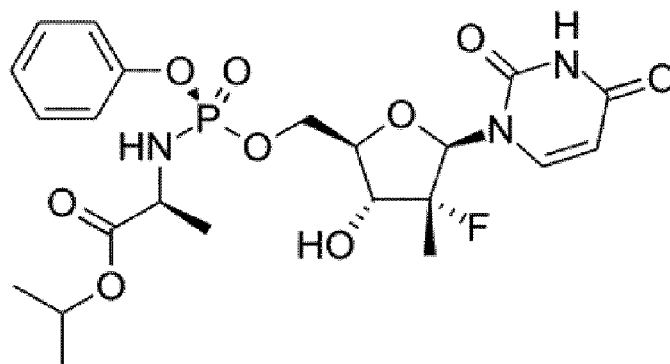




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(54) **Title:** A PROCESS FOR PREPARING A CRYSTALLINE FORM OF SOFOSBUVIR



(I)

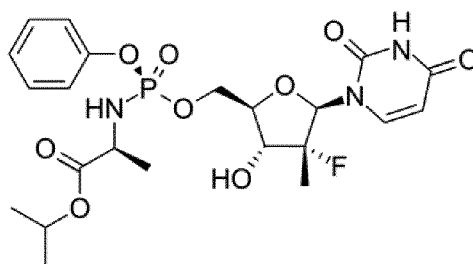
(57) **Abstract:** A process for preparing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, comprising (i) providing sofosbuvir in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms; (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having from 4 to 8 carbon atoms and optionally at least one aprotic non-ketonic organic solvent; (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir in its mother liquor. Further a composition comprising a solid crystalline form 7 and at least one ketone having from 4 to 8 carbon atoms as stabilizer is provided. Further a process for preparing said composition is provided. Further a process for preparing a solid crystalline form of sofosbuvir of formula having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° with a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent which does not comprise toluene is provided.

## A Process for Preparing a Crystalline Form of Sofosbuvir

The present invention relates to a process for preparing a solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, wherein the process comprises preparing a mixture comprising sofosbuvir and a solvent system comprising at least one ketone having from 4 to 8, preferably from 5 to 7 carbon atoms and optionally at least one aprotic non-ketonic organic solvent and subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions. The present invention also relates to the use of a ketone having from 4 to 8, preferably from 5 to 7 carbon atoms, optionally in combination with at least one aprotic non-ketonic organic solvent, for solvent mediated transformation of sofosbuvir. The present invention also relates to the use of a ketone having from 4 to 8, preferably from 5 to 7 carbon atoms, optionally in combination with at least one aprotic non-ketonic organic solvent, for stabilizing sofosbuvir crystalline form 7.

The present invention further relates to a process for preparing a solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, wherein the process comprises preparing a mixture comprising sofosbuvir and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent which does not comprise toluene and subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions. The present invention also relates to the use of a ketone having 9 carbon atoms, optionally in combination with at least one aprotic non-ketonic organic solvent which does not comprise toluene, for solvent mediated transformation of sofosbuvir.

Sofosbuvir according to formula (I)



(I)

with IUPAC name (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-amino)propanoate is a drug inhibiting the RNA polymerase used by the hepatitis C virus to replicate its RNA.

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WO 2010/135569 A1 discloses amorphous sofosbuvir and crystalline forms 1 to 5 as well as processes for their preparation. According to WO 2010/135569 A1, crystalline form 1 is an anhydrate, crystalline forms 2 and 3 are solvates with dichloromethane and chloroform respectively. However, no sufficient data could be collected to determine whether crystalline forms 4 and 5 are unsolvated, hydrated or solvated forms of sofosbuvir. It is further mentioned that all crystalline forms transform to crystalline form 1 on isolation and that crystalline form 1 liquefies when exposed to elevated humidity levels.

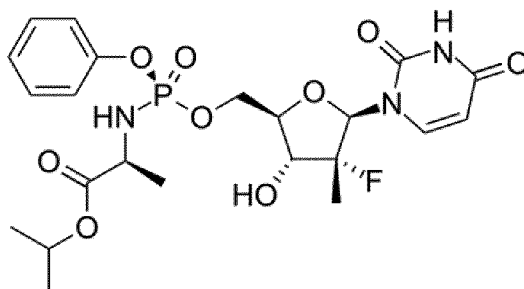
WO 2011/123645 A1 discloses an additional crystalline form, form 6, of sofosbuvir. According to example 21 of WO 2011/123645 A1, crystalline form 6 can be prepared in two different ways. On the one hand, crystalline form 6 is obtained by exposing crystalline form 1 to atmospheric humidity for 6 to 10 weeks, whereby a solidified gum is formed which needs to be ground prior to further storage in order to obtain crystalline form 6. On the other hand, crystalline form 6 is prepared by stirring a mixture of crystalline form 1 in water. However, according to WO 2011/123645 A1, a gum-like material is obtained when contacting crystalline form 1 with water, which transforms to an oil upon heating, and only after further stirring form 6 crystallizes from the inhomogeneous mixture.

Apparently, there are several drawbacks related to the hygroscopic nature of sofosbuvir having crystalline form 1. Using crystalline form 1 as starting material to prepare crystalline form 6, for example, leads to the appearance of gum-like and oily material which is cumbersome to handle especially on scale. Moreover, crystalline form 1 tends to liquefy at elevated relative humidity and therefore needs to be protected from moisture which requires precautionary measures and consequently renders formulation processes, packaging, and storage complex and costly.

Hence there is a need for crystalline forms of sofosbuvir with improved physicochemical properties; there is a particular need for non-hygroscopic crystalline forms of sofosbuvir with improved behaviour upon contact with water and moisture, respectively. Surprisingly, it was found that such a novel crystalline form of sofosbuvir with improved physicochemical properties, in particular exhibiting non-hygroscopic behaviour upon contact with moisture and water can be provided.

Said novel crystalline form of sofosbuvir, also referred to herein as form 7, can be characterized by the following embodiments and combination of embodiments as indicated by the respective back-references:

- 5 1. A crystalline form of sofosbuvir of formula (I) (form 7)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

- 10 2. The crystalline form of embodiment 1, having an X-ray powder diffraction pattern comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.
- 15 3. The crystalline form of embodiment 1 or 2, exhibiting a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3252 ± 2) cm<sup>-1</sup>, (2928 ± 2) cm<sup>-1</sup>, (1718 ± 2) cm<sup>-1</sup>, (1668 ± 2) cm<sup>-1</sup>, (1456 ± 2) cm<sup>-1</sup>, when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell.
- 20 4. The crystalline form of any of embodiments 1 to 3, having the monoclinic space group symmetry P2<sub>1</sub> and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:  
a = (5.16 ± 0.04) Angstrom;  
b = (16.86 ± 0.12) Angstrom;  
c = (14.44 ± 0.10) Angstrom;  
alpha = 90.0 °;  
25 beta = (100.2 ± 0.8) °;  
gamma = 90.0 °.
5. The crystalline form of any of embodiments 1 to 4, having a melting point in the range of from 122 to 126 °C when measured via differential scanning calorimetry at a heating rate of 10 K/min at a pressure in the range of from 0.95 to 1.05 bar.

6. The crystalline form of any of embodiments 1 to 5, comprising at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form, as determined via thermogravimetric analysis.
7. The crystalline form of any of embodiments 1 to 6, comprising at most 0.4 weight-% of water based on the weight of the crystalline form as determined via gravimetric moisture sorption / desorption analysis at a temperature of  $(25.0 \pm 0.1) ^\circ\text{C}$  and a relative humidity of from 0 to 95 %.

This crystalline form 7 of sofosbuvir is the only crystalline form of sofosbuvir showing no peak at 2-theta angles in the range of from 2 to  $7.8^\circ$  in the XRPD pattern when measured at a temperature in the range of from 15 to  $25^\circ\text{C}$  with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. All other known crystalline forms according to the prior art show at least one significant peak in this range, as summarized in the following Table:

**Table 1**

XRPD peaks of prior art crystalline forms in the range of from 2 to  $7.8^\circ$  2-theta

| Prior art forms | Peak Positions / $^\circ$ 2-theta | Prior art document                 |
|-----------------|-----------------------------------|------------------------------------|
| form 1          | 5.0, 7.3, 7.8                     | table 2 ex WO 2010/135569 A1       |
| form 2          | 4.9, 5.1, 6.9                     | table 3 ex WO 2010/135569 A1       |
| form 3          | 5.0, 6.9                          | table 4 ex WO 2010/135569 A1       |
| form 4          | 5.0, 6.8                          | table 5 ex WO 2010/135569 A1       |
| form 5          | 5.2, 6.6, 7.1                     | table 6 ex WO 2010/135569 A1       |
| form 6          | 6.1                               | table page 95-96 WO 2011/123645 A1 |

Hence, the absence of an XRPD peak in said range is unique and therefore a characteristic property of this crystalline form of sofosbuvir. Additionally, this crystalline form 7 of sofosbuvir can be, for example, further distinguished from crystalline form 1 of WO 2010/135569 A1 by a characteristic XRPD peak at  $(12.4 \pm 0.2) ^\circ$  2-theta since the crystalline form 1 shows no such characteristic peak in this range when measured at room temperature with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

An advantageous process for the preparation of this crystalline form 7 of sofosbuvir could be, for example, a process which makes use of seed crystals of a known crystalline form of sofosbuvir, for example of crystalline form 6 of sofosbuvir. Such an advantageous process may comprise, for example

- (a) providing sofosbuvir in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (b) preparing seed crystals of crystalline form 7 of sofosbuvir by a method comprising
- (b.1) providing sofosbuvir in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (b.2) providing seed crystals of crystalline form 6 of sofosbuvir, having an X-ray powder diffraction pattern with reflections at 2-theta values of  $(6.1 \pm 0.2)^\circ$ ,  $(8.2 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.7 \pm 0.2)^\circ$ ,  $(17.2 \pm 0.2)^\circ$ ,  $(17.7 \pm 0.2)^\circ$ ,  $(18.0 \pm 0.2)^\circ$ ,  $(18.8 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ ,  $(19.8 \pm 0.2)^\circ$ ,  $(20.1 \pm 0.2)^\circ$ ,  $(20.8 \pm 0.2)^\circ$ ,  $(21.8 \pm 0.2)^\circ$ ,  $(23.3 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- (b.3) preparing a solution of the sofosbuvir provided in (b.1) in a C<sub>2</sub>-C<sub>10</sub> alcohol or in a mixture of two or more thereof, preferably in a C<sub>5</sub>-C<sub>10</sub> alcohol or in a mixture of two or more thereof, more preferably in a C<sub>8</sub> alcohol, more preferably in 2-octanol;
- (b.4) subjecting the solution provided in (b.3) to crystallization conditions, comprising seeding the solution with the seed crystals provided in (b.2), wherein during crystallization, the solution is not stirred, preferably not mechanically agitated, more preferably not agitated, obtaining the crystalline form 7 of sofosbuvir in its mother liquor;
- (b.5) separating at least a portion of the crystalline form 7 of sofosbuvir from its mother liquor;
- (c) preparing a solution of sofosbuvir provided in (a) in a C<sub>2</sub>-C<sub>5</sub> alcohol or in a mixture of two or more thereof, and in one or more anti-solvents;
- (d) subjecting the solution provided in (c) to crystallization conditions, comprising seeding the solution with the seed crystals prepared in (b), wherein during crystallization, the solution is not stirred, preferably not mechanically agitated, more preferably not agitated, obtaining the crystalline form 7 of sofosbuvir in its mother liquor;
- (e) separating the crystalline form 7 of sofosbuvir from its mother liquor.

The term "agitation" as used throughout this invention relates to any motion of a macroscopic constituent of the solution comprising sofosbuvir which is induced from outside, relative to another macroscopic constituent of the solution. The term "mechanical agitation" as used herein relates to any motion of a macroscopic constituent of the solution comprising sofosbuvir which is induced from outside via a device, such as shaking or stirring or sonication, relative to another macroscopic constituent of the solution. The term "stirring" as used herein relates to any motion of a macroscopic constituent of the solution comprising sofosbuvir which is induced from outside via a stirring device, relative to another macroscopic constituent of the solution.

While from this process, the crystalline form 7 of sofosbuvir may be obtained in a reliable manner, the feature according to which during crystallization, the solution is not stirred, preferably not mechanically agitated, more preferably not agitated, may render the process ineffective and, thus, commercially irrelevant. In particular in view of a scaled-up process for the preparation of form 7 wherein, compared to lab-scale processes according to which, for example, from 0.1 to 0.5 g of sofosbuvir are employed as starting material, higher amounts of sofosbuvir have to be employed as starting material, such as at least 0.6 g of sofosbuvir, it may be conceivable that as to the process described above, the essential absence of agitation may lead to a crystallization of at least a portion of the crystalline form 7 at the walls of the respectively used reaction vessel, thus necessitating scratching crystallized material off the walls of the vessel and making it unacceptably difficult to have access to desired product.

CN 104130302 A, published on 05 November 2014, describes the preparation of a crystalline form A of sofosbuvir which is neither a solvate nor a hydrate. According to this process, it is mandatory that in order to obtain said crystalline form, no stirring should be carried out during crystallization. In particular the examples of CN 104130302 A show that as soon as the mixture from which the crystalline form A is crystallized is stirred and not left to stand without any agitation, no pure form A is obtained but a mixture of said form A and form 6. Thus, the process of CN 104130302 A is not suitable for preparing the crystalline form A according to an industrially suitable procedure.

Hence there is a need for providing a process for the preparation of the crystalline form 7 of sofosbuvir which avoids the above-mentioned drawback and which, in particular, allows to be employed not only in a laboratory scale, but also in an scaled up process using an industrial-scale process design allowing a fast crystallization step. Further, it was an object of the present invention to provide a process in which the number of different components of the solvent system used for the preparation of the crystalline form 7 of sofosbuvir is as low as possible.

Surprisingly, it was found that this object can be solved if, for a solvent-mediated transformation to obtain the solid crystalline form 7 of sofosbuvir, a solvent system is used which comprises a ketone having a specific number of carbon atoms. Further, it found that an especially preferably solvent system comprises a ketone having a specific number of carbon atom in combination with a specific non-ketonic aprotic organic solvent.

Crystalline form 7 is physically stable when dry, i.e. when no or very low amounts of certain residual solvent is present. In the context of the present invention the terms “physically stable” and “stable” are used synonymously and mean that the crystalline form 7 does not trans-

form into another crystalline form, in particular in crystalline form 6, or such transformation is slow.

It has been observed that the presence of some solvents (e.g. alcohol, alcohol / alkane mixture, and water) even in a low amount can affect the stability of crystalline form 7 when subjected to mechanical stress conditions, such as those present during reaction workup, filtration, processing of the filter cake, agitation, stirring and so on. It has been observed that under such conditions crystalline form 7 tends to transform into another polymorphic form such as crystalline form 6.

It has been surprisingly found that, on the contrary, some solvents are capable of inhibiting or slowing down the polymorphic transformation of form 7. This has the advantage of making the isolation of crystalline form 7 more reliable, and therefore the whole process suitable for industrial applicability. In particular, the present inventors have found that certain solvents such as ketones having from 4 to 8 carbon atoms stabilize the crystalline form 7 and avoid or slow down the transformation of crystalline form 7 into crystalline form 6 under mechanical stress.

Hence, as mentioned above stable or stabilized crystalline form 7 according to the invention is a crystalline form 7 that does not transform into another crystalline form, in particular crystalline form 6. This applies for example when form 7 undergoes mechanical stress. Alternatively such transformation is slowed down. The slowdown is with respect to solvents or solvent systems that affects the stability of crystalline form 7, for example when subjected to mechanical stress, as disclosed above.

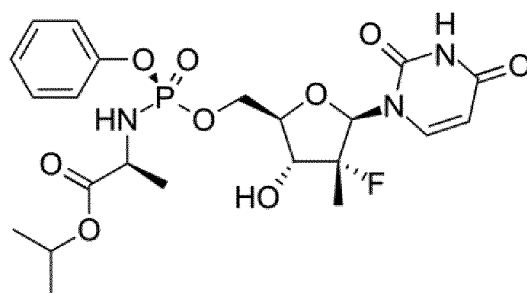
For example, the workup of crystalline form 7 crystallized from solvents that can affect the polymorphic stability of crystalline form 7 when subjected to mechanical stress conditions leads to partial or complete transformation of form 7 into another polymorphic form, preferably into crystalline form 6. Advantageously, the present invention allows the workup of solid crystalline form 7, even when obtained from a solvent or a solvent system that affect the stability of crystalline form 7 such as alcohol, alcohol / alkane mixture, and water without observing the transformation of the solid crystalline form 7 into another solid polymorphic form.

Therefore, the present invention relates to a process for preparing a crystalline form of sofosbuvir of formula (I), wherein the crystalline form is form 7, preferably a stable form 7.

Therefore, the present invention relates to the use of a ketone having from 4 to 8 carbon atoms for solvent mediated transformation of sofosbuvir to obtain sofosbuvir crystalline form 7.

Therefore, the present invention relates to the use of a ketone having from 4 to 8 carbon atoms for stabilizing sofosbuvir crystalline form 7, preferably stabilizing crystalline form 7 from mechanical stress.

- 5 Therefore the present invention relates to a composition comprising sofosbuvir crystalline form 7 and at least one ketone having from 4 to 8 carbon atoms wherein the at least one ketone having from 4 to 8 carbon atoms is present in an amount that allows the stabilization of the solid crystalline form 7.
- 10 Therefore, the present invention relates to a process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising
- 15 (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- 20 (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having from 4 to 8, preferably from 5 to 7 carbon atoms and optionally at least one aprotic non-ketonic organic solvent;
- 25 (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in its
- 30 mother liquor.

According to (i), sofosbuvir according to formula (I) is provided in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms.

No specific restrictions exist regarding the specific form of sofosbuvir which is employed in (i). Preferably, according to (i), sofosbuvir according to formula (I) is provided in a crystalline form which does not comprise, more preferably which is not, crystalline form 6 of sofosbuvir according to formula (I) having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(6.1 \pm 0.2)^\circ$ ,  $(8.2 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.7 \pm 0.2)^\circ$ ,  $(17.2 \pm 0.2)^\circ$ ,  $(17.7 \pm 0.2)^\circ$ ,  $(18.0 \pm 0.2)^\circ$ ,  $(18.8 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ ,  $(19.8 \pm 0.2)^\circ$ ,  $(20.1 \pm 0.2)^\circ$ ,  $(20.8 \pm 0.2)^\circ$ ,  $(21.8 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. More preferably, according to (i), sofosbuvir according to formula (I) is provided in crystalline form 1, amorphous form, or as a mixture of two or more of these forms. More preferably, according to (i), sofosbuvir according to formula (I) is provided in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, or is provided in amorphous form.

