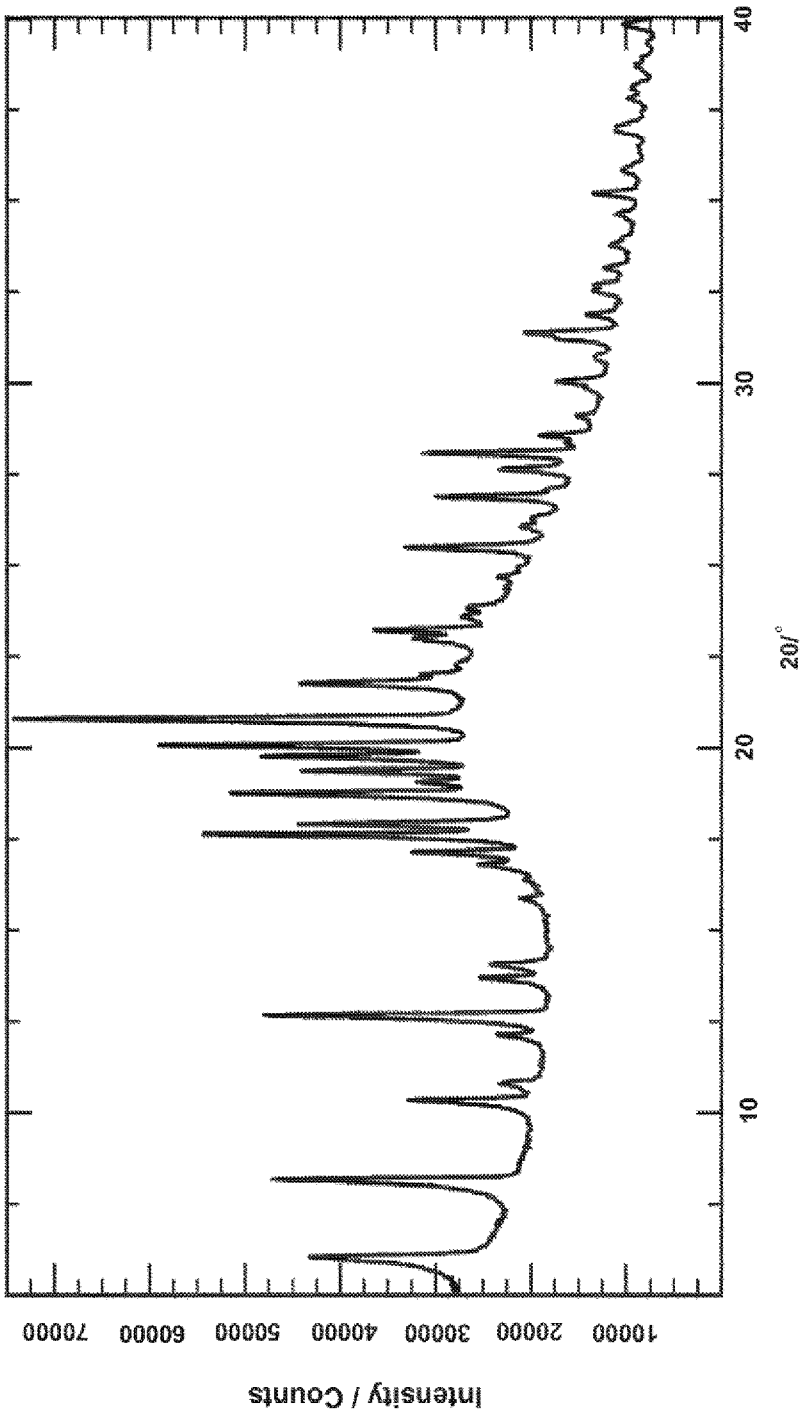


Figure 4 – X-Ray Powder diffraction listings for Form 7 sofosbuvir

Angle [° 2-theta ± 0.2° 2-theta]	Relative Intensity
6.2	0.5%
8.1	56%
10.4	26%
12.1	11%
12.4	100%
13.5	16%
16.2	13%
16.8	28%
17.2	41%
18.0	8%
18.7	24%
19.4	75%
20.0	55%
20.9	37%
21.4	5%
21.8	3%
22.0	8%
23.1	5%
23.3	15%
23.6	12%
24.4	6%
24.9	14%
25.3	18%
25.5	10%
27.2	20%
28.0	15%
28.1	11%
28.6	8%
29.0	5%
29.6	7%
31.3	12%
32.0	6%
32.3	7%
32.8	6%
33.1	6%
33.4	5%
34.7	4%
35.1	6%
35.9	1%
36.8	4%
37.2	3%
37.9	8%
38.2	5%
39.2	6%
39.4	6%
40.6	4%
41.0	6%
42.0	4%
42.4	6%
43.6	2%
44.5	6%
44.8	4%