The crystalline form 1 and the amorphous form of sofosbuvir can be prepared, for example, as disclosed in WO 2010/135569 A1.

The crystalline form 7 of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° preferably

- comprises XRPD reflections at 2-theta angles of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and preferably comprises additional XRPD reflections at 2-theta angles of  $(12.1 \pm 0.2)^\circ$ ,  $(13.5 \pm 0.2)^\circ$ ,  $(16.2 \pm 0.2)^\circ$ ,  $(16.8 \pm 0.2)^\circ$ ,  $(18.0 \pm 0.2)^\circ$ ,  $(18.7 \pm 0.2)^\circ$ ,  $(20.2 \pm 0.2)^\circ$ ,  $(20.9 \pm 0.2)^\circ$ ,  $(22.1 \pm 0.2)^\circ$ ,  $(23.4 \pm 0.2)^\circ$ ,  $(25.4 \pm 0.29)^\circ$ ,  $(28.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm; and/or
- exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of  $(3252 \pm 2) \text{ cm}^{-1}$ ,  $(2928 \pm 2) \text{ cm}^{-1}$ ,  $(1718 \pm 2) \text{ cm}^{-1}$ ,  $(1668 \pm 2) \text{ cm}^{-1}$ ,  $(1456 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of  $(1494 \pm 2) \text{ cm}^{-1}$ ,  $(1373 \pm 2) \text{ cm}^{-1}$ ,  $(1265 \pm 2) \text{ cm}^{-1}$ ,  $(1223 \pm 2) \text{ cm}^{-1}$ ,  $(945 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell; and/or

- has the monoclinic space group symmetry  $P2_1$  and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:  
a = (5.16 ± 0.04) Angstrom;  
b = (16.86 ± 0.12) Angstrom;  
5 c = (14.44 ± 0.10) Angstrom;  
alpha = 90.0 °;  
beta = (100.2 ± 0.8) °;  
gamma = 90.0 °; and/or
- has a melting point in the range of from 122 to 126 °C when measured via differential  
10 scanning calorimetry at a heating rate of 10 °C/min at a pressure in the range of from 0.95 to 1.05 bar, in particular determined according to Reference Example 3; and/or
- comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystal-  
line form having an X-ray powder diffraction pattern comprising no reflection at 2-theta  
angles in the range of from 2.0 to 7.9 ° when measured at a temperature in the range of  
15 from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, as determined via thermogravimetric analysis; and/or
- comprising at most 0.4 weight-% of water based on the weight of the crystalline form  
having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in  
the range of from 2.0 to 7.9 ° when measured at a temperature in the range of from 15 to  
20 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, as determined via gravimetric moisture sorption / desorption analysis at a temperature of (25.0 ± 0.1) °C and a relative humidity of from 0 to 95 %.

#### Steps (ii) and (iii)

25 According to (ii), a mixture is prepared comprising the sofosbuvir provided in (i) and a solvent system, wherein the solvent system comprises at least one ketone having from 4 to 8, preferably from 5 to 7 carbon atoms and optionally at least one aprotic non-ketonic organic solvent.

#### Ketone

30 The at least one ketone used in (ii) has 4 to 8 carbon atoms, such as 4, 5, 6, 7, or 8 carbon atoms. Preferably, the at least one ketone used in (ii) has 5 to 7 carbon atoms, such as 5, 6, or 7  
35 carbon atoms.

Preferably, the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl

group (C=O) wherein the number of the carbon atoms of the alkyl residues or of the alkanediyl group, together with the carbon atom of the carbonyl group, add up to the preferred total number of carbon atoms of from 4 to 8, preferably from 5 to 7. If more than one ketone is used, the ketones may have the same or different numbers of carbon atoms provided that the respective number of carbon atoms is in the above-defined ranges. Preferably, the at least one ketone is one or more of cyclopentanone, cyclohexanone, cycloheptanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, ethyl isopropyl ketone, methyl n-pentyl ketone, methyl 2-pentyl ketone, methyl 3-pentyl ketone, methyl 2-methylbutyl ketone, methyl 3-methylbutyl ketone, methyl 3-methylbut-2-yl ketone, methyl 2-methylbut-2-yl ketone, methyl 2,2-dimethylpropyl ketone, ethyl n-butyl ketone, ethyl isobutyl ketone, ethyl tert-butyl ketone, di-n-propyl ketone, di-isopropyl ketone, and n-propyl isopropyl ketone.

More preferably, the at least one ketone used in (ii) has 5 or 6 carbon atoms, wherein it is more preferred that the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group (C=O). Preferably, the at least one ketone is one or more of cyclopentanone, cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, and ethyl isopropyl ketone. More preferably, the at least one ketone is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone. More preferably, the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone. Especially preferred ketones are methyl isopropyl ketone and methyl isobutyl ketone.

Therefore, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, and optionally at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

Further, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, and optionally at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

Further, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising one ketone which is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, and optionally at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

According to the present invention, it was found that the solvent-mediated transformation according to (iii) can be accomplished if, according to (ii), the solvent system comprises one the at least one ketone described above and does not comprise at least one aprotic non-ketonic organic solvent. In particular, it was found that the solvent-mediated transformation according to (iii) can be accomplished if the solvent system according to (ii) consists of the at least one ketone described above.

Aprotic non-ketonic organic solvent

Without wanting to be bound by any theory, it was found that with regard to the solvent-mediated transformation according to (iii), the process may be advantageous if in addition to the at least one ketone described above, at least one aprotic non-ketonic organic solvent is used as additional component of the solvent system according to (ii). An advantage of the process may be, for example, an increased yield of (iii) with regard to the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor. Therefore, the present invention relates to the process described above, wherein the solvent system according to (ii) further comprises at least one aprotic non-ketonic organic solvent. Further, the present invention relates to the process described above, wherein the solvent system according to (ii) consists of the at least one ketone described above and the at least one aprotic non-ketonic organic solvent.

Therefore, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising, preferably consisting of, at least one ketone having 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, and at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

Further, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising, preferably consisting of, at least one ketone which is one or more of cyclo-

hexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, and at least one aprotic non-ketonic organic solvent;

- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

Further, the present invention relates to the above-defined process, comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms, preferably in crystalline form 1;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising, preferably consisting of, one ketone which is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, and at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

While there are no specific restrictions with regard to the chemical nature of the at least one aprotic non-ketonic organic solvent, it is preferred that the at least one aprotic non-ketonic organic solvent consists of carbon and hydrogen or consists of carbon, hydrogen and oxygen.

It is also preferred that the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, or one or more ether compounds, or one or more ester compounds, or a mixture of one two or more thereof. If a mixture of two or more aprotic non-ketonic organic solvent is used, the can be composed of two or more aromatic compounds, two or more ether compounds, two or more ester compounds, one or more aromatic compounds and one or more ether compounds, one or more aromatic compounds and one or more ester compounds, one or more ether compounds and one or more ester compounds, or one or more aromatic compounds and one or more ether compounds and one or more ester com-

pounds, wherein for every mixture, it is preferred that the respectively used compounds consist of carbon, hydrogen and optionally oxygen.

A preferred solvent system according to (ii) comprises, preferably consists of, the at least one  
5 ketone described above and at least one aromatic compound preferably consisting of carbon, hydrogen and optionally oxygen, more preferably of carbon and hydrogen.

Preferably, the at least one aromatic compound is one or more of toluene, dimethyl benzenes  
such as 1,2-dimethyl benzene or 1,3-dimethyl benzene or 1,4-dimethyl benzene, benzene,  
10 methoxy benzene, chlorobenzene. More preferably, the at least one aromatic compound is one or more of toluene, dimethyl benzenes such as 1,2-dimethyl benzene or 1,3-dimethyl benzene and 1,4-dimethyl benzene. More preferably, the at least one aromatic compound is toluene. Therefore, a preferred solvent system according to (ii) comprises, preferably consists of, the at least one ketone described above and toluene.

Preferably, the at least one ether compound is one or more of methyl tert-butyl ether, diethyl  
ether, and diisopropyl ether. More preferably, the at least one ether compound is methyl tert-  
butyl ether. Therefore, a preferred solvent system according to (ii) comprises, preferably con-  
sists of, the at least one ketone described above and methyl tert-butyl ether.

Preferably, the at least one ester compound is one or more of acetates, more preferably one or  
more of 1-methyl ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, and ethyl  
acetate. More preferably, the at least one ester compound is 1-methyl ethyl acetate. Therefore,  
a preferred solvent system according to (ii) comprises, preferably consists of, the at least one  
25 ketone described above and 1-methyl ethyl acetate.

For example, preferred solvent systems according to (ii) comprise, preferably consist of, di-  
ethyl ketone and toluene, methyl n-propyl ketone and toluene, methyl-isopropyl ketone and  
toluene, methyl-isopropyl ketone and 1-methyl ethyl acetate, methyl-isopropyl ketone and  
30 methyl tert-butyl ether, methyl isobutyl ketone and toluene, methyl isobutyl ketone and 1-  
methyl ethyl acetate, methyl isobutyl ketone and methyl tert-butyl ether, cyclohexanone and  
toluene.

Preferably, the mixture according to (ii) consists of the sofosbuvir provided in (i), the at least  
35 one ketone and optionally the at least one aprotic non-ketonic organic solvent.

In the mixture according to (ii), the volume ratio of the at least one ketone relative to the at  
least one aprotic non-ketonic organic solvent, if present, is not specifically restricted. Prefera-  
bly, it is in the range of from 0.1:1 to 10:1, more preferably of from 0.2: 1 to 5:1, more prefer-

ably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably of from 0.9:1 to 1.1:1, such as from 0.95:1 to 1.05:1 or from 0.99:1 to 1.01:1.

In the mixture according to (ii), the content of the sofosbuvir relative to the solvent system is not specifically restricted. Preferably, the mixture contains the sofosbuvir, relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, if present, in an amount in the range of from 100 to 500 mg/mL, more preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL, such as from 150 to 200 mg/mL or from 175 to 225 mg/mL or from 200 to 250 mg/mL.

According to the present invention, there are no specific restriction how the mixture according to (ii) is prepared. It is preferred that according to (ii), a solution is prepared comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

According to a first alternative, the solution can be prepared by suspending the sofosbuvir provided in (i) in at least a portion of the solvent system preferably comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent. According to this alternative, it is preferred that suspending the sofosbuvir provided in (i) is carried out at a temperature of the at least a portion of the solvent system in the range of from 5 to 35 °C, preferably of from 10 to 35 °C, more preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. It is further preferred that the respectively prepared suspension is suitably heated to dissolve the suspended sofosbuvir, preferably to a temperature of above 35 °C, more preferably at least 40 °C, more preferably in the range of from 40 °C to the less than the boiling point of the solvent system. If the solvent system comprises two or more component, the term "boiling point of the solvent system" refers to the boiling point of the component having the lowest boiling point. Preferred temperature ranges may be, for example, from 40 to 50 °C or from 40 to 48 °C or from 40 to 46 °C or from 40 to 44 °C.

According to a second alternative, the solution can be prepared by dissolving the sofosbuvir provided in (i) in at least a portion of one or more of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I), and adding at least a portion of one or more of the at least one aprotic non-ketonic organic solvent. Preferred temperature ranges for preparing the solution and adding the at least one aprotic non-ketonic organic solvent ranges may be, for example, from 15 to 35 °C or from 20 to 30 °C, wherein the temperature refers to the temperature of the solution.

Surprisingly, it was found that the specific choice of ketones having from 4 to 8 carbon atoms, preferably 5 to 7 carbon atoms, allows agitation, preferably mechanical agitation, more preferably stirring of the mixture during its preparation without having any negative influences on

the solvent-mediated transformation to obtain solid crystalline form 7 of sofosbuvir. The terms “agitation”, “mechanical agitation” and “stirring” are as defined above. Even more surprisingly, it was found that not only during preparing the mixture according to (ii) but also during subjecting this mixture to solvent-mediated transformation conditions according to (iii), it is possible to agitate, preferably to mechanically agitate, more preferably to stir the mixture. It is noted that according to prior art processes, for example disclosed in CN 104130302 A, it is mandatory that no stirring is carried out. However, the strict avoidance of stirring usually results in crystallized material deposited at the walls of the reaction vessel and the like, thus rendering the overall process non-suitable for industrial purposes, and limiting the process solely to academic interests. Therefore, the present invention relates to the process as described above, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

#### Solvent-mediated transformation conditions

According to (iii), it is preferred that the mixture is agitated, preferably mechanically agitated, more preferably stirred. According to (iii), it is preferred that agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more suitable temperatures of the mixture which are preferably in the range of from -5 to 35 °C, preferably from 0 to 30 °C. In order to achieve this temperature, it may be necessary to cool the mixture prepared in (ii), in particular in case the mixture was prepared including heating to a temperature preferably in the range of from at least 40 °C to less than the boiling point of the solvent system as described above. Therefore, it may be preferred that subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises cooling the mixture. If the mixture is respectively cooled, suitable temperature to which the mixture is cooled are in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture during cooling of the mixture.

According to the present invention, it is preferred that subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises seeding the mixture. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture during seeding of the mixture. It is preferred that if the mixture is seeded, seed crystals of sofosbuvir are

used which exhibit crystalline form 7. The amount of the seed crystals added during seeding of the mixture is not subject to any specific restrictions. Preferably, based on the amount of sofosbuvir contained in the mixture to be seeded, seed crystals in an amount in the range of from 1 to 15 weight-%, preferably of from 5 to 12 weight-%, more preferably of from 8 to 10 weight-%, are added to the mixture. Generally, adding the seed crystals can be carried out at any suitable temperature of the mixture. Preferably, this temperature is in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. If the mixture was cooled as described above, it may be preferred that the seed crystals are added to the mixture at the temperature to which the mixtures was cooled. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture after seeding of the mixture wherein agitating, preferably mechanical agitating, more preferably stirring is carried out preferably for a period of time in the range of from 0.1 to 48 h, more preferably of from 0.2 to 24 h, more preferably of from 0.5 to 12 h, at a temperature of the mixture which is preferably in the range of from -5 to 35 °C, more preferably from 0 to 30 °C.

As found and shown in the Examples of the present invention, the specific choice of the solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, allows to prepare the crystalline form 7 of sofosbuvir also without adding seed crystals. Therefore, the process of the invention also serves as an ideal basis for preparing seed crystals. No other process has to be established or developed leading to a suitable seed crystals material.

#### Steps (iv) and (v)

From step (iii), the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, is obtained in its mother liquor. While it may be conceivable to suitably use the mother liquor comprising the solid crystalline form of sofosbuvir, it is usually preferred to separate the solid crystalline form of sofosbuvir from the mother liquor and optionally dry the separated solid crystalline form of sofosbuvir. Therefore, the present invention relates to the process described above, further comprising

- (iv) separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$

$^{\circ}$ ,  $(12.4 \pm 0.2)^{\circ}$ ,  $(17.3 \pm 0.2)^{\circ}$ ,  $(19.4 \pm 0.2)^{\circ}$ , when measured at a temperature in the range of from 15 to 25  $^{\circ}\text{C}$  with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, from its mother liquor;

- (v) drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8  $^{\circ}$  and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^{\circ}$ ,  $(10.4 \pm 0.2)^{\circ}$ ,  $(12.4 \pm 0.2)^{\circ}$ ,  $(17.3 \pm 0.2)^{\circ}$ ,  $(19.4 \pm 0.2)^{\circ}$ , when measured at a temperature in the range of from 15 to 25  $^{\circ}\text{C}$  with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.

For separation purposes according to (iv), the mother liquor comprising the solid crystalline form of sofosbuvir can be suitably concentrated or diluted, prior to the separation of the solid crystalline form of sofosbuvir. According to the present, it may be preferred to suitably dilute the mother liquor comprising the solid crystalline form of sofosbuvir. Therefore, step (iv) preferably comprises

- (iv.1) diluting the mother liquor comprising the solid crystalline form of sofosbuvir.

Preferably, diluting the mother liquor comprises adding at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably 5 or 6 carbon atoms, to the mother liquor comprising the solid crystalline form of sofosbuvir. With regard to preferred ketones, reference is made to the preferred ketones discussed above in the context of the solvent system according to (ii). Preferably, the at least one ketone used for diluting according to (iv.1) is the at least one ketone comprised in the mixture according to (ii).

In addition to the at least one ketone, at least one aprotic non-ketonic organic solvent can be added to the mother liquor comprising the solid crystalline form of sofosbuvir. While there are no specific restrictions to the chemical nature of the at least one aprotic non-ketonic organic solvent, it is preferred to employ the at least one aprotic non-ketonic organic solvent which is comprised in the mixture according to (ii).

If both the at least one ketone and the at least one aprotic non-ketonic organic solvent are employed according to (iv.1), the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is preferably in the range of from 0.1:1 to 10:1, more preferably of from 0.2: 1 to 5:1, more preferably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably from 0.9:1 to 1.1:1. More preferably, the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is the volume ratio of the at least one ketone comprised in the mixture according to (ii) relative to the at least aprotic non-ketonic organic solvent comprised in the mixture according to

(ii). Thus, it may be preferred to use the solvent system according to (ii) to dilute the mother liquor according to (iv.1).

The mother liquor comprising the solid crystalline form of sofosbuvir, as obtained from (iii), or the diluted mother liquor comprising the solid crystalline form of sofosbuvir as obtained from (iv.1) is preferably subjected to a solid-liquid separation process, preferably comprising filtration or centrifugation, more preferably filtration. Therefore, the separating according to (iv) preferably comprises

(iv.2) subjecting the mother liquor comprising the solid crystalline form of sofosbuvir, optionally the mother liquor comprising the solid crystalline form of sofosbuvir diluted according to (iv.1), to a solid-liquid separation process, preferably to filtration.

Preferably, separating according to (iv) comprises washing the solid crystalline form of sofosbuvir wherein said washing is preferably carried out after the solid-liquid separation as described above in (iv.2). Therefore, separating according to (iv) preferably comprises

(iv.3) washing the solid crystalline form of sofosbuvir separated from its mother liquor.