Figure 5: X-Ray Powder diffractogram of Form 7 of sofosbuvir

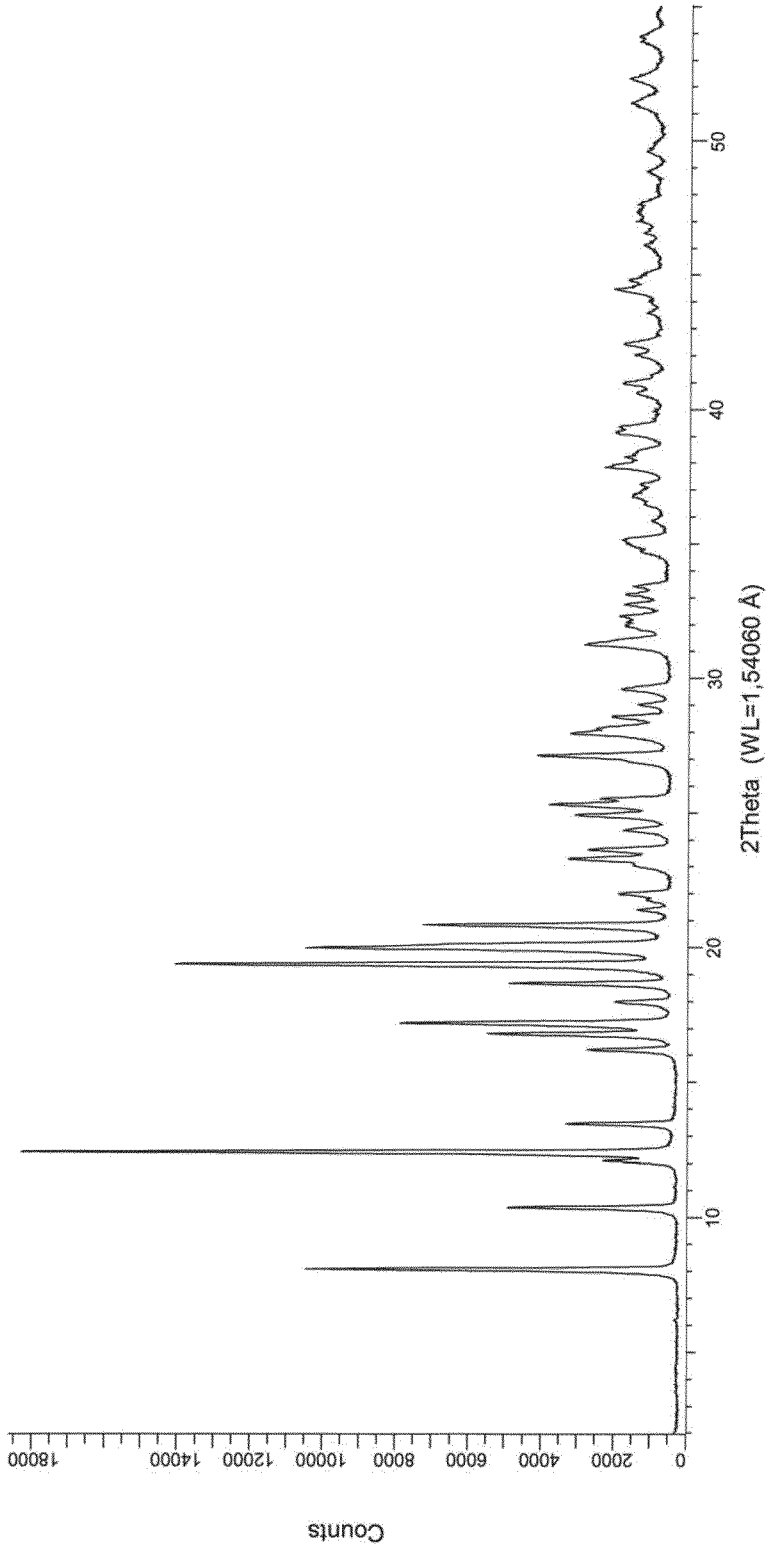


Figure 6: Powder diffraction peaks of sofosbuvir:L-proline (1:1) co-crystal

Angle° (2-theta ± 0.2 degrees 2-theta)	Relative Intensity %
5.8	100
7.3	10
9.0	10
9.5	33
10.7	25
11.7	29
12.5	20
13.8	10
14.7	19
16.8	13
17.2	17
17.4	19
18.0	37
18.3	19
18.7	21
19.2	15
19.7	13
19.9	11
20.2	13
20.9	93
21.5	10
22.1	22
24.1	39
24.5	7
25.8	5
27.0	14
27.8	3
28.7	4
29.1	3
29.7	8
30.1	8
31.5	10
32.5	3
33.3	6
33.7	5
34.2	7
35.0	7
36.6	9
38.1	2
39.1	6
39.8	4
41.0	2
42.2	4
43.4	6