Regarding the washing, no specific restrictions exist. Preferably the washing is carried out with at least one aprotic organic compound, optionally the at least one aprotic non-ketonic organic solvent as discussed above in the context of the solvent system according to (ii). Preferably, one or more of toluene and diethyl ether are employed. The at least one aprotic organic compound is optionally used in combination with at least one ketone, preferably the at least one ketone as discussed above in the context of the solvent system according to (ii).

Regarding the washing, the washing is preferably carried out with a solvent selected from the group consisting of a ketone having from 4 to 8 carbon atoms, preferably a ketone having 6 carbon atoms or with a mixture of a ketone having 6 carbon atoms and an ether. The washing comprises forming a suspension with the solid crystalline form of sofosbuvir obtained in (iv.2) and the solvent. Regarding the solvent preferably the ketone having 6 carbon atoms is methyl isobutyl ketone and the ether is diethyl ether. More preferably the solvent is methyl isobutyl ketone.

Regarding the temperature at which the washing is carried out, no specific restrictions exist. Preferably, the washing is carried out at a temperature in the range of from 0 to 30 °C, preferably from 15 to 30 °C.

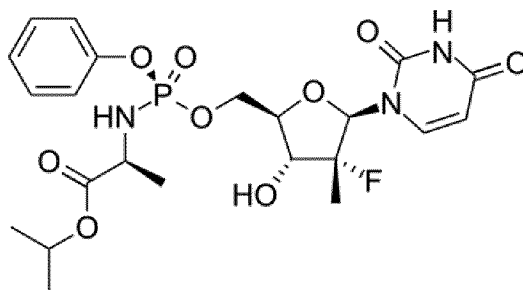
According to the present invention, it is preferred that the solid crystalline form of sofosbuvir which is obtained in (iii) comprised in its mother liquor, preferably obtained from the separation according to (iv), is suitably dried.

No specific restrictions exist regarding the drying conditions. Preferably, drying according to (v) is carried at elevated temperatures relative to ambient temperature, more preferably at a temperature of at least 30 °C. More preferably, drying is carried out at a temperature in the range of from 30 to 50 °C, more preferably of from 35 to 45 °C. Preferably, drying according to (v) is carried at a pressure below ambient pressure, preferably at an absolute pressure of at most 500 mbar. More preferably, drying is carried out at an absolute pressure below 1 bar, preferably in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar, more preferably of from 5 to 50 mbar. Therefore, more preferably, drying according to (v) is carried out at a temperature in the range of from 30 to 50 °C and an absolute pressure in the range of from 5 to 500 mbar, more preferably at a temperature in the range of from 35 to 45 °C and an absolute pressure in the range of from 5 to 50 mbar. Preferably, drying is carried out for a period of time in the range of from 1 to 48 hours, preferably of from 6 to 24 hours.

The present invention is further directed to a process for stabilizing crystalline form 7. Therefore, the present invention is further directed to a process for preparing a composition comprising solid crystalline form 7 and at least one ketone having from 4 to 8 carbon atoms wherein said at least one ketone is as disclosed herein below.

The composition according to the invention comprises

-a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein; and

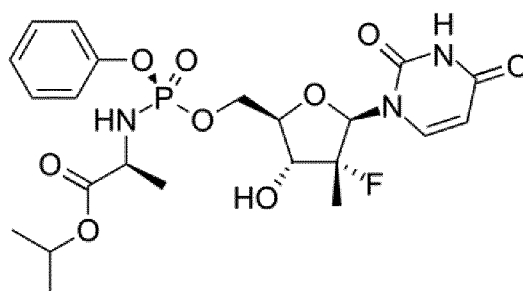
-at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or

in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

According to the invention, preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms wherein the ketone is in the residual amount as disclosed above.

The at least one ketone having from 4 to 8 carbon atoms is as herein below defined in section "Ketone" of step 2) of the process herein below disclosed.

Therefore, the present invention relates to a process for preparing a composition comprising -a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein; and

-at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

said process comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms, and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

According to 1), sofosbuvir is provided in the solid crystalline form 7 as characterized above. The solid crystalline form 7 can be provided under any condition. For example, solid crystalline form 7 is provided under conditions that do not affect the stability of said crystalline form. For example, the solid crystalline form 7 is provided as dry solid crystalline form. In the context of the present invention “dry solid crystalline form” and “dry crystalline form” are used synonymously and mean that no solvent is detectable by chromatographic method such

as the method disclosed in Reference Example 1.4.2 or the solvent is detectable in an amount less than 0.19 weight-%, preferably less than 0.15 weight-% more preferably less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form 7. Preferably, the solvent is a solvent system as defined below in relation to the solvent system of step 2).

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The solid crystalline compound of 1) can also be provided comprising of or in the presence of a solvent that affects the stability of the crystalline form of sofosbuvir of formula (I) of 1). Preferably the solvent is in an amount of less than 3 weight-% or less than 2 weight-% or less than 1 weight-% or less than 0.5 weight-%, more preferably less than 0.3 weight-%, more preferably less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form of sofosbuvir of formula (I) of 1). Preferably, the solvent is selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water. More preferably, the solvent selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water is in an amount of less than 3 weight-% or less than 2 weight-% or less than 1 weight-% or less than 0.5 weight-%, preferably less than 0.3 weight-%, preferably less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form 7. It is also conceived that, the solvent selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water is in an amount of in the range from 3 to 0.1 weight-% or in the range from 2 to 0.3 weight-% or in the range of from 1 to 0.5 weight-%, based on the weight of the solvent and the solid crystalline form 7.

Preferably the alcohol is an aliphatic alcohol, preferably the aliphatic alcohol is selected from the group consisting of a C1 alcohol, a C2 alcohol, a C3 alcohol, a C4 alcohol, a C5 alcohol, and a mixture of two or more thereof, more preferably the alcohol is selected from the group consisting of methanol, ethanol, n-propanol, n-butanol, n-pentanol or a mixture of two or more thereof, more preferably the alcohol is n-butanol. Preferably, the alkane is selected from the group consisting of a C5 alkane, a C6 alkane, a C7 alkane, a C8 alkane and a mixture of two or more thereof, more preferably the alkane is selected from the group consisting of hexane, n-pentane, cyclohexane and n-heptane, more preferably n-heptane. Preferably, the mixture of at least an alcohol and at least an alkane comprises, preferably consists of, at least an alcohol and at least an alkane as disclosed above. More preferably, the mixture consists of n-butanol and of n-heptane.

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of

0.15419 nm wherein the solid crystalline form is stable, preferably wherein the solid crystalline form is a dry solid crystalline form;

- 2) preparing a mixture comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;

- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms, said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms, and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm

in the presence of a solvent that affects the stability of the crystalline form of sofosbuvir of formula (I) of 1) in an amount of less than 3 weight % or less than 2 weight-% or less than 1% or less than 0.5 weight-%, preferably in an amount less than 0.3 weight-%,

preferably in an amount less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form of sofosbuvir of formula (I) of 1);

- 2) preparing a mixture comprising the sofosbuvir of formula (I) provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;

- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms, and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

wherein the crystalline form 7 is provided comprising of or in the presence of a solvent that affects the stability of the crystalline form of sofosbuvir of formula (I) wherein the

solvent is selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water,

wherein the alcohol is an aliphatic alcohol preferably selected from the group consisting of methanol, ethanol, n-propanol, n-butanol, n-pentanol and a mixture of two or more thereof, more preferably the alcohol is n-butanol; wherein the alkane is selected from the group consisting of a C5 alkane, a C6 alkane, a C7 alkane, a C8 alkane or a mixture of two or more thereof, wherein preferably the alkane is n-heptane, and wherein preferably the mixture of at least an alcohol and at least an alkane comprises, preferably consists of n-butanol and of n-heptane,

wherein the solvent is in an amount of less than 3 weight-%, or less than 2 weight-% or less than 1 weight-% or less than 0.5 weight-%, preferably in an amount less than 0.3 weight-%, preferably in an amount less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form of sofosbuvir of formula (I) of 1);

- 2) preparing a mixture comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

It is also conceived that, the solvent selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water is in an amount of in the range from 3 to 0.1 weight-% or in the range from 2 to 0.3 weight-% or in the range of from 1 to 0.5 weight-%, based on the weight of the solvent and the solid crystalline form 7.

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Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

wherein the crystalline form 7 is provided comprising of or in the presence of a solvent or a solvent system that affects the stability of the crystalline form of sofosbuvir of formula (I) provided in 1), wherein preferably the solvent is selected from the group consisting of cyclohexane, n-butanol, and a mixture that comprises, preferably consists of n-butanol and of n-heptane, wherein the solvent is in an amount of less than 3 weight-% or less than 2 weight-% or less than 1 weight-% or less than 0.5 weight-%, more preferably in an amount less than 0.3 weight-%, more preferably in an amount less than 0.1 weight-% based on the weight of the solvent or solvent system and the solid crystalline form of sofosbuvir of formula (I) of 1);

- 2) preparing a mixture comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;

- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

5 wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

#### Step 2)

10 According to 2), a mixture is prepared comprising the sofosbuvir provided in 1) as disclosed above and a solvent system, wherein the solvent system comprises, preferably consists of, at least one ketone having from 4 to 8 carbon atoms. The solvent system may optionally comprises at least one aprotic non-ketonic organic solvent.

15 The mixture can be a solution or a suspension. The mixture is preferably a suspension. Hence, it is conceived that in 2) the crystalline form 7 is not dissolved or not completely dissolved in the solvent system.

The amount of solvent system added to solid crystalline form of sofosbuvir of formula (I) of  
20 1) is hence such that a suspension or a solution is prepared.

According to the invention, it is preferred that at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir as defined  
25 above and of solvent system of 2).

It is conceived that the solvent of 1) if present in 1) is also present in the mixture of 2).

In the mixture according to 2), the content of the sofosbuvir relative to the solvent system is  
30 not specifically restricted. Preferably, the mixture contains the sofosbuvir, relative to solvent system in an amount in the range of from 100 to 500 mg/mL, more preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL, such as from 150 to 200 mg/mL or from 175 to 225 mg/mL or from 200 to 250 mg/mL.

#### Ketone

The at least one ketone used in 2) has 4 to 8 carbon atoms, such as 4, 5, 6, 7, or 8 carbon atoms. Preferably, the at least one ketone used in 2) has from 5 to 7 carbon atoms, such as 5, 6,

or 7 carbon atoms. More preferably the ketone has 6 carbon atoms, more preferably the ketone is methyl isobutyl ketone.

Preferably, the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group ( $C=O$ ) wherein the number of the carbon atoms of the alkyl residues or of the alkanediyl group, together with the carbon atom of the carbonyl group, add up to the preferred total number of carbon atoms of from 4 to 8, preferably from 5 to 7. If more than one ketone is used, the ketones may have the same or different numbers of carbon atoms provided that the respective number of carbon atoms is in the above-defined ranges. Preferably, the at least one ketone is one or more of cyclopentanone, cyclohexanone, cycloheptanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, ethyl isopropyl ketone, methyl n-pentyl ketone, methyl 2-pentyl ketone, methyl 3-pentyl ketone, methyl 2-methylbutyl ketone, methyl 3-methylbutyl ketone, methyl 3-methylbut-2-yl ketone, methyl 2-methylbut-2-yl ketone, methyl 2,2-dimethylpropyl ketone, ethyl n-butyl ketone, ethyl isobutyl ketone, ethyl tert-butyl ketone, di-n-propyl ketone, di-isopropyl ketone, and n-propyl isopropyl ketone.

More preferably, the at least one ketone used in 2) has 5 or 6 carbon atoms, wherein it is more preferred that the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group ( $C=O$ ). Preferably, the at least one ketone is one or more of cyclopentanone, cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, and ethyl isopropyl ketone. More preferably, the at least one ketone is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone. More preferably, the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone. Especially preferred ketones are methyl isopropyl ketone and methyl isobutyl ketone. Especially preferred ketone is methyl isobutyl ketone.

Therefore, the present invention relates to the above-defined process, said process comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm, preferably as defined in step 1);

- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of at least one ketone having from 4 to 8 carbon atoms;
- 3) recovering from the mixture of 2) a composition comprising

5 -the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

10 -the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

20 wherein at least 97 weight-%, or at least 99 weight-% or least at 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

25 wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms,

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm; and

-the at least one ketone having from 5 to 7 carbon atoms, preferably having 5 or 6 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount, which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, is more than one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, said residual amount relates to the total amount of ketones having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms and,

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of said the at least one ketone.

Further, the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone; and

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, wherein the at least one ketone is present in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone is more than one of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone said residual amount relates to the total amount of said ketones and,

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of said the at least one ketone or more ketones.

Further, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, one ketone which is methyl isobutyl ketone;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of the one ketone, and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the one ketone.

Further, the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising of the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, one ketone which is methyl isobutyl ketone;

3) recovering from the mixture of 2) a composition comprising

the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the

range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount in the range of from 13 to 0.2 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition and

wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the one ketone.

According to the present invention, it was found that the stabilization of crystalline form 7 can be accomplished if, according to 2), the solvent system comprises, preferably consists of one of the at least one ketone described above.

It is also contemplated that in all the above embodiments the mixture of 2) is a solution.

#### Aprotic non-ketonic organic solvent

It was found with regard to the solvent system of 2) that in addition to the at least one ketone as described above, at least one aprotic non-ketonic organic solvent can be used as additional component of the solvent system according to 2). Preferably, the aprotic non-ketonic organic solvent is selected to be a highly volatile solvent. The use of at least one aprotic non-ketonic organic solvent allows easily adjusting the residual amount of ketone in the composition of 3) to the desired amount.

Therefore, the present invention relates to the process described above, wherein the solvent system according to 2) may optionally further comprises at least one aprotic non-ketonic organic solvent. Further, the present invention relates to the process described above, wherein the solvent system according to 2) consists of the at least one ketone described above and the at least one aprotic non-ketonic organic solvent.

While there are no specific restrictions with regard to the chemical nature of the at least one aprotic non-ketonic organic solvent, it is preferred that the at least one aprotic non-ketonic organic solvent consists of carbon and hydrogen or consists of carbon, hydrogen and oxygen.

It is further preferred that the one aprotic non-ketonic organic solvent has a boiling point lower than the boiling point of the ketone of the solvent system of 2). It is in fact preferred that in step 3) the one aprotic non-ketonic organic solvent is removed, preferably completely re-

moved from the solvent system. The removal of the aprotic non-ketonic organic solvent can be easily carried out by evaporation of the aprotic non-ketonic organic solvent having a boiling point lower than the boiling point of the ketone.

5 It is also preferred that the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, or one or more ether compounds, or one or more ester compounds, or a mixture of one, two, or more thereof. If a mixture of two or more aprotic non-ketonic organic solvent is used, they can be composed of two or more aromatic compounds, two or more ether compounds, two or more ester compounds, one or more aromatic compounds and one or more ether compounds, one or more aromatic compounds and one or more ester compounds, one or more ether compounds and one or more ester compounds, or one or more aromatic compounds and one or more ether compounds and one or more ester compounds, wherein for every mixture, it is preferred that the respectively used compounds consist of carbon, hydrogen and optionally oxygen.

15 A preferred solvent system according to 2) comprises, preferably consists of, the at least one ketone described above and at least one aromatic compound preferably consisting of carbon, hydrogen and optionally oxygen, more preferably of carbon and hydrogen.

20 Preferably, the at least one aromatic compound is one or more of toluene, dimethyl benzenes such as 1,2-dimethyl benzene or 1,3-dimethyl benzene or 1,4-dimethyl benzene, benzene, methoxy benzene, chlorobenzene. More preferably, the at least one aromatic compound is one or more of toluene, dimethyl benzenes such as 1,2-dimethyl benzene or 1,3-dimethyl benzene and 1,4-dimethyl benzene. More preferably, the at least one aromatic compound is toluene.

25 Therefore, a preferred solvent system according to 2) comprises, preferably consists of, the at least one ketone described above and toluene.

Preferably, the at least one ether compound is one or more of methyl tert-butyl ether, diethyl ether, and diisopropyl ether. More preferably, the at least one ether compound is methyl tert-butyl ether or diethyl ether, more preferably is diethyl ether. Therefore, a preferred solvent system according to 2) comprises, preferably consists of, the at least one ketone described above and diethyl ether.

35 Preferably, the at least one ester compound is one or more of acetates, more preferably one or more of 1-methyl ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, and ethyl acetate. More preferably, the at least one ester compound is 1-methyl ethyl acetate. Therefore, a preferred solvent system according to 2) comprises, preferably consists of, the at least one ketone described above and 1-methyl ethyl acetate.

For example, preferred solvent systems according to 2) comprise, preferably consist of, diethyl ketone and toluene, methyl n-propyl ketone and toluene, methyl-isopropyl ketone and toluene, methyl-isopropyl ketone and 1-methyl ethyl acetate, methyl-isopropyl ketone and methyl tert-butyl ether, methyl isobutyl ketone and toluene, methyl isobutyl ketone and 1-methyl ethyl acetate, methyl isobutyl ketone and methyl tert-butyl ether, cyclohexanone and toluene, and methyl isobutyl ketone and diethyl ether. More preferably the solvent system according to 2) comprises, preferably consists of, methyl isobutyl ketone and diethyl ether.

According to the present invention it is hence contemplated that the mixture according to 2) consists of the sofosbuvir provided in 1), optionally the solvent of 1), the at least one ketone and optionally the at least one aprotic non-ketonic organic solvent as defined above.

In the mixture according to 2), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is not specifically restricted. Preferably, it is in the range of from 0.1 : 1 to 10 : 1, preferably of from 0.2 : 1 to 5 : 1, preferably of from 0.3 : 1 to 2 : 1, preferably from 0.5 : 1 to 2 : 1, more preferably is 1 : 1.

Therefore according to 2), more preferably the solvent system comprises, preferably consists of methyl isobutyl ketone and diethyl ether in a volume ratio of methyl isobutyl ketone relative to diethyl ether in the range of from 0.3 : 1 to 2 : 1, preferably in a volume ratio in the range of from 0.5 : 1 to 2 : 1, more preferably is 1 : 1.

More preferably, the volume ratio of the methyl isobutyl ketone relative to diethyl ether is in the range of from 0.3 : 1 to 2 : 1, preferably of from 0.5 : 1 to 1 : 1.