Figure 7: X-ray powder diffractogram of sofosbuvir:L-proline (1:1) co-crystal

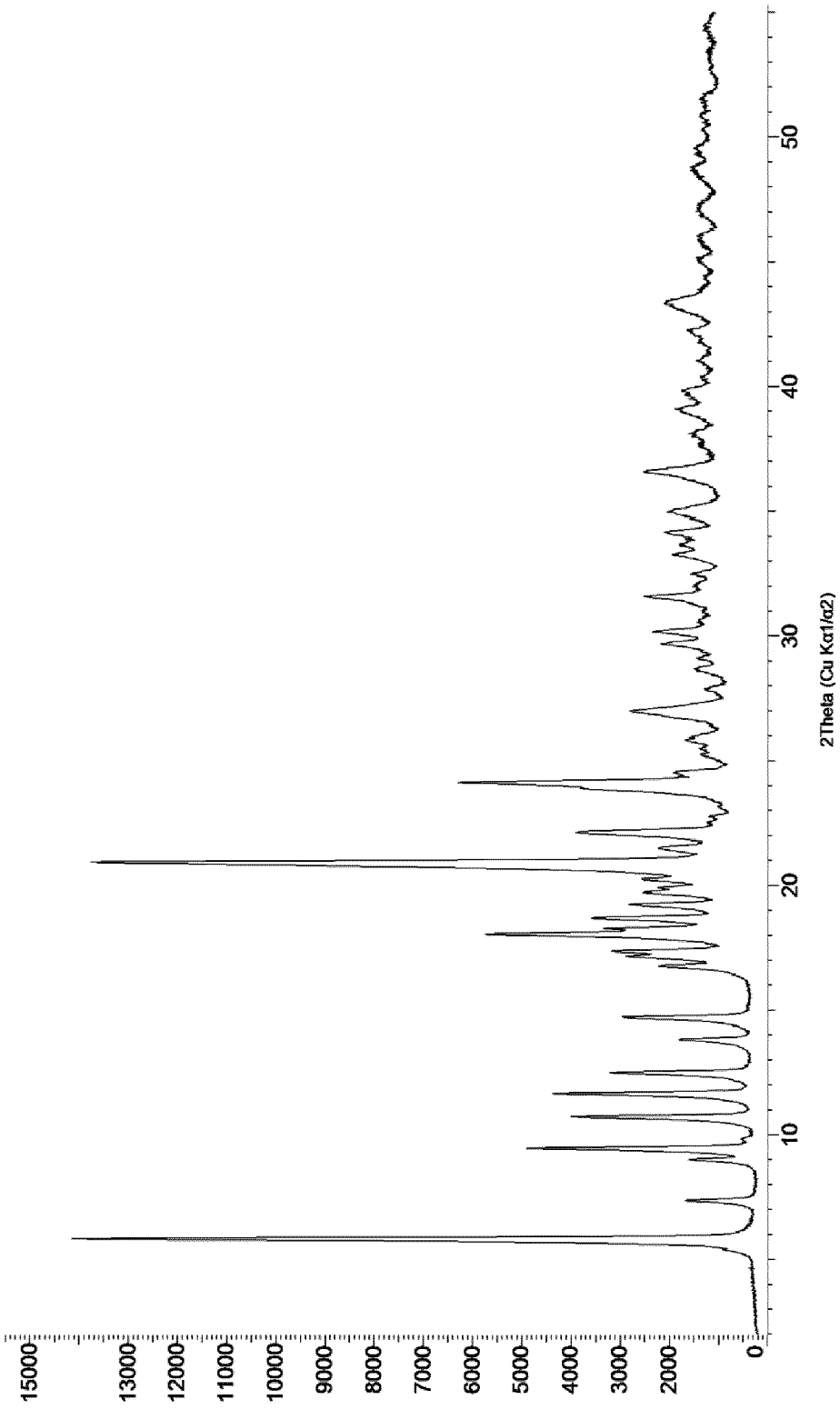


Figure 8: Differential Scanning Calorimetry plot of sofosbuvir:L-proline (1:1) co-crystal

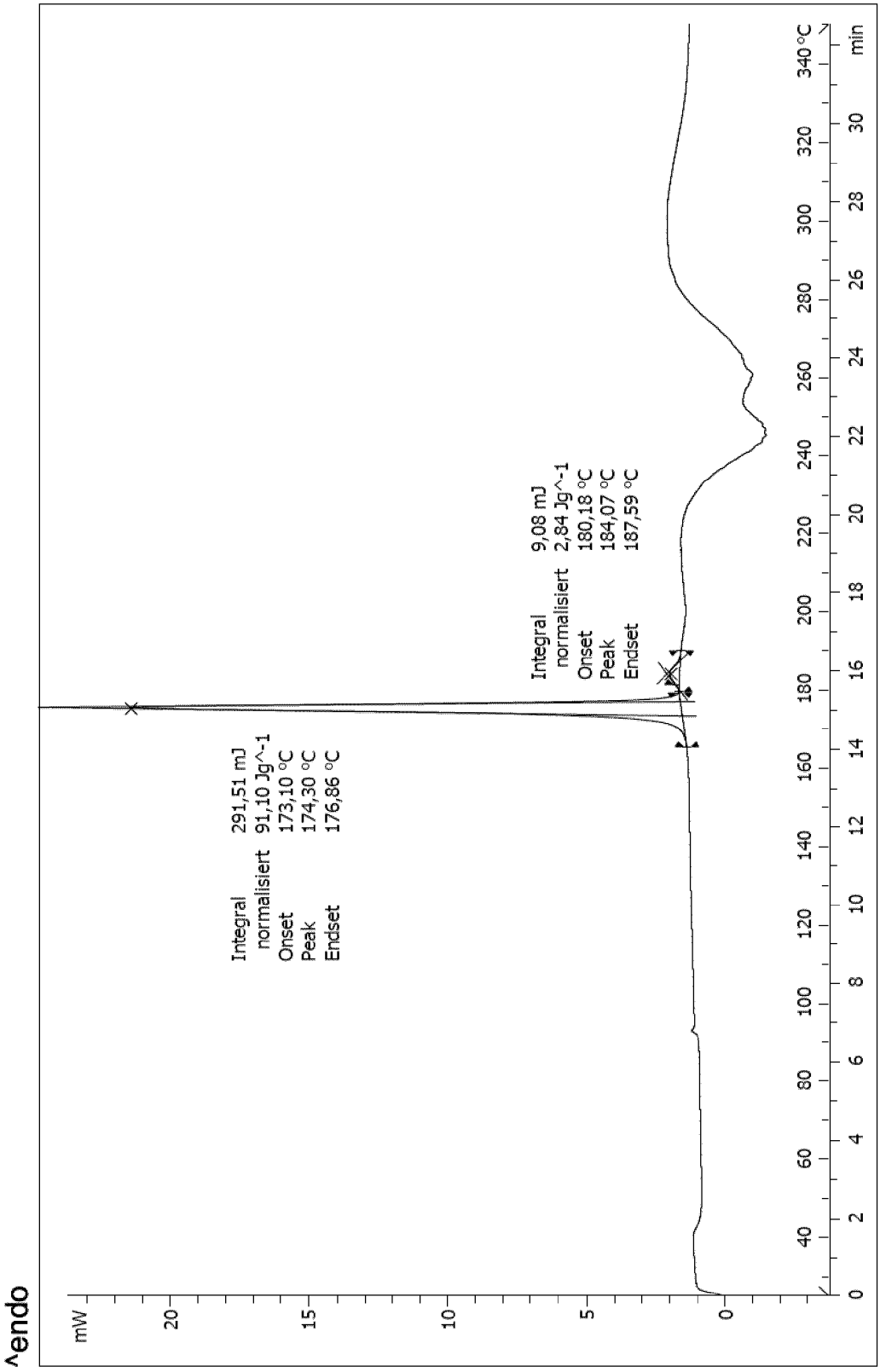