In the mixture according to 2), the content of the sofosbuvir relative to the solvent system is not specifically restricted. Preferably, the mixture contains the sofosbuvir, relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent as disclosed above in an amount in the range of from 100 to 500 mg/mL, more preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL, such as from 150 to 200 mg/mL or from 175 to 225 mg/mL or from 200 to 250 mg/mL.

Therefore, the present invention relates to the above-defined process, said process comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent is preferably diethyl ether;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the one ketone having from 4 to 8 carbon atoms .

Therefore, preferably the present invention relates to the above-defined process, said process comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in

the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm;

- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent is preferably diethyl ether;

- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the one ketone having from 4 to 8 carbon atoms, and

wherein the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.2 : 1 to 5 : 1, preferably in the range of from 0.3 : 1 to 2 : 1, preferably in the range of from 0.5 : 1 to 2 : 1, more preferably is 1 : 1.

Therefore, preferably the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent is preferably diethyl ether;
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, is more than one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, said residual amount relates to the total amount of ketones having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of

the solid crystalline form of sofosbuvir of formula (I) and of the one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms .

In the above process, it is further preferred that the volume ratio of the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.2 : 1 to 5:1, preferably in the range of from 0.3 : 1 to 2 : 1, preferably in the range of from 0.5 : 1 to 2 : 1, more preferably is 1 : 1.

Therefore preferably, the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent is diethyl ether;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, wherein the at least one ketone is present in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

wherein in case the at least one ketone is more than one of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone said residual amount relates to the total amount of said ketones, and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of at least one ketone.

In the above process, it is further preferred that the volume ratio of the at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.2 : 1 to 5 : 1, preferably in the range of from 0.3 : 1 to 2 : 1, preferably in the range of from 0.5 : 1 to 2 : 1, more preferably is 1 : 1.

Therefore, preferably, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature *in* the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, one ketone which is methyl isobutyl ketone, and at least one aprotic non-ketonic organic solvent which is diethyl ether;
- 3) recovering from the mixture of 2) a composition comprising
  - the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and
  - one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight or in the range of from 24 to 12 weight-%

or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir of formula (I) and of the one ketone.

Therefore, preferably, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, one ketone which is methyl isobutyl ketone, and at least one aprotic non-ketonic organic solvent which is diethyl ether;
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

- 5 wherein in 2) the volume ratio of the methyl isobutyl ketone relative to diethyl ether is in the range of from 0.3 : 1 to 2 : 1, preferably of from 0.5 : 1 to 1 : 1, and

wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the  
10 solid crystalline form of sofosbuvir and of the one ketone which is methyl isobutyl ketone.

It is also contemplated that in all the above embodiments the mixture of 2) is a solution.

According to the present invention, there is no specific restriction how the mixture according  
15 to 2) is prepared. The mixture can be a solution or a suspension. It is preferred that according to 2) a suspension is prepared comprising the solid crystalline form of sofosbuvir of 1).

Surprisingly, it was found that the specific choice of ketones having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, stabilizes crystalline form 7 against mechanical stress  
20 such as the stress due to mechanical agitation or stirring during e.g. its preparation, reaction workup, filtration, processing of the filter cake. No negative influence of these solvents on crystalline form 7 of sofosbuvir is observed, in particular no transformation into crystalline form 6 is observed.

25 Step 3)

The composition of the invention is obtained from step 3).

As explained above, it has been found that the crystalline form 7 in the composition of the invention is stable. The crystalline form 7 does not transform in another polymorphic form,  
30 preferably does not transform in form 6 or the transformation of the crystalline form 7 is slow down. Stability is measured according Reference Example 1.7 b). Preferably, the crystalline form 7 in the composition of the invention when undergoes the oscillatory ball mill test as described in Reference Example 1.7 b) does not undergo polymorphic transformation into crystalline form 6. The crystalline form of sofosbuvir of formula (I) in the composition of 3)  
35 has preferably a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b).

The composition of the invention comprises

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of less than 27 weight-%. Preferably the residual amount of the at least one ketone is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%. More preferably, the residual amount of the at least one ketone is in the range of from 5.5 to 0.2 weight-%. The weight-% is based on the total amount of the composition, and in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms, said residual amount relates to the total amount of the ketones having from 4 to 8 carbon atoms.

As already disclosed above, according to the invention, preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of the invention obtained according to the processes of the invention in step 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone having from 4 to 8 carbon atoms in the residual amount as disclosed above. As mentioned above it is preferred that the composition of 3) does not comprise the aprotic non-ketonic organic solvent. The presence of aprotic non-ketonic organic solvent is detected according to the gas-chromatographic method disclosed in Reference Example 1.4.2.

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising of the sofosbuvir provided in 1) and at least one ketone having from 4 to 8 carbon atoms;
- 3) recovering from the mixture of 2) a composition comprising

the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,

( $12.4 \pm 0.2$ ) °, ( $17.3 \pm 0.2$ ) °, ( $19.4 \pm 0.2$ ) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

at least one ketone having from 4 to 8 carbon atoms wherein the at least one ketone is present in a residual amount in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, wherein in case the at least one ketone having from 4 to 8 carbon atoms is more one ketone having from 4 to 8 carbon atoms, said residual amount relates to the total amount of said ketones and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone having from 4 to 8 carbon atom.

Therefore preferably, the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of ( $8.1 \pm 0.2$ ) °, ( $10.4 \pm 0.2$ ) °, ( $12.4 \pm 0.2$ ) °, ( $17.3 \pm 0.2$ ) °, ( $19.4 \pm 0.2$ ) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms,

3) recovering from the mixture of 2) a composition comprising

the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of ( $8.1 \pm 0.2$ ) °, ( $10.4 \pm 0.2$ ) °, ( $12.4 \pm 0.2$ ) °, ( $17.3 \pm 0.2$ ) °, ( $19.4 \pm 0.2$ ) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, wherein the at least one ketone is present in a residual amount in the range of from 13 to

0.2 weight-% or in the range of from 12 to 6 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms is more than one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, said residual amount relates to the total amount of said ketone, and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms.

Therefore preferably, the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension comprising of the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably is methyl isobutyl ketone;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably is methyl isobutyl ketone, wherein the at least one ketone is present in a residual amount in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone is more than one of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, said residual amount relates to the total amount of said ketones and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone which is one or more than one of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone.

Therefore preferably, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone which is methyl isobutyl ketone;
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone which is methyl isobutyl ketone, wherein methyl isobutyl ketone is present in a residual amount in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone which is methyl isobutyl ketone.

It is contemplated that in all the above embodiments the mixture of 2) can be a solution.

- 5 The amount of ketone of the solid crystalline form 7 of 3) is equal or less, preferably less than the amount of the ketone in the solvent system or of the amount of the solvent system of 2). The purpose of 3) is to remove or reduce the excess of solvent system and/or of the solvents that affect the stability of the crystalline form to obtain the composition of the invention.

10 It is preferred that the composition of 3) does not comprise the solvents, as defined above that affect the stability of the crystalline form 7 and the aprotic non-ketonic organic solvent.

As to step 3), any method for recovering the composition of 3) from 2) is a method suitable according to the present invention.

15 It is contemplated that the solid crystalline form 7 in the mixture of 2) which is a suspension is separated from the solvent system of 2). Hence it is contemplated that the recovering of 3) comprises a separating step (3-1). In the separating of (3-1) the solid crystalline form of sofosbuvir of formula (I) of 2) is separated from the mixture of 2). A composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3) is obtained. The composition of (3-1) comprises an amount of solvent system which is less than the amount of the solvent system of  
20 the mixture of 2).

The separating step (3-1) can comprise or consist of a solid-liquid separation process. Preferably the solid-liquid separation process comprises filtration or centrifugation, more preferably filtration. The solid-liquid separation process optionally comprises a washing step, preferably in addition to the filtration or the centrifugation steps.

25 As disclosed above it is contemplated that the separating step according to (3-1) preferably comprises a filtration step.

Hence step (3-1) preferably further comprises

(A) subjecting the mixture of 2) comprising the solid crystalline form of sofosbuvir of formula (I), to a solid-liquid separation process, preferably to filtration.

30

It is contemplated that the separating step according to (3-1), preferably the solid-liquid separation according to (A) may further comprise washing the solid crystalline form of sofosbuvir wherein said washing is preferably carried out after the solid-liquid separation as described above in (A). Preferably, the washing is carried out with the at least one ketone having from 4

to 8 carbon atoms of the solvent system of 2). More preferably, the solvent for washing is methyl isobutyl ketone.

From the separating step (3-1) the composition of 3) is preferably obtained. This is easily achieved when the solvent system of 2) does not comprise the aprotic non-ketonic organic solvent and/or a solvent that affect the crystalline form 7 stability.

Alternatively, from the separating step (3-1) a composition that comprises the solid crystalline form 7 and the solvent system of 2) is obtained. In said composition the amount of solvent system is not yet the residual amount of the ketone of the composition of 3), albeit in said composition the amount of solvent system of 2) is reduced by the separation step (3-1) relative to the amount in 2). In this case, further to the separating step a drying step can be carried out.

According to the present invention, it is preferred that the solid crystalline form of sofosbuvir which is obtained in 2), preferably is obtained from the separation according to (3-1), is suitably dried according to (3-2).

It is conceived that the drying according to (3-2) is carried out to obtain the composition of the invention. Hence, the drying step may be used to remove from the composition of (3-1) the one aprotic non-ketonic organic solvent and/or to reduce the amount of the at least one ketone to the amount of the composition of 3). Hence, according to the present invention, the aprotic non-ketonic organic solvent is removed, preferably completely removed from the composition of (3-1) to obtain the composition of 3).

The term “completely removed” means that no aprotic non-ketonic organic solvent is detectable in the composition of 3) when it is measured according to the gas chromatographic analysis as disclosed in Reference Example 1.4.2.

No specific restrictions exist regarding the drying conditions of (3-2) provided that the composition of the invention is obtained.

Preferably, drying according to (3-2) is carried out at temperatures in the range of from 20 to 50 °C, more preferably of from 20 to 45 °C, more preferably of from 20 to 30 °C, more preferably of from 22 to 25 °C.

Preferably, drying according to (3-2) is carried out at a pressure below ambient pressure, preferably at an absolute pressure of at most 500 mbar. More preferably, drying is carried out at an absolute pressure in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar, more preferably of from 5 to 50 mbar. Therefore, more preferably, drying according to

(3-2) is carried out at a temperature in the range of from 20 to 50 °C and an absolute pressure in the range of from 5 to 500 mbar, more preferably at a temperature in the range of from 20 to 30 °C and an absolute pressure in the range of from 5 to 50 mbar. Preferably, drying is carried out for a period of time in the range of from 0.1 to 48 hours, preferably of from 0.1 to 24 hours.

It is also conceived that step (3-2) is omitted if the amount of solvent system of (3-1) is the residual amount of solvent of the composition of 3).

It is also conceived that step (3-1) is omitted and step (3-2) is directly carried out on the mixture of 2).

Hence, the recovering of 3) comprises

- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); and
- (3-2) optionally drying the composition of (3-1) and obtaining the composition of 3).

Hence, the recovering of 3) comprises

- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); wherein the separating of (3-1) comprises
  - (A) subjecting the mixture of 2) comprising the solid crystalline form of sofosbuvir of formula (I), to a solid-liquid separation process, preferably to filtration; and
- (3-2) optionally drying the composition of (3-1) and obtaining the composition of 3).

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms;

3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms, said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms and

wherein the recovering of 3) comprises

(3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); and

(3-2) optionally drying the composition of (3-1) and obtaining the composition of 3) and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone.

It is preferred in the above process that the separating of step (3-1) comprises step (A).

Therefore, preferably the present invention relates to the above-defined process, comprising

1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm$

0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;

2) preparing a mixture, wherein the mixture is a suspension, comprising the sofosbuvir provided in 1) and at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms;

3) recovering from the mixture of 2) a composition comprising

the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

the at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, wherein the at least one ketone is present in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, wherein in case the an at least one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, is more than one ketone having from 5 to 7 carbon atoms, preferably 5 or 6 carbon atoms, said residual amount relates to the total amount of said ketones and

wherein the recovering of 3) comprises

(3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); and

(3-2) optionally drying the composition of (3-1) and obtaining the composition of 3) and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone.

It is preferred in the above process that the separating of step (3-1) comprises step (A).

Further, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably is methyl isobutyl;
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

-the at least one ketone which is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably is methyl isobutyl, wherein said at least one ketone is present in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, wherein in case the at least one ketone is more than one of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone said residual amount relates to the total amount of said ketones;

wherein the recovering of 3) comprises

- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); and
- (3-2) optionally drying the composition of (3-1) and obtaining the composition of 3), and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

- 5 wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone.

It is preferred in the above process that the separating of step (3-1) comprises step (A).

Further, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 15 2) preparing a mixture, wherein the mixture is a suspension comprising, the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, one ketone which is methyl isobutyl ketone;
- 3) recovering from the mixture of 2) a composition comprising
  - the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and
  - 25 -one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition and

30 wherein the recovering of 3) comprises

- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2) comprising, preferably consisting of, one ketone which is methyl isobutyl ketone, wherein preferably said composition is the composition of 3); and
- 35

(3-2) optionally drying the composition of (3-1) and obtaining the composition of 3), and

wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the at least one ketone.

It is preferred in the above process that the separating of step (3-1) comprises step (A).

Therefore, the present invention relates to the above-defined process, comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture, wherein the mixture is a suspension, comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of one ketone which is methyl isobutyl ketone and at least one aprotic non-ketonic organic solvent which is diethyl ether;
- 3) recovering from the mixture of 2) a composition comprising

the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

one ketone which is methyl isobutyl ketone, wherein the one ketone is present in a residual amount is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition and

wherein the recovering of 3) comprises

- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of

sofosbuvir of formula (I) and the solvent system of 2),

(3-2) drying the composition of (3-1) and obtaining the composition of 3), and

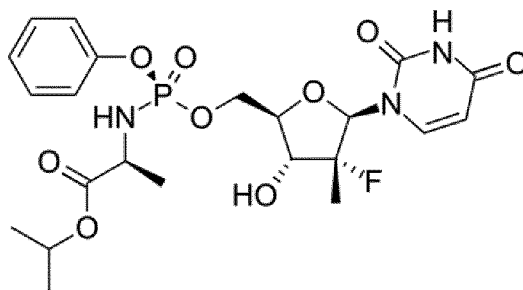
wherein at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at  
5 least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of  
the solid crystalline form of sofosbuvir and of solvent system of 2), and

wherein at least 99.7 weight-%, preferably at least 99.9 weight-% of the composition of 3)  
consists of the solid crystalline form of sofosbuvir and of the one ketone.

10 It is contemplated that step (3-1) and/or step (3-2) is omitted, in case one or both of these  
steps is not necessary in order to obtain the composition of the invention.

It is contemplated that in the above embodiments the mixture of 2) can also be a solution. In  
this case the recovering of 3) further encompasses a crystallization step wherein the solid  
15 crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising  
no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising  
reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  
 $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-  
Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm is obtained. The separation of (3-1)  
20 and the drying of (3-2) are then carried out.

It is further conceived that the present invention is directed to a process for preparing the  
composition comprising a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the  
25 range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  
 $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temper-  
ature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of  
0.15419 nm, in particular as described in Reference Example 1.1 herein; and  
at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present  
30 in the composition in a residual amount which is equal or less than 27 weight-%, preferably in

a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

5 the process comprising

- 1') providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in  
10 the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2') preparing a mixture, wherein the mixture is a composition comprising the solid crystalline form of sofosbuvir of formula (I) provided in 1') and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms wherein  
15 the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total  
20 amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

Step 1') is the same as step 1) as discloses above. Preferably, the solid crystalline form in 1')  
25 is provided as dry solid crystalline form.

The at least one ketone having from 4 to 8 carbon atoms is as defined above in the "Ketone" section of step 2). It is preferred that said at least one ketone is methyl isobutyl ketone.

It is contemplated that preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of  
30 2') consists of the solid crystalline form 7 of sofosbuvir and of at least one ketone having from 4 to 8 carbon atoms. It is preferred that the mixture does not comprise an aprotic non-ketonic organic solvent. The presence of an aprotic non-ketonic organic solvent is detected according to the gas-chromatographic method disclosed in Reference Example 1.4.2. It is further preferred that at least 99 weight-% or at least 99.5 weight-% or at least 99.7 weight-%,  
35 preferably at least 99.9 weight-% of the mixture consists of the solid crystalline form 7 of sofosbuvir and methyl isobutyl ketone.

Hence, according to the present invention it is further conceived that the composition of the invention is prepared by directly adding to the solid crystalline form 7 of sofosbuvir of 1'), preferably by directly adding to the dry solid crystalline form 7 of sofosbuvir of 1') an amount of solvent system, wherein the solvent system is as disclosed above, to achieve the desired amount of residual solvent of the composition of the invention. In this case, the composition of 3) is the mixture of 2').

According to the present invention, the term "crystalline form 7 of sofosbuvir", the term "solid crystalline form 7 of sofosbuvir", the term "crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm" and the term "solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm" are similar and used interchangeably.

The solid crystalline form 7 of sofosbuvir according to the present invention has an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably

- comprises XRPD reflections at 2-theta angles of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and preferably comprises additional XRPD reflections at 2-theta angles of (12.1 ± 0.2) °, (13.5 ± 0.2) °, (16.2 ± 0.2) °, (16.8 ± 0.2) °, (18.0 ± 0.2) °, (18.7 ± 0.2) °, (20.2 ± 0.2) °, (20.9 ± 0.2) °, (22.1 ± 0.2) °, (23.4 ± 0.2) °, (25.4 ± 0.29 °, (28.0 ± 0.2)°, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm; and/or
- exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3252 ± 2) cm<sup>-1</sup>, (2928 ± 2) cm<sup>-1</sup>, (1718 ± 2) cm<sup>-1</sup>, (1668 ± 2) cm<sup>-1</sup>, (1456 ± 2) cm<sup>-1</sup>, when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of (1494 ± 2) cm<sup>-1</sup>, (1373 ± 2) cm<sup>-1</sup>, (1265 ± 2) cm<sup>-1</sup>, (1223 ± 2) cm<sup>-1</sup>, (945 ± 2) cm<sup>-1</sup>, when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell; and/or
- has the monoclinic space group symmetry P2<sub>1</sub> and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:  
a = (5.16 ± 0.04) Angstrom;

b = (16.86 ± 0.12) Angstrom;

c = (14.44 ± 0.10) Angstrom;

alpha = 90.0 °;

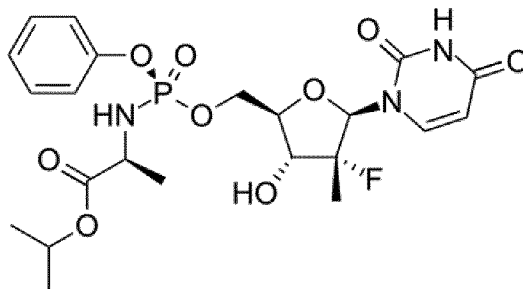
beta = (100.2 ± 0.8) °;

gamma = 90.0 °; and/or

- has a melting point in the range of from 122 to 126 °C when measured via differential scanning calorimetry at a heating rate of 10 °C/min at a pressure in the range of from 0.95 to 1.05 bar, in particular determined according to Reference Example 3; and/or
- comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.9 ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, as determined via thermogravimetric analysis; and/or
- comprising at most 0.4 weight-% of water based on the weight of the crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.9 ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, as determined via gravimetric moisture sorption / desorption analysis at a temperature of (25.0 ± 0.1) °C and a relative humidity of from 0 to 95 %.

The present invention is further directed to a process for preparing a solid crystalline form 7 of sofosbuvir of formula (I), wherein the workup is carried out with a solvent system according to the present invention. Advantageously, the use of solvent system according to the present invention as defined for step 2) above in the workup step allows to carry out the workup easily and to recover pure solid crystalline form 7 in a stable form, even when the solid crystalline form 7 is prepared or crystallized in a solvent, such as disclosed above or in patent application CN 104130302 A, that affects the stability of the crystalline form 7, preferably under mechanical stress. Advantageously, the solid crystalline form 7 during the workup and the final recovered solid crystalline form 7 are stable i.e., no transformation into another crystalline form is observed or a transformation which is slower than the transformation in the presence of solvent that affects the stability of the solid crystalline form 7 is observed.

Hence, the present invention is further directed to a process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

- (x) providing sofosbuvir according to formula (I) in a crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in a solvent; and
- (xx) carrying out the work up of step (x) with a solvent system comprising, preferably consisting of at least one ketone having from 4 to 8 carbon atoms, and obtaining said solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 wherein said solid crystalline form is dry or comprises less than 0.5 weight-%, preferably less than 0.3 weight-%, more preferably less than 0.1 weight-%, more preferably less than 0.05 weight-%, more preferably less than 0.01 weight-% of the solvent of x) and/or of the solvent system of xx) based on the total amount of said solid crystalline form and the solvent of x) and/or of the solvent system xx).

Preferably the crystalline form obtained in (xx) does not contain the solvent of (x).

The providing of (x) contemplates any process for preparing solid crystalline form 7 of sofosbuvir. It preferably contemplates the crystallization step that leads to the solid crystalline form

7. It may also contemplate the synthesis of sofosbuvir and the crystallization thereof to crystalline form 7.

The solvent of (x) is any solvent suitable for crystallizing form 7 of sofosbuvir. The solvent of (x) preferably is not the solvent system of step (xx). The solvent system of (x) is for example selected from group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water. These solvents are as disclosed in details and individualized above in connection with step 1) of the present invention.

The solvent system and the ketone of (xx) are disclosed in details and individualized above in connection with step 2) and the section "Ketone".

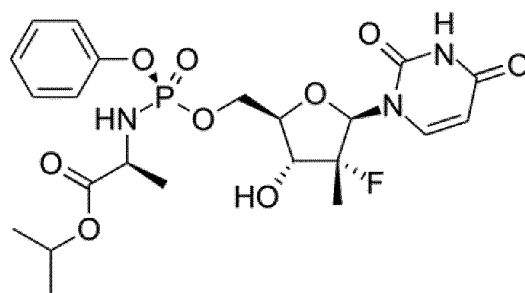
Preferably in the process as disclosed above after (x) and before (xx), the crystalline form is separated from the solvent of (x). It is preferred that in the separation, mechanical stress is avoided as much as possible. Hence after step (x), the process may further comprise the step

(x-1) separating the crystalline form of sofosbuvir of (x) from the solvent of (x).

Preferably the workup of (xx) comprises preparing a suspension or a solution of the crystalline form 7 of (x) or (x-1). The suspension is preferably according to step 2) as disclosed above.

Preferably the workup of (xx) comprises separating the crystalline form 7 from the solvent system of (xx), more preferably the separating comprises a filtering step and/or a drying step. Preferably the workup of (xx) comprises steps 2) and 3) as disclosed above. More preferably, the workup of (xx) comprises steps 2), 3) and (3-1) and discloses above. Optionally the workup of (xx) comprises steps (3-2) and/or (A) as discloses above.

Further, the present invention relates to a process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of

0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

- (i') providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- 5 (ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
- 10 (iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  in its mother liquor.

15 Step (i')

According to (i'), sofosbuvir according to formula (I) is provided in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms.

- 20 No specific restrictions exist regarding the specific form of sofosbuvir which is employed in (i'). Preferably, according to (i'), sofosbuvir according to formula (I) is provided in a crystalline form which does not comprise, more preferably which is not, crystalline form 6 of sofosbuvir according to formula (I) having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(6.1 \pm 0.2)^\circ$ ,  $(8.2 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.7 \pm 0.2)^\circ$ ,  $(17.2 \pm 0.2)^\circ$ ,  $(17.7 \pm 0.2)^\circ$ ,  $(18.0 \pm 0.2)^\circ$ ,  $(18.8 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ ,  $(19.8 \pm 0.2)^\circ$ ,  $(20.1 \pm 0.2)^\circ$ ,  $(20.8 \pm 0.2)^\circ$ ,  $(21.8 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. More preferably, according to (i'), sofosbuvir according to formula (I) is provided in crystalline form 1, amorphous form, or as a mixture of two or more of these forms. More preferably, according to (i'), sofosbuvir according to formula (I) is provided in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, or is provided in amorphous form.

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The crystalline form 1 and the amorphous form of sofosbuvir can be prepared, for example, as disclosed in WO 2010/135569 A1.

The crystalline form 7 of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° preferably

- comprises XRPD reflections at 2-theta angles of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, and preferably comprises additional XRPD reflections at 2-theta angles of  $(12.1 \pm 0.2)^\circ$ ,  $(13.5 \pm 0.2)^\circ$ ,  $(16.2 \pm 0.2)^\circ$ ,  $(16.8 \pm 0.2)^\circ$ ,  $(18.0 \pm 0.2)^\circ$ ,  $(18.7 \pm 0.2)^\circ$ ,  $(20.2 \pm 0.2)^\circ$ ,  $(20.9 \pm 0.2)^\circ$ ,  $(22.1 \pm 0.2)^\circ$ ,  $(23.4 \pm 0.2)^\circ$ ,  $(25.4 \pm 0.29)^\circ$ ,  $(28.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm; and/or
- exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of  $(3252 \pm 2) \text{ cm}^{-1}$ ,  $(2928 \pm 2) \text{ cm}^{-1}$ ,  $(1718 \pm 2) \text{ cm}^{-1}$ ,  $(1668 \pm 2) \text{ cm}^{-1}$ ,  $(1456 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of  $(1494 \pm 2) \text{ cm}^{-1}$ ,  $(1373 \pm 2) \text{ cm}^{-1}$ ,  $(1265 \pm 2) \text{ cm}^{-1}$ ,  $(1223 \pm 2) \text{ cm}^{-1}$ ,  $(945 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell; and/or
- has the monoclinic space group symmetry P2<sub>1</sub> and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:  
 $a = (5.16 \pm 0.04) \text{ Angstrom}$ ;  
 $b = (16.86 \pm 0.12) \text{ Angstrom}$ ;  
 $c = (14.44 \pm 0.10) \text{ Angstrom}$ ;  
 $\alpha = 90.0^\circ$ ;  
 $\beta = (100.2 \pm 0.8)^\circ$ ;  
 $\gamma = 90.0^\circ$ ; and/or
- has a melting point in the range of from 122 to 126 °C when measured via differential scanning calorimetry at a heating rate of 10 °C/min at a pressure in the range of from 0.95 to 1.05 bar, in particular determined according to Reference Example 3; and/or
- comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.9 °, as determined via thermogravimetric analysis; and/or
- comprising at most 0.4 weight-% of water based on the weight of the crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.9 ° as determined via gravimetric moisture sorption / desorption analysis at a temperature of  $(25.0 \pm 0.1)^\circ\text{C}$  and a relative humidity of from 0 to 95 %.

Steps (ii') and (iii')

According to (ii'), a mixture is prepared comprising the sofosbuvir provided in (i') and a solvent system, wherein the solvent system comprises at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent which does not comprise toluene.

## 5 Ketone

Preferably, the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group ( $C=O$ ) wherein the number of the carbon atoms of the alkyl residues or of the alkanediyl group, together with the carbon atom of the carbonyl group, add up to the total number of carbon atoms of 9. Preferably, the at least one ketone is one or more of diisobutyl ketone, di-n-butyl ketone, di-tert-butyl ketone, 2-methyl-4-octanone, 2-nonanone, 3-nonanone, and 5-nonanone. More preferably, the at least one ketone comprises diisobutyl ketone. More preferably, the at least one ketone is diisobutyl ketone.

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Therefore, the present invention relates to the above-defined process, comprising

- (i') providing sofosbuvir according to formula (I) in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms; preferably in crystalline form 1;
  - (ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
  - (iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  in its mother liquor;
- wherein according to (ii'), the at least one ketone is diisobutyl ketone

## 35 Aprotic non-ketonic organic solvent

According to the present invention, the solvent system according to (ii') does not comprise toluene. The term "does not comprise toluene" as used in this context of the present relates a solvent system which, if at all, contains toluene only as an impurity of one of the components

of the solvent system. Preferably, the term "does not comprise toluene" as used in this context of the present preferably relates to a solvent system having a toluene content of at most 5000 weight-ppm, preferably at most 2000 weight-ppm, more preferably at most 1000 weight-ppm, based on the total weight of the solvent system.

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Surprisingly, it was found that with regard to the solvent-mediated transformation according to (iii'), the essential absence of toluene has an advantageous influence on the reproducibility of the crystallization process. Further, it was surprisingly found that the essential absence of toluene allows carrying out step (iii') of the process of the invention involving an industrial  
10 scale process design comprising agitation, preferably mechanically agitating, more preferably stirring, leading to short crystallization times.

With regard to the chemical nature of the at least one aprotic non-ketonic organic solvent, it is preferred that the at least one aprotic non-ketonic organic solvent consists of carbon and hy-  
15 drogen or consists of carbon, hydrogen and oxygen.

It is also preferred that the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, or one or more ether compounds, or one or more ester compounds, or a mixture of one two or more thereof. If a mixture of two or more aprotic non-  
20 ketonic organic solvent is used, the can be composed of two or more aromatic compounds, two or more ether compounds, two or more ester compounds, one or more aromatic compounds and one or more ether compounds, one or more aromatic compounds and one or more ester compounds, one or more ether compounds and one or more ester compounds, or one or more aromatic compounds and one or more ether compounds and one or more ester com-  
25 pounds, wherein for every mixture, it is preferred that the respectively used compounds consist of carbon, hydrogen and optionally oxygen.

A preferred solvent system according to (ii') may comprise, preferably consist of, the at least one ketone described above and at least one aromatic compound preferably consisting of car-  
30 bon, hydrogen and optionally oxygen, more preferably of carbon and hydrogen. Conceivably, the at least one aromatic compound may be one or more of dimethyl benzenes such as 1,2-dimethyl benzene or 1,3-dimethyl benzene or 1,4-dimethyl benzene, benzene, methoxy benzene, chlorobenzene.

A preferred solvent system according to (ii') may comprise, preferably consist of, the at least one ketone described above and at least one ether compound preferably consisting of carbon, hydrogen and optionally oxygen, more preferably of carbon and hydrogen. Conceivably, the at least one ether compound may be one or more of methyl tert-butyl ether, diethyl ether, and diisopropyl ether.

A preferred solvent system according to (ii') comprises, preferably consists of, at least one ester compound which is one or more of acetates, more preferably one or more of 1-methyl ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, and ethyl acetate. More preferably, the at least one ester compound comprises 1-methyl ethyl acetate. More preferably, the at least one ester compound consists of 1-methyl ethyl acetate. Therefore, a preferred solvent system according to (ii') comprises, preferably consists of, the at least one ketone described above and 1-methyl ethyl acetate.

Preferably, the mixture according to (ii') consists of the sofosbuvir provided in (i'), the at least one ketone having 9 carbon atoms and the at least one aprotic non-ketonic organic solvent which does not comprise toluene. More preferably, the mixture according to (ii') consists of sofosbuvir provided in (i'), diisobutyl ketone and the at least one aprotic non-ketonic organic solvent which does not comprise toluene. Also more preferably, the mixture according to (ii') consists of sofosbuvir provided in (i'), the at least one ketone having 9 carbon atoms and 1-methyl ethyl acetate. More preferably, the mixture according to (ii') consists of sofosbuvir provided in (i'), diisobutyl ketone and 1-methyl ethyl acetate. The term "consists of" as used in this context of the present invention relates to a mixture which, in addition to the specifically mentioned compounds, only contains impurities which may be present in these compounds.

In the mixture according to (ii'), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is not specifically restricted. Preferably, it is in the range of from 0.1:1 to 10:1, more preferably of from 0.2: 1 to 5:1, more preferably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably of from 0.9:1 to 1.1:1, such as from 0.95:1 to 1.05:1 or from 0.99:1 to 1.01:1.

In the mixture according to (ii'), the content of the sofosbuvir relative to the solvent system is not specifically restricted. Preferably, the mixture contains the sofosbuvir, relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 100 to 500 mg/mL, more preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL, such as from 150 to 200 mg/mL or from 175 to 225 mg/mL or from 200 to 250 mg/mL.

According to the present invention, there are no specific restriction how the mixture according to (ii') is prepared. It is preferred that according to (ii'), a solution is prepared comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

According to a first alternative, the solution can be prepared by suspending the sofosbuvir

provided in (i') in at least a portion of the solvent system preferably comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent. According to this alternative, it is preferred that suspending the sofosbuvir provided in (i') is carried out at a temperature of the at least a portion of the solvent system in the range of from 5 to 35 °C, preferably of from 10 to 35 °C, more preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. It is further preferred that the respectively prepared suspension is suitably heated to dissolve the suspended sofosbuvir, preferably to a temperature of above 35 °C, more preferably at least 40 °C, more preferably in the range of from 40 °C to the less than the boiling point of the solvent system. If the solvent system comprises two or more component, the term "boiling point of the solvent system" refers to the boiling point of the component having the lowest boiling point. Preferred temperature ranges may be, for example, from 40 to 50 °C or from 40 to 48 °C or from 40 to 46 °C or from 40 to 44 °C.

According to a second alternative, the solution can be prepared by dissolving the sofosbuvir provided in (i') in at least a portion of one or more of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I), and adding at least a portion of one or more of the at least one aprotic non-ketonic organic solvent. Preferred temperature ranges for preparing the solution and adding the at least one aprotic non-ketonic organic solvent ranges may be, for example, from 15 to 35 °C or from 20 to 30 °C, wherein the temperature refers to the temperature of the solution.

Surprisingly, it was found that the specific choice of ketones having 9 carbon atoms in combination with an aprotic non-ketonic organic solvent which does not comprise toluene allows agitation, preferably mechanical agitation, more preferably stirring of the mixture during its preparation without having any negative influences on the solvent-mediated transformation to obtain solid crystalline form 7 of sofosbuvir. Even more surprisingly, it was found that not only during preparing the mixture according to (ii') but also during subjecting this mixture to solvent-mediated transformation conditions according to (iii'), it is possible to agitate, preferably to mechanically agitate, more preferably to stir the mixture. It is noted that according to prior art processes, for example disclosed in CN 104130302 A, it is mandatory that no stirring is carried out. However, the strict avoidance of stirring usually results in crystallized material deposited at the walls of the reaction vessel and the like, or results in very long crystallization times, thus rendering the overall process non-suitable for industrial purposes, and limiting the process solely to academic interests.

Therefore, the present invention relates to the process as described above, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

Surprisingly, it was found that the inventive use of a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene allows for agitating, preferably mechanically agitating, more preferably stirring the mixture during subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') for a very short period of time. In particular, it was found that the crystalline form 7 can be obtained in a very pure form if, when subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii'), the mixture is agitated, preferably mechanically agitated, more preferably stirred for a period of time of less than 3 h, preferably at most 2.5 h, more preferably in the range of from 0.25 to 2.5 h, more preferably in the range of from 0.5 to 2 h, more preferably in the range of from 0.5 to 1.5 h.

Therefore, the present invention also relates to the use of a ketone having 9 carbon atoms for reducing the crystallization time of the solvent mediated transformation of sofosbuvir to obtain crystalline form 7 of sofosbuvir. Further, the present invention also relates to the use of a combination of at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more ester compounds, more preferably comprising 1-methyl ethyl acetate, more preferably being 1-methyl ethyl acetate, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, for reducing the crystallization time of the solvent mediated transformation of sofosbuvir to obtain crystalline form 7 of sofosbuvir.

#### Solvent-mediated transformation conditions

According to (iii'), it is preferred that agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more suitable temperatures of the mixture which are preferably in the range of from -5 to 35 °C, preferably from 0 to 30 °C. In order to achieve this temperature, it may be necessary to cool the mixture prepared in (ii'), in particular in case the mixture was prepared including heating to a temperature preferably in the range of from at least 40 °C to less than the boiling point of the solvent system as described above. Therefore, it may be preferred that subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises cooling the mixture. If the mixture is respectively cooled, suitable temperature to which the mixture is cooled are in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture during cooling of the mixture.