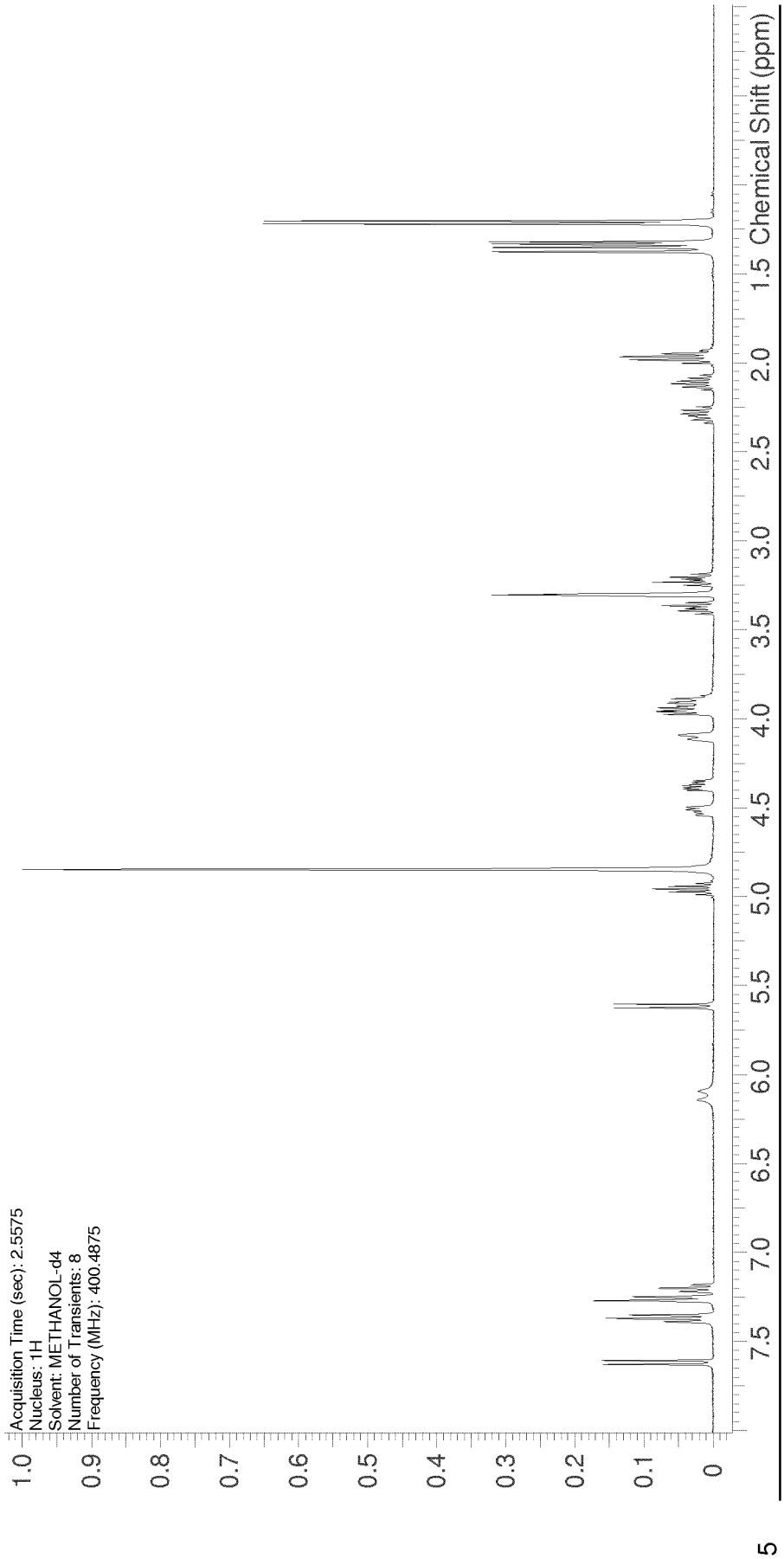