According to the present invention, it is preferred that subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises seeding the mixture. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having 9 carbon atoms and an aprotic non-ketonic organic solvent which does not comprise toluene allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture during seeding of the mixture. It is preferred that if the mixture is seeded, seed crystals of sofosbuvir are used which exhibit crystalline form 7. The amount of the seed crystals added during seeding of the mixture is not subject to any specific restrictions. Preferably, based on the amount of sofosbuvir contained in the mixture to be seeded, seed crystals in an amount in the range of from 1 to 15 weight-%, preferably of from 5 to 12 weight-%, more preferably of from 8 to 10 weight-%, are added to the mixture. Generally, adding the seed crystals can be carried out at any suitable temperature of the mixture. Preferably, this temperature is in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C, such as from 15 to 20 °C or from 20 to 25 °C or from 25 to 30 °C. If the mixture was cooled as described above, it may be preferred that the seed crystals are added to the mixture at the temperature to which the mixtures was cooled. Surprisingly, it was found that the specific choice of the solvent system comprising at least one ketone having 9 carbon atoms and an aprotic non-ketonic organic solvent which does not comprise toluene allows to agitate, preferably to mechanically agitate, more preferably to stir the mixture after seeding of the mixture wherein agitating, preferably mechanical agitating, more preferably stirring is carried out preferably for a period of time in the range of from 0.1 to 48 h, more preferably of from 0.2 to 24 h, more preferably of from 0.5 to 12 h, at a temperature of the mixture which is preferably in the range of from -5 to 35 °C, more preferably from 0 to 30 °C.

#### Steps (iv') and (v')

From step (iii'), the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  is obtained in its mother liquor. While it may be conceivable to suitably use the mother liquor comprising the solid crystalline form of sofosbuvir, it is usually preferred to separate the solid crystalline form of sofosbuvir from the mother liquor and optionally dry the separated solid crystalline form of sofosbuvir. Therefore, the present invention relates to the process described above, further comprising

(iv') separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  from its mother liquor;

(v') drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ .

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For separation purposes according to (iv'), the mother liquor comprising the solid crystalline form of sofosbuvir can be suitably concentrated or diluted, prior to the separation of the solid crystalline form of sofosbuvir. According to the present, it may be preferred to suitably dilute the mother liquor comprising the solid crystalline form of sofosbuvir. Therefore, step (iv') preferably comprises

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(iv'.1) diluting the mother liquor comprising the solid crystalline form of sofosbuvir.

Preferably, diluting the mother liquor comprises adding at least one ketone having 9 carbon atoms to the mother liquor comprising the solid crystalline form of sofosbuvir. With regard to preferred ketones, reference is made to the preferred ketones discussed above in the context of the solvent system according to (ii'). Preferably, the at least one ketone used for diluting according to (iv'.1) is the at least one ketone comprised in the mixture according to (ii').

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In addition to the at least one ketone, at least one aprotic non-ketonic organic solvent can be added to the mother liquor comprising the solid crystalline form of sofosbuvir. While there are no specific restrictions to the chemical nature of the at least one aprotic non-ketonic organic solvent, it is preferred to employ the at least one aprotic non-ketonic organic solvent which is comprised in the mixture according to (ii').

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If both the at least one ketone and the at least one aprotic non-ketonic organic solvent are employed according to (iv'.1), the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is preferably in the range of from 0.1:1 to 10:1, more preferably of from 0.2: 1 to 5:1, more preferably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably from 0.9:1 to 1.1:1. More preferably, the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is the volume ratio of the at least one ketone comprised in the mixture according to (ii') relative to the at least aprotic non-ketonic organic solvent comprised in the mixture according to (ii'). Thus, it may be preferred to use the solvent system according to (ii') to dilute the mother liquor according to (iv'.1).

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The mother liquor comprising the solid crystalline form of sofosbuvir, as obtained from (iii'), or the diluted mother liquor comprising the solid crystalline form of sofosbuvir as obtained from (iv'.1) is preferably subjected to a solid-liquid separation process, preferably compris-

ing filtration or centrifugation, more preferably filtration. Therefore, the separating according to (iv') preferably comprises

(iv'.2) subjecting the mother liquor comprising the solid crystalline form of sofosbuvir, optionally the mother liquor comprising the solid crystalline form of sofosbuvir diluted according to (iv'.1), to a solid-liquid separation process, preferably to filtration.

Preferably, separating according to (iv') further comprises washing the solid crystalline form of sofosbuvir wherein said washing is preferably carried out after the solid-liquid separation as described above. Therefore, separating according to (iv') preferably comprises

(iv'.3) washing the solid crystalline form of sofosbuvir separated from its mother liquor.

Regarding the washing, no specific restrictions exist. Preferably the washing is carried out with at least one aprotic organic compound, optionally the at least one aprotic non-ketonic organic solvent as discussed above in the context of the solvent system according to (ii').

Preferably, one or more of 1-methyl ethyl acetate and diethyl ether are employed. The at least one aprotic organic compound is optionally used in combination with at least one ketone, preferably the at least one ketone as discussed above in the context of the solvent system according to (ii').

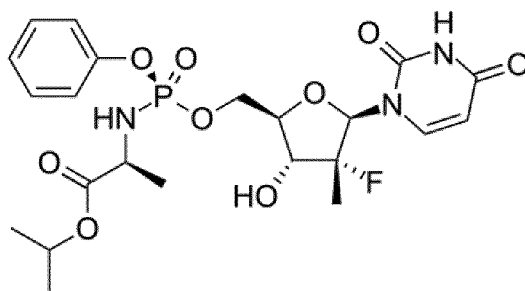
Regarding the temperature at which the washing is carried out, no specific restrictions exist. Preferably, the washing is carried out at a temperature in the range of from 0 to 30 °C, preferably from 15 to 30 °C.

According to the present invention, it is preferred that the solid crystalline form of sofosbuvir which is obtained in (iii') comprised in its mother liquor, preferably obtained from the separation according to (iv'), is suitably dried.

No specific restrictions exist regarding the drying conditions. Preferably, drying according to (v') is carried at elevated temperatures relative to ambient temperature, more preferably at a temperature of at least 30 °C. More preferably, drying is carried out at a temperature in the range of from 30 to 50 °C, more preferably of from 35 to 45 °C. Preferably, drying according to (v') is carried at a pressure below ambient pressure, preferably at an absolute pressure of at most 500 mbar. More preferably, drying is carried out at an absolute pressure below 1 bar, preferably in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar, more preferably of from 5 to 50 mbar. Therefore, more preferably, drying according to (v') is carried out at a temperature in the range of from 30 to 50 °C and an absolute pressure in the range of from 5 to 500 mbar, more preferably at a temperature in the range of from 35 to 45 °C and an absolute pressure in the range of from 5 to 50 mbar. Preferably, drying is carried out for a period of time in the range of from 1 to 48 hours, preferably of from 6 to 24 hours.

Compositions

Further, the present invention relates to a mixture comprising sofosbuvir of formula (I)

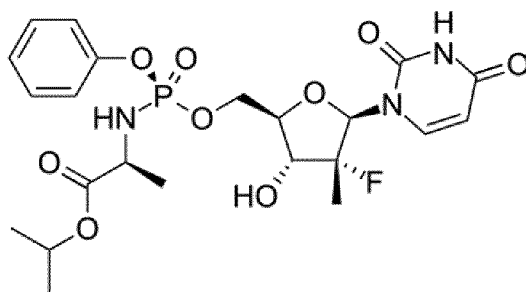


(I),

and a solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably 5 or 6 carbon atoms, and optionally at least one aprotic non-ketonic organic solvent. With regard to specific, preferred ketones, specific, preferred aprotic non-ketonic organic solvents and specific, preferred combinations thereof, reference is made to the respective discussion concerning the solvent system according to (ii). Preferably, in said mixture, the sofosbuvir of formula (I) comprises a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. More preferably, in said mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, relative to the total content of solid crystalline sofosbuvir is at least 99%, preferably at least 99.5 %, more preferably at least 99.9 %.

Further, the present invention relates to a composition comprising

- solid crystalline form 7 of sofosbuvir of formula (I)



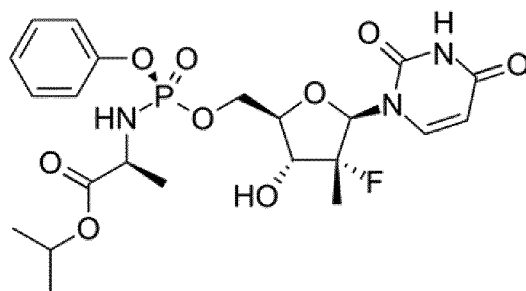
(I),

wherein the crystalline form 7 of sofosbuvir has an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

-at least one ketone having from 4 to 8 carbon atoms in a residual amount. The residual amount is preferably equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms, said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

The ketone is as defined above in the “Ketone” paragraph related to the process for stabilization the crystalline form 7.

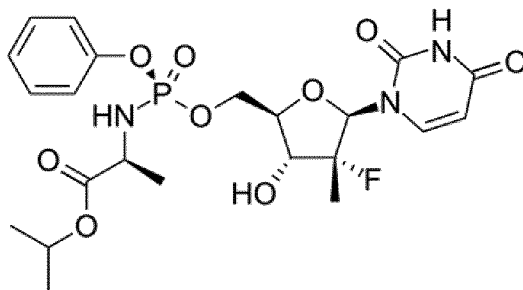
Further, the present invention relates to solid crystalline form of sofosbuvir of formula (I)



(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , obtainable or obtained by a process as described above comprising steps 1) to 3).

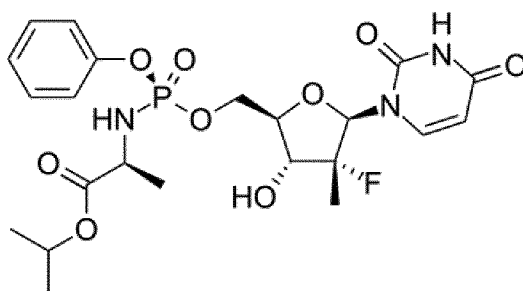
Further, the present invention relates to solid crystalline form of sofosbuvir of formula (I)



(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, obtainable or obtained by a process as described above comprising steps (1') and (2').

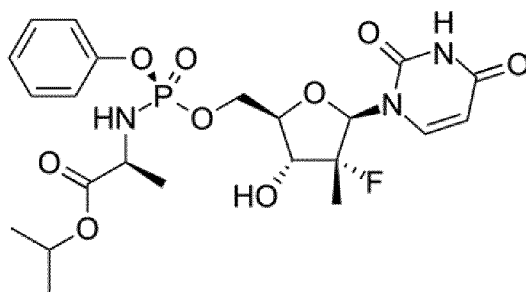
Further, the present invention relates to solid crystalline form of sofosbuvir of formula (I)



(I),

10 having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, obtainable or obtained by a process, as described above, comprising steps (x) and (xx).

15 Therefore, the present invention relates to a composition comprising crystalline form 7 of sofosbuvir of formula (I)



(I),

wherein the crystalline form 7 of sofosbuvir has an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm and

methyl isobutyl ketone in a residual amount. The residual amount is preferably equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

It is further preferred that the composition comprises crystalline form 7 as defined above and a residual amount of methyl isobutyl ketone, wherein the residual amount is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition. It is further preferred that the composition comprises crystalline form 7 as defined above and a residual amount of methyl isobutyl ketone, wherein the residual amount is in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

According to the invention, preferably at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the solid crystalline form 7 of sofosbuvir and of at least one ketone having from 4 to 8 carbon atoms, said at least one ketone having from 4 to 8 carbon atoms being in the residual amount as specified above. It is preferred that the composition does not comprise aprotic non-ketonic organic solvent. The presence of aprotic non-ketonic organic solvent is detected according to the gas-chromatographic method disclosed in Reference Example 1.4.2.

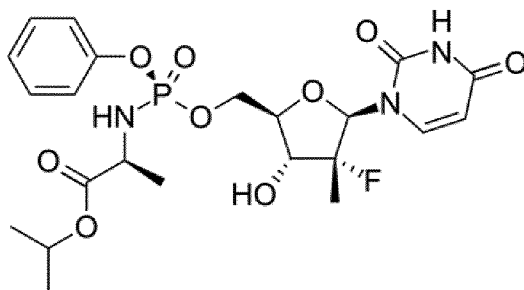
A preferred composition according to the invention composition comprises the solid crystalline form 7 of sofosbuvir and methyl isobutyl ketone, the methyl isobutyl ketone being in the

residual amount specified above and wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the solid crystalline form 7 of sofosbuvir and methyl isobutyl ketone.

- 5 It has been found that the crystalline form 7 in the composition is stable. The crystalline form 7 in the composition when undergoes the oscillatory ball mill test as described in Reference Example 1.7 b) does not undergo polymorphic transformation into crystalline form 6. The crystalline form 7 of sofosbuvir of formula (I) in the composition has preferably a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b).

- Preferably, in said composition, the sofosbuvir of formula (I) comprises a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm. More preferably, in said mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, relative to the total content of solid crystalline sofosbuvir is at least 99%, preferably at least 99.5%, more preferably at least 99.9 %.

Further, the present invention relates to a mixture comprising sofosbuvir of formula (I)

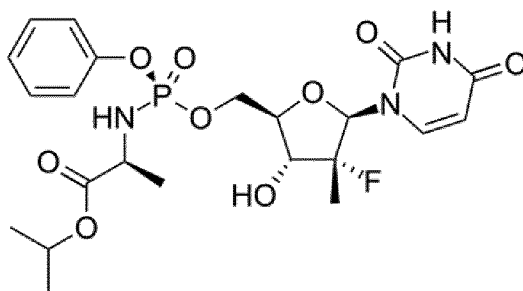


(I),

- and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic solvent does not comprise toluene. With regard to specific, preferred ketones, specific, preferred aprotic

non-ketonic organic solvents and specific, preferred combinations thereof, reference is made to the respective discussion concerning the solvent system according to (ii'). Preferably, in said mixture, the sofosbuvir of formula (I) comprises a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm. More preferably, in said mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  relative to the total content of solid crystalline sofosbuvir is at least 99 %, preferably at least 99.5 %, more preferably at least 99.9 %.

Further, the present invention relates to solid crystalline form of sofosbuvir of formula (I)



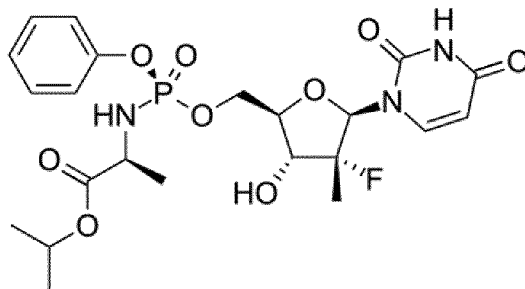
(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , obtainable or obtained by a process as described above, preferably comprising steps (iv') and (v') as described above.

The composition of the invention as disclosed above is obtainable or obtained according to any of the processes of the invention as disclosed above.

## Uses

Further, the present invention relates to solid crystalline form of sofosbuvir of formula (I)

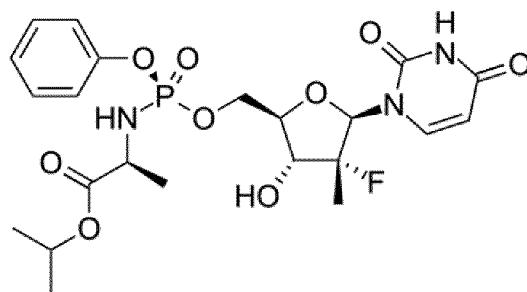


(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, obtainable or obtained by a process as described above, preferably comprising steps (iv) and (v) as described above.

Still further, the present invention relates to the use of the crystalline form of sofosbuvir obtainable or obtained by the process according to the present invention for the preparation of a pharmaceutical composition; to a method of using said crystalline form for the preparation of a pharmaceutical composition; to a pharmaceutical composition comprising, in an pharmaceutically effective amount, said crystalline form and at least one pharmaceutically acceptable excipient; to said pharmaceutical composition for use in a method for treating hepatitis C in a human; to the use of said pharmaceutical composition for treating hepatitis C in a human; to a method of treating hepatitis C in a human comprising administering said pharmaceutical composition to a human; to the use of said crystalline form for preparing a medicament for the treatment hepatitis C in a human; to the use of said crystalline form for the treatment of hepatitis C in a human; to said crystalline form for use in the treatment of hepatitis C in a human; to said crystalline form for the treatment of hepatitis C in a human; to a method of treating hepatitis C in a human comprising administering said crystalline form.

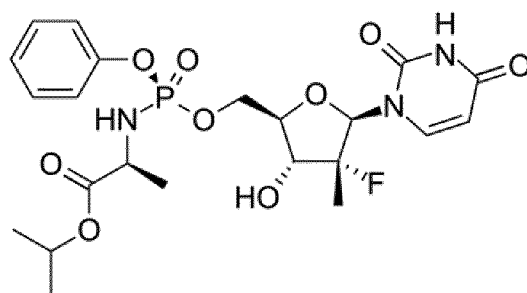
Further, the present invention relates to the use of a ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably 5 or 6 carbon atoms, for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. With regard to specific, preferred ketones, reference is made to the respective discussion concerning the solvent system according to (ii). In particular, the present invention relates to said use wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.

Yet further, the present invention relates to the use of at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably 5 or 6 carbon atoms, and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more aromatic compounds, one or more ether compounds, one or more ester compounds, or a mixture of one two or more thereof, as medium for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm. With regard to specific, preferred ketones, specific, preferred aprotic non-ketonic organic solvents and specific, preferred combinations thereof, reference is made to the respec-

tive discussion concerning the solvent system according to (ii). In particular, the present invention relates to said use wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.

Furthermore it was surprisingly found that the solid crystalline form of sofosbuvir obtainable or obtained by the process of the present invention can be mechanically stressed without any influence on the crystalline form. As shown in Example 4 herein, this advantageous stress resistance can be observed for the solid material in wet form, for example comprised in its mother liquor, as well as for the solid material in its dried form. As shown in Example 4 (Ex 4.1 and Ex4.2) herein, this advantageous stress resistance can be observed for the solid material in wet form, for example comprised in its mother liquor, as well as for the solid material in its dried form. Preferably, the solid crystalline form of sofosbuvir has a mechanical stress resistance of at least 1 min at 20 Hz and at least 1 min at 10 Hz, preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 5 min at 10 Hz, more preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 8 min at 10 Hz, as determined by ball-milling, in particular as described in Reference Example 1.7 and Examples 3 herein. Also this particular feature of the obtained solid material shows the superiority of the process of the invention in that it is especially industrially applicable since avoidance of mechanical stress during filtering or drying on industrial scale is unacceptably difficult.