Figure 9: ^{1}H-NMR-spectrum of sofosbuvir:L-proline (1:1) co-crystal



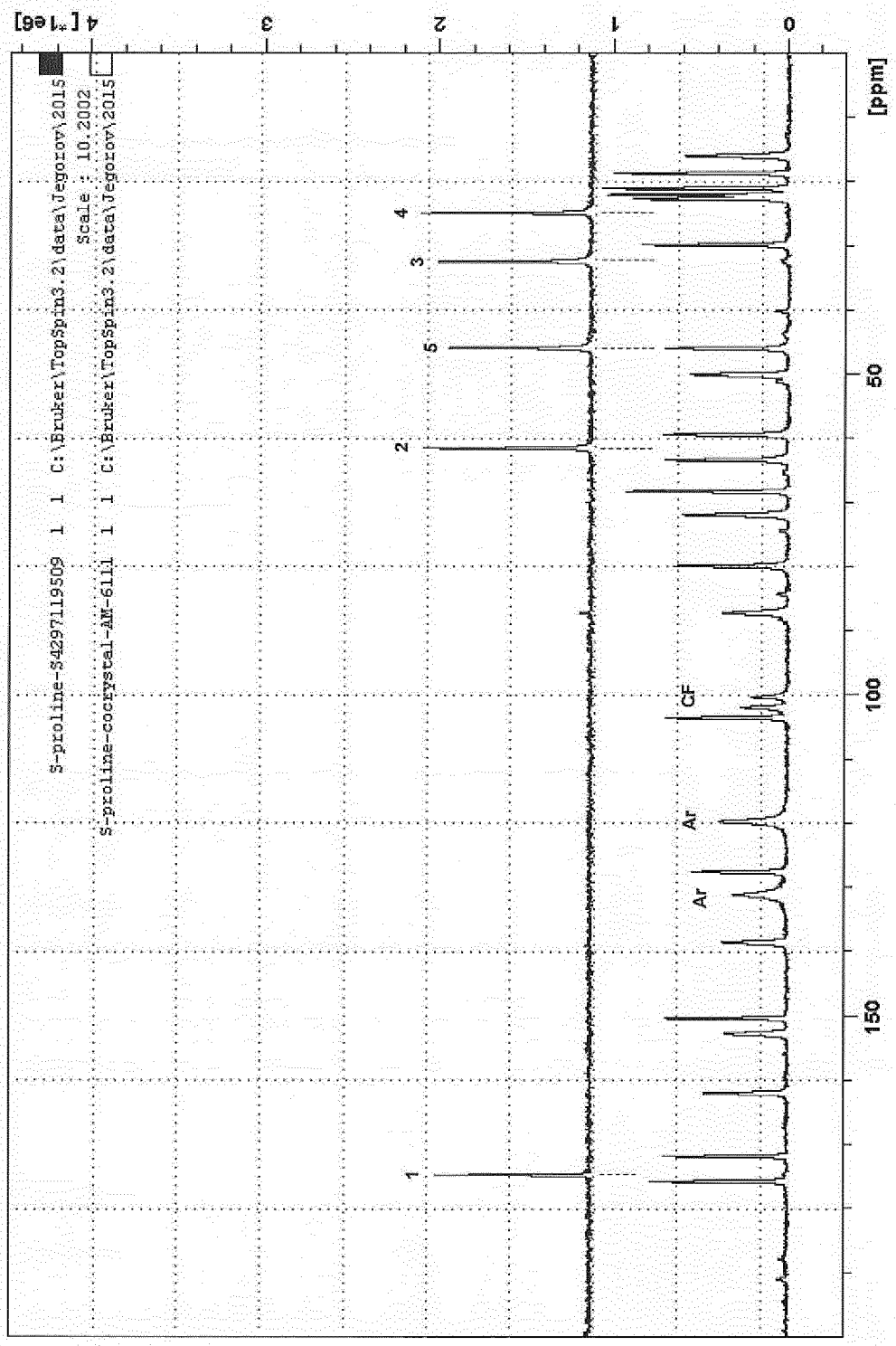
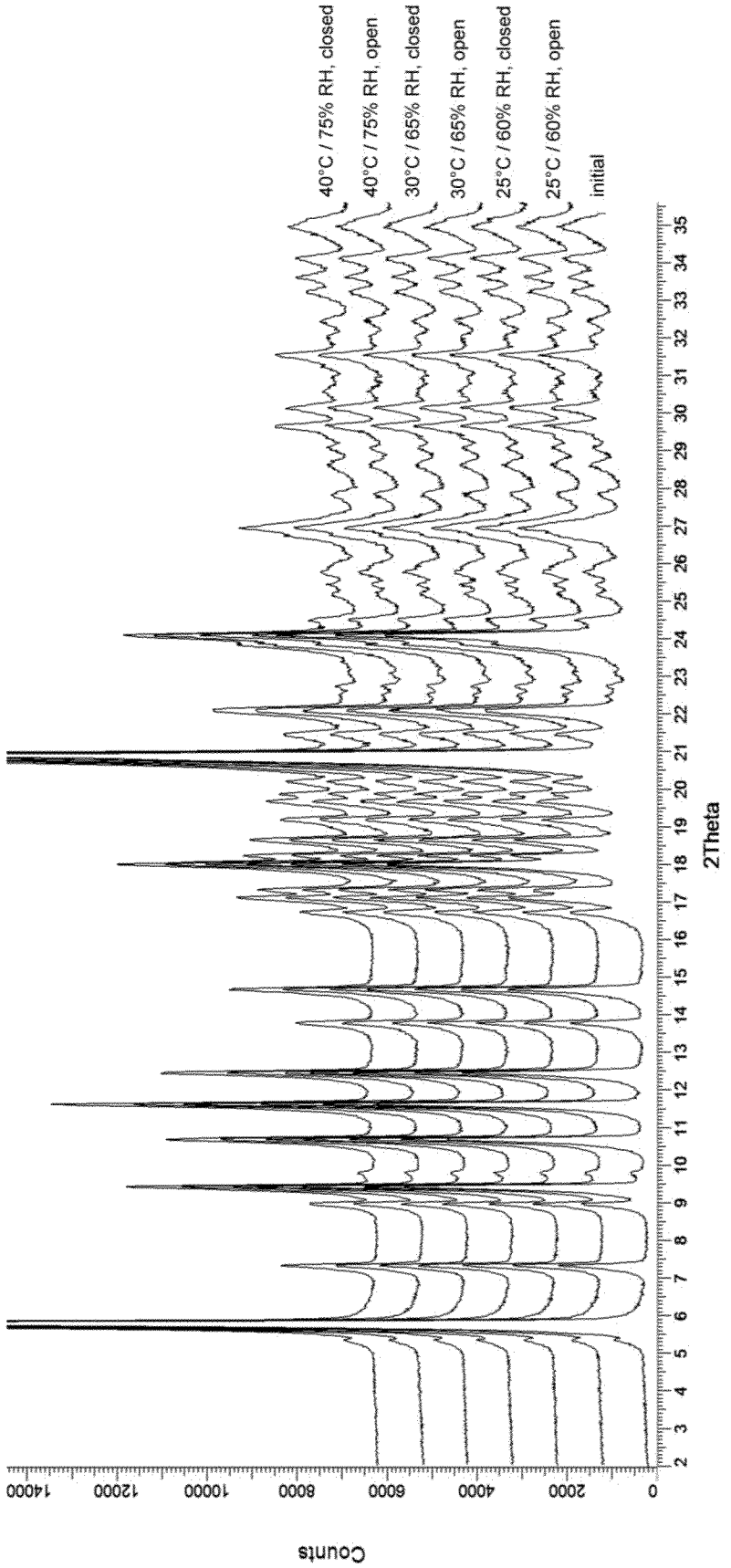


Figure 10: ^{13}C SS NMR Spectra of Pure (S)-Proline (upper spectrum) and Sofosbuvir-(S)-Proline cocrystal (lower spectrum)

Figure 11: XRPD of sofosbuvir:proline cocrystal samples from stability studies



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/069749

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07H19/10 C07D207/16 C07H1/00 A61K31/7072 A61P31/14
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)
C07H 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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 2015/175646 A1 (CASTEEL MELISSA JEAN [US] ET AL) 25 June 2015 (2015-06-25) Claims, examples 1-4 and figures 1-10	1-22
Y	CN 104 130 302 A (GUANGDONG HEC PHARMACEUTICAL) 5 November 2014 (2014-11-05) cited in the application Claims, examples and Figure 1	1-22

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 October 2016	14/10/2016

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

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	CN 104 804 054 A (CHARM PHARMATECH NANJING CO LTD) 29 July 2015 (2015-07-29) Claims, examples and Figures 1-7	1-22
Y	MICHAEL J. SOFIA ET AL: "Discovery of a beta-D-2'-Deoxy-2'-alpha-fluoro-2'-beta-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus", JOURNAL OF MEDICINAL CHEMISTRY, vol. 53, no. 19, 16 September 2010 (2010-09-16), pages 7202-7218, XP055004442, ISSN: 0022-2623, DOI: 10.1021/jm100863x Compound 51 its preparation and characterization	1-22
Y	YADAV A V ET AL: "Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients", INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, MEDKNOW PUBLICATIONS PVT LTD, IN , vol. 71, no. 4 1 July 2009 (2009-07-01), pages 359-370, XP002635211, ISSN: 0250-474X, DOI: 10.4103/0250-474X.57283 Retrieved from the Internet: URL:http://www.ijpsonline.com/printarticle.asp?issn=0250-474X [retrieved on 2011-05-03] Whole document, in particular Abstract, 4th paragraph on page 360 and 3rd and 4th paragraphs on page 361.	1-22
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Y,P	Claims 13-14 and example 25	2-6,20

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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