Further it was surprisingly found that a ketone having from 4 to 8 carbon atoms, preferably a ketone having from 5 to 7 carbon atoms, more preferably 6 carbon atoms, more preferably being methyl isobutyl ketone, acts as stabilizer of the sofosbuvir crystalline form 7. In particular it has surprisingly been found that the polymorphic stability of sofosbuvir crystalline form 7 when subjected to mechanical stress is directly influenced by the nature and the amount of residual solvent. It has been found that a defined residual amount of ketone having from 4 to 8 carbon atoms, preferably of a ketone having from 5 to 7 carbon atoms, more preferably of a ketone having 6 carbon atoms, more preferably of a ketone being methyl isobutyl ketone can ensure polymorphic stability despite mechanical stress. Advantageously, the ketone having from 4 to 8 carbon atoms, preferably a ketone having from 5 to 7 carbon atoms, more preferably a ketone having 6 carbon atoms, more preferably a ketone being methyl isobutyl ketone, can be used in the workup of any process for obtaining the crystalline form 7 of sofosbuvir, since when this solvent is used crystalline form 7 of sofosbuvir undergoes mechanical stress without transformation into other polymorphic form.

Advantageously the crystalline form 7, preferably the crystalline form 7 in the composition of the invention having a residual amount of at least one ketone having from 4 to 8 carbon atoms can be used in industrial process, requiring subjecting crystalline form 7 to mechanical stress

such as the stress due to filtration, centrifugation, processing of the filter cake, drying, mechanical agitation and stirring without observing polymorphic transformation.

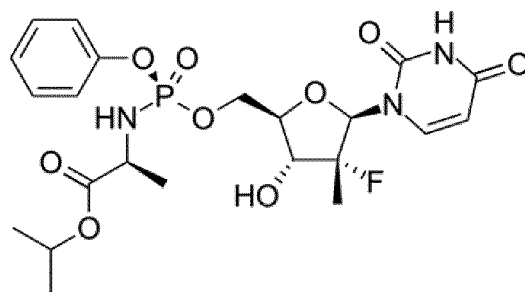
Preferably, the solid crystalline form of sofosbuvir has a mechanical stress resistance of at least 1 min at 20 Hz and at least 1 min at 10 Hz, preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 5 min at 10 Hz, more preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 8 min at 10 Hz, as determined by ball-milling, in particular as described in Reference Example 1.7 and Example 4 herein.

Preferably, the crystalline form 7 of sofosbuvir of formula (I) in the composition of the invention comprising at least one ketone having from 4 to 8 carbon atoms, preferably having from 5 to 7 carbon atoms, more preferably having 6 carbon atoms, more preferably being methyl isobutyl ketone, in a residual amount as disclosed above, has preferably a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b)

Also this particular feature of the obtained solid material shows the superiority of the process of the invention in that it is especially industrially applicable since avoidance of mechanical stress during filtering or drying on industrial scale is unacceptably difficult.

Still further, the present invention relates to the use of the crystalline form of sofosbuvir obtainable or obtained by the process according to the present invention for the preparation of a pharmaceutical composition; to a method of using said crystalline form for the preparation of a pharmaceutical composition; to a pharmaceutical composition comprising, in an pharmaceutically effective amount, said crystalline form and at least one pharmaceutically acceptable excipient; to said pharmaceutical composition for use in a method for treating hepatitis C in a human; to the use of said pharmaceutical composition for treating hepatitis C in a human; to a method of treating hepatitis C in a human comprising administering said pharmaceutical composition to a human; to the use of said crystalline form for preparing a medicament for the treatment hepatitis C in a human; to the use of said crystalline form for the treatment of hepatitis C in a human; to said crystalline form for use in the treatment of hepatitis C in a human; to said crystalline form for the treatment of hepatitis C in a human; to a method of treating hepatitis C in a human comprising administering said crystalline form.

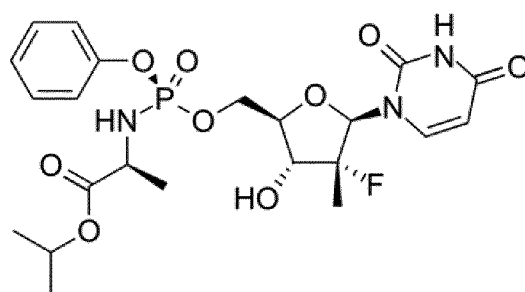
Further, the present invention relates to the use of a ketone having 9 carbon atoms for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm. With regard to specific, preferred ketones, reference is made to the respective discussion concerning the solvent system according to (ii'). In particular, the present invention relates to said use wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.

Yet further, the present invention relates to the use of a combination of at least one ketone having 9 carbon atoms, preferably diisobutyl ketone, and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more ester compounds, more preferably comprising 1-methyl ethyl acetate, more preferably being 1-methyl ethyl acetate, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, as medium for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

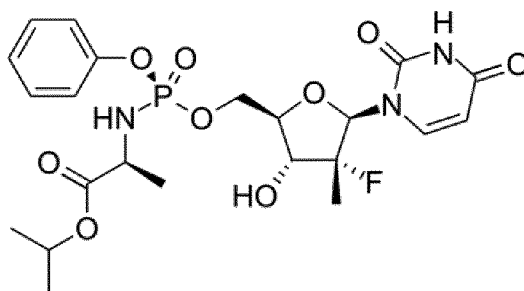
having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm. In particular, the present invention relates to said use wherein the solvent-

mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.

The present invention is further illustrated by the following embodiments and combinations of embodiments resulting from the given dependencies and back-references:

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1. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

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- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having from 4 to 8 carbon atoms and optionally at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in its mother liquor.

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2. The process of embodiment 1, wherein according to (i), the sofosbuvir is provided in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of (5.0 ± 0.2) °, (7.3 ± 0.2) °, (9.4 ± 0.2) °, (16.6 ± 0.2) °, (17.3 ± 0.2) °, (18.1 ± 0.2) °, (22.0 ± 0.2) °, (25.0 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in

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particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms, preferably in crystalline form 1.

3. The process of embodiment 1 or 2, wherein according to (ii), the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group ( $C=O$ ).
4. The process of any of embodiments 1 to 3, wherein according to (ii), the at least one ketone has from 5 to 7 carbon atoms.
5. The process of embodiment 4, wherein the at least one ketone is one or more of cyclopentanone, cyclohexanone, cycloheptanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, ethyl isopropyl ketone, methyl n-pentyl ketone, methyl 2-pentyl ketone, methyl 3-pentyl ketone, methyl 2-methylbutyl ketone, methyl 3-methylbutyl ketone, methyl 3-methylbut-2-yl ketone, methyl 2-methylbut-2-yl ketone, methyl 2,2-dimethylpropyl ketone, ethyl n-butyl ketone, ethyl isobutyl ketone, ethyl tert-butyl ketone, di-n-propyl ketone, di-isopropyl ketone, and n-propyl isopropyl ketone.
6. The process of any of embodiments 1 to 5, wherein according to (ii), the at least one ketone has 5 or 6 carbon atoms.
7. The process of embodiment 6, wherein the at least one ketone is one or more of cyclopentanone, cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, and ethyl isopropyl ketone.
8. The process of embodiment 6 or 7, wherein the at least one ketone is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone.
9. The process of embodiment 7 or 8, wherein the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone.
10. The process of embodiment 8 or 9, wherein the at least one ketone is methyl isopropyl ketone or methyl isobutyl ketone.

11. The process of embodiment 8 or 9, wherein the at least one ketone is methyl isobutyl ketone.
12. The process of any of embodiments 1 to 11, said process comprising
- 5 (i) providing sofosbuvir according to formula (I) in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms; preferably in crystalline form 1;
- 10 (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone and preferably at least one aprotic non-ketonic organic solvent;
- 15 (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a
- 20 temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor;
- wherein according to (ii), the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, preferably methyl isopropyl ketone or methyl isobutyl ketone, more preferably methyl isobutyl
- 25 ketone.
13. The process of any of embodiments 1 to 12, wherein the solvent system according to (ii) further comprises at least one aprotic non-ketonic organic solvent.
- 30 14. The process of any of embodiments 1 to 13, wherein according to (ii), the at least one aprotic non-ketonic organic solvent consists of carbon, hydrogen, and optionally oxygen.
- 35 15. The process of any of embodiments 1 to 14, wherein according to (ii), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, one or more ether compounds, one or more ester compounds, or a mixture of one two or more thereof.

16. The process of any of embodiments 1 to 14, wherein according to (ii), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, preferably is one or more aromatic compounds.
- 5 17. The process of embodiment 16, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, toluene.
18. The process of any of embodiments 1 to 14, wherein according to (ii), the at least one aprotic non-ketonic organic solvent comprises one or more ether compounds, preferably is one or more ether compounds.
- 10 19. The process of embodiment 18, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, methyl tert-butyl ether.
- 15 20. The process of any of embodiments 12 to 14, wherein according to (ii), the at least one aprotic non-ketonic organic solvent comprises one or more ester compounds, preferably is one or more ester compounds.
21. The process of embodiment 20, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, 1-methyl ethyl acetate.
- 20 22. The process of any of embodiments 1 to 21, wherein the mixture according to (ii) does not comprise ethanol.
- 25 23. The process of any of embodiments 1 to 22, wherein the mixture according to (ii) does not comprise one or more of methanol, ethanol, acetone, butanone, and acetonitrile.
24. The process of any of embodiments 1 to 23, wherein the mixture according to (ii) does not comprise n-butanol.
- 30 25. The process of any of embodiments 1 to 24, wherein the mixture according to (ii) does not comprise one or more of n-propanol, n-butanol, and n-pentanol.
26. The process of any of embodiments 1 to 25, wherein the mixture according to (ii) does not comprise one or more of a C<sub>3</sub> alcohol, a C<sub>4</sub> alcohol, and a C<sub>5</sub> alcohol.
- 35 27. The process of any of embodiments 1 to 26, wherein the mixture according to (ii) does not comprise an aliphatic alcohol.

28. The process of any of embodiments 1 to 27, wherein the mixture according to (ii) does not comprise n-heptane.
29. The process of any of embodiments 1 to 28, wherein the mixture according to (ii) does not comprise one or more of hexane, n-pentane, cyclohexane, and n-heptane.
30. The process of any of embodiments 1 to 29, wherein the mixture according to (ii) does not comprise a C<sub>7</sub> alkane.
31. The process of any of embodiments 1 to 29, wherein the mixture according to (ii) does not comprise one or more of a C<sub>5</sub> alkane, a C<sub>6</sub> alkane, a C<sub>7</sub> alkane, a C<sub>8</sub> alkane, or a mixture of two or more thereof, more preferably a C<sub>7</sub> alkane.
32. The process of any of embodiments 1 to 31, wherein the mixture according to (ii) does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 600 g/mol.
33. The process of any of embodiments 1 to 32, wherein the mixture according to (ii) does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 1000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 2000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 3000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 6000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 300 to 7000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 200 to 8000 g/mol, more preferably does not comprise a polyethylene glycol.
34. The process of any of embodiments 1 to 33, said process comprising
- (i) providing sofosbuvir according to formula (I) in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of (5.0 ± 0.2) °, (7.3 ± 0.2) °, (9.4 ± 0.2) °, (16.6 ± 0.2) °, (17.3 ± 0.2) °, (18.1 ± 0.2) °, (22.0 ± 0.2) °, (25.0 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms; preferably in crystalline form 1;

(ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone and preferably at least one aprotic non-ketonic organic solvent;

(iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor;

wherein according to (ii), the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, preferably methyl isopropyl ketone or methyl isobutyl ketone; and

wherein according to (ii), the at least one aprotic non-ketonic organic solvent is toluene or methyl tert-butyl ether or 1-methyl ethyl acetate, more preferably toluene.

35. The process of embodiment 34, wherein the at least one ketone is methyl isobutyl ketone.

36. The process of any of embodiments 1 to 35, wherein in the mixture according to (ii), the combination of the at least one ketone and the at least one aprotic non-ketonic organic solvent is not, preferably does not comprise, the combination of diethyl ketone with 1-methyl ethyl acetate or with methyl tert-butyl ether.

37. The process of any of embodiments 1 to 36, wherein in the mixture according to (ii), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.1 : 1 to 10 : 1, preferably of from 0.2 : 1 to 5 : 1, more preferably of from 0.5 : 1 to 2 : 1, more preferably of from 0.8 : 1 to 1.2 : 1, more preferably of from 0.9 : 1 to 1.1 : 1.

38. The process of any of embodiments 1 to 37, wherein the mixture according to (ii) contains the sofosbuvir according to formula (I), relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 100 to 500 mg/mL, preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL.

39. The process of any of embodiments 1 to 38, wherein the mixture according to (ii) contains the sofosbuvir according to formula (I), relative to the at least one ketone and the

at least one aprotic non-ketonic organic solvent, in an amount in the range of from 175 to 225 mg/mL.

- 5 40. The process of any of embodiments 1 to 39, wherein preparing the mixture according to (ii) comprises preparing a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.
- 10 41. The process of any of embodiments 1 to 40, wherein preparing the mixture according to (ii) comprises suspending the sofosbuvir provided in (i) in at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent.
- 15 42. The process of embodiment 41, wherein suspending the sofosbuvir provided in (i) in at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent is carried out at a temperature of the at least a portion of the solvent system in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.
- 20 43. The process of embodiment 41 or 42, wherein preparing the mixture according to (ii) comprises suspending the sofosbuvir provided in (i) in at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent, and heating the obtained suspension, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.
- 25 44. The process of embodiment 43, wherein the obtained suspension is heated to a temperature of at least 40 °C, preferably to a temperature in the range of from 40 °C to less than the boiling point of the component of the solvent system having the lowest boiling point.
- 30 45. The process of any of embodiments 1 to 40, wherein preparing the mixture according to (ii) comprises dissolving the sofosbuvir provided in (i) in at least a portion of one or more of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I).
- 35 46. The process of embodiment 45, wherein preparing the mixture according to (ii) comprises dissolving the sofosbuvir provided in (i) in at least a portion of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I).

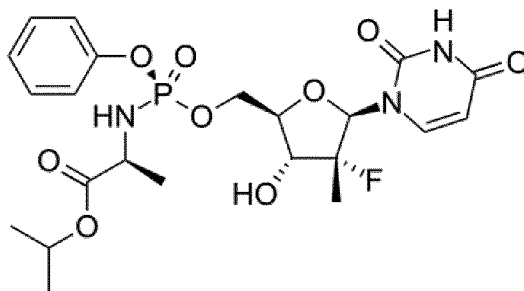
47. The process of embodiment 45 or 46, further comprising adding at least a portion of one or more of the at least one aprotic non-ketonic organic solvent, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

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48. The process of embodiment 47, comprising adding at least a portion of the at least one aprotic non-ketonic organic solvent, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

10 49. The process of any of embodiments 1 to 48, wherein preparing the mixture according to (ii) comprises agitation, preferably mechanical agitation, more preferably stirring.

50. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

15 having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

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- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having from 4 to 8 carbon atoms and optionally at least one aprotic non-ketonic organic solvent;
- 25 (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a

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temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in its mother liquor;  
preferably the process of any of embodiments 1 to 49,  
wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises agitating the mixture, preferably mechanically agitating the mixture.

51. The process of embodiment 50, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises stirring the mixture.

52. The process of embodiment 50 or 51, wherein according to (ii), the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, preferably methyl isopropyl ketone or methyl isobutyl ketone; and wherein according to (ii), the at least one aprotic non-ketonic organic solvent is toluene or methyl tert-butyl ether or 1-methyl ethyl acetate.

53. The process of embodiment 52, wherein the at least one ketone is methyl isobutyl ketone.

54. The process of any of embodiments 50 to 53, wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.

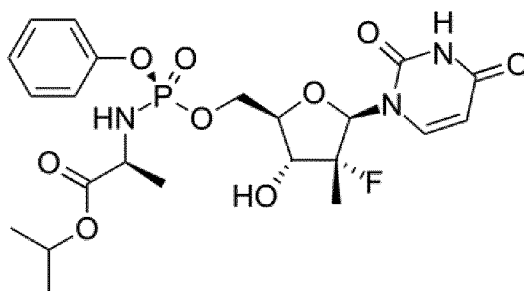
55. The process of any of embodiments 1 to 54, preferably of embodiment 43 or 44, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises cooling the mixture.

56. The process of embodiment 55, wherein the mixture is cooled to a temperature in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.

57. The process of embodiment 55 or 56, wherein cooling the mixture comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

58. The process of any of embodiments 1 to 57, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises seeding the mixture.

59. The process of embodiment 58, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises seeding the solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system obtained according to the process of embodiment 40, preferably of embodiment 43 or 44, or of any of embodiments 45 to 48.
60. The process of embodiment 58 or 59, wherein seeding the mixture comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.
61. The process of any of embodiments 58 to 60, wherein the mixture is seeded with seed crystals of sofosbuvir of formula (I)



(I)

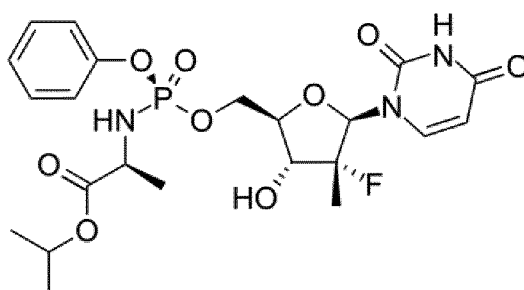
- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.
62. The process of embodiment 61, wherein, based on the amount of sofosbuvir contained in the mixture, seed crystals in an amount in the range of from 1 to 15 weight-%, preferably of from 5 to 12 weight-%, more preferably of from 8 to 10 weight-%, are added to the mixture.
63. The process of any of embodiments 58 to 62, wherein seeding the mixture is carried out at a temperature of the mixture in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.
64. The process of any of embodiments 58 to 63, wherein after seeding, the mixture is agitating, preferably mechanically agitating, more preferably stirring.

65. The process of embodiment 64, wherein after seeding, the mixture is agitated, preferably mechanically agitated, more preferably stirred, for a period of time in the range of from 0.1 to 48 h, preferably of from 0.2 to 24 h, more preferably of from 0.5 to 12 h.

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66. The process of embodiment 64 or 65, wherein after seeding, the mixture is agitated, preferably mechanically agitated, more preferably stirred, at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.

- 10 67. The process of any of embodiments 1 to 66, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) does not comprise adding seed crystals of sofosbuvir of formula (I)



(I)

15 having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.

- 20 68. The process of any of embodiments 1 to 67, further comprising
- (iv) separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, from its mother liquor;
  - (v) drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a
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wavelength of 0.15419 nm.

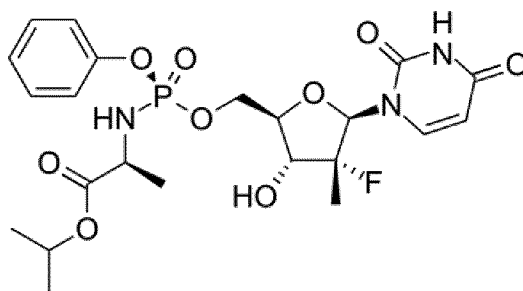
69. The process of any of embodiments 61 to 66, wherein the seed crystals of sofosbuvir of formula (I) are prepared by a process according to embodiment 67, preferably by a process according to embodiment 68 insofar as embodiment 68 is dependent on embodiment 67.
70. The process of embodiment 68 or 69, wherein (iv) comprises  
(iv.1) diluting the mother liquor comprising the solid crystalline form of sofosbuvir.
71. The process of embodiment 70, wherein diluting comprises adding at least one ketone having from 4 to 8 carbon atoms to the mother liquor comprising the solid crystalline form of sofosbuvir, preferably the at least one ketone comprised in the mixture according to (ii).
72. The process of embodiment 71, wherein in addition to the at least one ketone having from 4 to 8 carbon atoms, at least one aprotic non-ketonic organic solvent is added to the mother liquor comprising the solid crystalline form of sofosbuvir, preferably the at least one aprotic non-ketonic organic solvent comprised in the mixture according to (ii).
73. The process of embodiment 72, wherein the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is in the range of from 0.1 : 1 to 10 : 1, preferably of from 0.2 : 1 to 5 : 1, more preferably of from 0.5 : 1 to 2 : 1, more preferably of from 0.8 : 1 to 1.2 : 1, more preferably from 0.9:1 to 1.1:1.
74. The process of embodiment 72 or 73, wherein the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is the volume ratio of the at least one ketone comprised in the mixture according to (ii) relative to the at least aprotic non-ketonic organic solvent comprised in the mixture according to (ii).
75. The process of any of embodiments 68 to 74, wherein separating according to (iv) comprises  
(iv.2) subjecting the mother liquor comprising the solid crystalline form of sofosbuvir, optionally the mother liquor comprising the solid crystalline form of sofosbuvir diluted according to any of embodiments 70 to 74, to a solid-liquid separation process, preferably to filtration.

76. The process of any of embodiments 68 to 75, wherein the separation of (iv) or (iv.2) is by filtration.
77. The process of any of embodiments 68 to 76, wherein separating according to (iv) comprises  
(iv.3) washing the solid crystalline form of sofosbuvir separated from its mother liquor.
78. The process of embodiment 77, wherein washing according to (iv.3) is carried out with at least one aprotic organic compound, optionally the at least one aprotic non-ketonic organic solvent as defined in any of embodiments 14 to 21, preferably with one or more of toluene and diethyl ether, wherein the at least one aprotic organic compound is optionally used in combination with at least one ketone, preferably the at least one ketone as defined in any of embodiments 1 to 11.
79. The process of embodiment 77 or 78, wherein washing according to (iv.3) is carried out at a temperature in the range of from 0 to 30 °C, preferably of from 15 to 30 °C.
80. The process of any of embodiments 68 to 79, wherein according to (v), drying is carried out at a temperature in the range of from 30 to 50 °C, preferably of from 35 to 45 °C.
81. The process of any of embodiments 68 to 80, wherein according to (v), drying is carried out at an absolute pressure below 1 bar, preferably in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar, more preferably of from 5 to 50 mbar.
82. The process of any of embodiments 68 to 81, wherein according to (v), drying is carried out for a period of time in the range of from 1 to 48 hours, preferably of from 6 to 24 hours.
83. The process of any of embodiments 1 to 82, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of  $(3252 \pm 2) \text{ cm}^{-1}$ ,  $(2928 \pm 2) \text{ cm}^{-1}$ ,  $(1718 \pm 2) \text{ cm}^{-1}$ ,  $(1668 \pm 2) \text{ cm}^{-1}$ ,  $(1456 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of  $(1494 \pm 2) \text{ cm}^{-1}$ ,  $(1373 \pm 2) \text{ cm}^{-1}$ ,  $(1265 \pm 2) \text{ cm}^{-1}$ ,  $(1223 \pm 2) \text{ cm}^{-1}$ ,  $(945 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, in particular as described in Reference Example 1.2 herein.

84. The process of any of embodiments 1 to 83, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° has the monoclinic space group symmetry  $P2_1$  and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:
- 5  
a = (5.16 ± 0.04) Angstrom;  
b = (16.86 ± 0.12) Angstrom;  
c = (14.44 ± 0.10) Angstrom;  
alpha = 90.0 °;  
10 beta = (100.2 ± 0.8) °;  
gamma = 90.0 °.
85. The process of any of embodiments 1 to 84, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, has a melting point in the range of from 122 to 126 °C when measured via differential scanning calorimetry at a heating rate of 10 K/min at a pressure in the range of from 0.95 to 1.05 bar, in particular as described in Reference Example 1.3 herein.
- 15  
20
86. The process of any of embodiments 1 to 85, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form, as determined via thermogravimetric analysis, in particular as described in Reference Example 1.4 herein.
- 25
87. The process of any of embodiments 1 to 86 wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, comprises at most 0.4 weight-% of water based on the weight of the crystalline form as determined via gravimetric moisture sorption / desorption analysis at a temperature of (25.0 ± 0.1) °C and a relative humidity of from 0 to 95 %, in particular as described in Reference Example 1.5 herein.
- 30  
35
88. The process of any of embodiments 1 to 87, wherein the crystalline form of sofosbuvir of formula (I) has a mechanical stress resistance of at least 10 min at 10 Hz, preferably

at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b)

- 5 89. A process for preparing a composition comprising a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein and

at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

said process comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture comprising the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of at least one ketone having from 4 to 8 carbon atoms; and
- 3) recovering from the mixture of 2) a composition comprising

-the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

-the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

90. The process of embodiment 89, wherein the solid crystalline form of 1) is provided in conditions that do not affect the polymorphic stability of the crystalline form of 1).

91. The process of embodiment 90, wherein solid crystalline form of 1) is dry.

92. The process of embodiment 89, wherein the solid crystalline compound of 1) is provided comprising of or in the presence of a solvent that affects the stability of the crystalline form of sofosbuvir of formula (I) of 1) wherein the solvent is in an amount of less than 3 weight-% or less than 2 weight-% or less than 1 weight-% or less than 0.5 weight-%, preferably less than 0.3 weight-%, more preferably less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form 7.

93. The process of embodiment 92, wherein the solvent is selected from the group consisting of an alcohol, a mixture of at least an alcohol and at least an alkane, and water.

94. The process of embodiment 93, wherein the alcohol is an aliphatic alcohol, more preferably a C1 alcohol, a C2 alcohol, a C3 alcohol, a C4 alcohol, a C5 alcohol, or a mixture of two thereof.

95. The process of embodiment 94, wherein the alcohol is selected from the group consisting of methanol, ethanol, n-propanol, n-butanol, n-pentanol or a mixture of two thereof.

96. The process of embodiment 93, wherein wherein the alkane is selected form the group consisting of a C5 alkane, a C6 alkane, a C7 alkane, a C8 alkane or a mixture thereof.
97. The process of embodiment 96, wherein the alkane is selected from the group consisting of hexane, n-pentane, cyclohexane, and n-heptane, more preferably n-heptane.
98. The process of embodiment 93, wherein the mixture of at least an alcohol and at least an alkane comprises preferably consists of at least and alcohol and at least an alkane wherein preferably the alcohol is an aliphatic alcohol, more preferably a C1 alcohol, a C2 alcohol, a C3 alcohol, a C4 alcohol, a C5 alcohol, or a mixture of two thereof and wherein preferably the alkane is selected form the group consisting of a C5 alkane, a C6 alkane, a C7 alkane, a C8 alkane or a mixture thereof.
99. The process of embodiment 93, wherein the mixture of at least an alcohol and at least an alkane comprises the alcohol selected from the group consisting of methanol, ethanol, n-propanol, n-butanol, n-pentanol or a mixture of two thereof and the alkane selected from the group consisting of hexane, n-pentane, cyclohexane, and n-heptane, more preferably n-heptane, preferably wherein the mixture consists of n-butanol and of n-heptane.
100. The process of any of embodiments 93 to 99, wherein the solvent is in an amount of less than 0.5 weight-%, preferably less than 0.3 weight-%, more preferably less than 0.1 weight-% based on the weight of the solvent and the solid crystalline form of sofosbuvir of formula (I) of 1).
101. The process of any of embodiments 89 to 100, wherein the mixture of 2) is a solution or a suspension.
102. The process of any of embodiments 89 to 101, wherein the mixture of 2) is a suspension.
103. The process of any of embodiments 89 to 102, wherein in 2) at least 97 weight-%, or at least 99 weight-% or at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the mixture of 2) consists of the solid crystalline form of sofosbuvir and of solvent system of 2).
104. The process of any of embodiments 89 to 103 wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition of 3) consists of the solid crystalline form of sofosbuvir and of the one ketone which is methyl isobutyl ketone.

105. The process of embodiment 104, wherein at least 99.9 weight-% of the composition consists of the solid crystalline form of sofosbuvir and of at least one ketone having from 4 to 8 carbon atoms.

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106. The process of any of embodiments 89 to 105, wherein the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or wherein  $R_1$  and  $R_2$  together form an alkanediyl group forming a ring with the carbonyl group ( $C=O$ ).

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107. The process of any of embodiments 89 to 106, wherein the at least one ketone has from 5 to 7 carbon atoms.

108. The process of embodiment 107, wherein the at least one ketone is one or more of cyclopentanone, cyclohexanone, cycloheptanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, ethyl isopropyl ketone, methyl n-pentyl ketone, methyl 2-pentyl ketone, methyl 3-pentyl ketone, methyl 2-methylbutyl ketone, methyl 3-methylbutyl ketone, methyl 3-methylbut-2-yl ketone, methyl 2-methylbut-2-yl ketone, methyl 2,2-dimethylpropyl ketone, ethyl n-butyl ketone, ethyl isobutyl ketone, ethyl tert-butyl ketone, di-n-propyl ketone, di-isopropyl ketone, and n-propyl isopropyl ketone.

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109. The process of any of embodiments 89 to 108, wherein the at least one ketone has 5 or 6 carbon atoms.

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110. The process of embodiment 109, wherein the at least one ketone is one or more of cyclopentanone, cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, ethyl n-propyl ketone, and ethyl isopropyl ketone.

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111. The process of embodiment 109 or 110, wherein the at least one ketone is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone.

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112. The process of embodiment 110 or 111, wherein the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone.

113. The process of embodiment 112, wherein the at least one ketone is methyl isopropyl ketone or methyl isobutyl ketone.
- 5 114. The process of any of embodiments 111 to 113, wherein the at least one ketone is methyl isobutyl ketone.
115. The process of any of embodiments 89 to 114, wherein the solvent system according to (2) further comprises at least one aprotic non-ketonic organic solvent.
- 10 116. The process of embodiment 115, wherein according to 2), the at least one aprotic non-ketonic organic solvent consists of carbon, hydrogen, and optionally oxygen.
117. The process of embodiment 115 or 116, wherein according to 2), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, one or more  
15 ether compounds, one or more ester compounds, or a mixture of one two or more thereof.
118. The process of any of embodiments 115 to 117, wherein according to 2), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, preferably  
20 is one or more aromatic compounds.
119. The process of embodiment 118, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, toluene.
- 25 120. The process of any of embodiments 115 to 119, wherein according to 2), the at least one aprotic non-ketonic organic solvent comprises one or more ether compounds, preferably is one or more ether compounds.
121. The process of embodiment 120, wherein the at least one aprotic non-ketonic organic  
30 solvent comprises, preferably is, methyl tert-butyl ether or diethyl ether.
122. The process of any of embodiments 115 to 121, wherein the at least one aprotic non-ketonic organic solvent comprises one or more ester compounds, preferably is one or  
35 more ester compounds.
123. The process of embodiment 122, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, 1-methyl ethyl acetate or isopropyl-acetate.

124. The process of any of embodiments 115 to 123, wherein the at least one ketone is cyclohexanone or diethyl ketone or methyl n-propyl ketone or methyl isopropyl ketone or methyl isobutyl ketone, preferably methyl isopropyl ketone or methyl isobutyl ketone; and wherein according to 2), the at least one aprotic non-ketonic organic solvent is toluene or methyl tert-butyl ether or diethyl ether or 1-methyl ethyl acetate, more preferably diethyl ether.
125. The process of embodiment 124, wherein the at least one ketone is methyl isobutyl ketone.
126. The process of embodiment 124 or 125, wherein the solvent system consists of the at least one ketone, preferably the solvent system consists of methyl isobutyl ketone.
127. The process of embodiment 124, wherein the solvent system consists of a ketone and of a aprotic non-ketonic organic solvent, preferably consists of methyl isobutyl ketone and diethyl ether.
128. The process of embodiments 115 to 127, wherein in the mixture according to 2), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.1 : 1 to 10 : 1, preferably of from 0.2 : 1 to 5 : 1, more preferably of from 0.3 : 1 to 2 : 1.
129. The process of embodiment 128, wherein in the mixture according to 2), the volume ratio of the methyl isobutyl ketone relative to diethyl ether is in the range of from 0.3 : 1 to 2 : 1, preferably of from 0.5 : 1 to 1 : 1.
130. The process of any of embodiments 115 to 129, wherein the one aprotic non-ketonic organic solvent has a boiling point lower than the boiling point of the ketone.
131. The process of any of embodiments 89 to 130, wherein preparing the mixture, wherein the mixture is a suspension, comprises suspending the sofosbuvir provided in 1) in at least a portion of the solvent system of 2).
132. The process of any of embodiments 89 to 131, wherein the mixture of 2) is a suspension and 3) comprises
- (3-1) separating the solid crystalline form of sofosbuvir of formula (I) of 2) from the mixture of 2) and obtaining a composition comprising the solid crystalline form of sofosbuvir of formula (I) and the solvent system of 2), wherein preferably said composition is the composition of 3); and

(3-2) optionally drying the composition of (3-1) and obtaining the composition of 3).

133. The process of embodiment 132, wherein the composition of (3-1) is the composition of 3).

134. The process of embodiment 132 or 133, wherein (3-1) comprises

(A) subjecting the mixture of 2) comprising the solid crystalline form of sofosbuvir of formula (I) to a solid-liquid separation process, preferably to filtration

135. The process of embodiment 132 to 134, wherein according to (3-2), the drying is carried out at a temperature in the range of from 20 to 30 °C, preferably of from 22 to 25 °C.

136. The process of any of embodiments 132 to 135, wherein according to (3-2), the drying is carried out at an absolute pressure below 1 bar, preferably in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar.

137. The process of any of embodiments 115 to 136, wherein in 3) or in (3-2) the aprotic non-ketonic organic solvent is removed, preferably completely removed from the composition.

138. The process of any of embodiments 89 to 137, wherein the mixture of 2) is a solution and wherein the recovering of 3) comprises crystallizing the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.

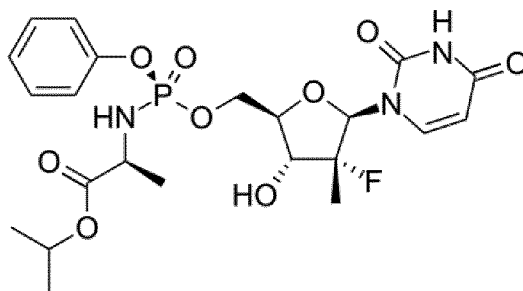
139. The process of embodiment 138, wherein after the crystallization, steps (3-1) and (3-2) are carried out.

140. The process of any of embodiments 89 to 139, wherein the at least one ketone having from 4 to 8 carbon atoms is present in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

141. The process of any of embodiments 89 to 140, wherein the at least one ketone having from 4 to 8 carbon atoms is present in a residual amount in the range of from 13 to 0.2 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

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142. A process for preparing a composition comprising a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein and

at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, said process comprising

- 1') providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2') preparing a mixture wherein the mixture is a composition comprising the sofosbuvir provided in 1') and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in

a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

143. The process of embodiment 142, wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the crystalline form of sofosbuvir of formula (I) and of the at least one ketone having from 4 to 8 carbon atoms.

144. The process of embodiment 142 or 143, wherein the at least one ketone having from 4 to 8 carbon atoms is according to any of embodiments 106 to 114, preferably according to embodiment 114.

145. The process of any of embodiments 142 to 144, wherein 1') is according to step 1) of embodiment 90 or 91.

146. The process of any of embodiments 142 to 145, wherein the at least one ketone having from 4 to 8 carbon atoms is present in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

147. The process of any of embodiments 89 to 146, wherein the at least one ketone having from 4 to 8 carbon atoms is present in a residual amount in the range of from 13 to 0.2 weight-%, preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

148. The process of any of embodiments 89 to 147, wherein the crystalline form 7 of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of  $(3252 \pm 2) \text{ cm}^{-1}$ ,  $(2928 \pm 2) \text{ cm}^{-1}$ ,  $(1718 \pm 2) \text{ cm}^{-1}$ ,  $(1668 \pm 2) \text{ cm}^{-1}$ ,  $(1456 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of  $(1494 \pm 2) \text{ cm}^{-1}$ ,  $(1373 \pm 2) \text{ cm}^{-1}$ ,  $(1265 \pm 2) \text{ cm}^{-1}$ ,  $(1223 \pm 2)$

$\text{cm}^{-1}$ ,  $(945 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, in particular as described in Reference Example 1.2 herein.

149. The process of any of embodiments 89 to 148, wherein the crystalline form of sofos-  
5 buvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° has the monoclinic space group symmetry  $P2_1$  and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K

$a = (5.16 \pm 0.04) \text{ Angstrom}$ ;

10  $b = (16.86 \pm 0.12) \text{ Angstrom}$ ;

$c = (14.44 \pm 0.10) \text{ Angstrom}$ ;

$\alpha = 90.0^\circ$ ;

$\beta = (100.2 \pm 0.8)^\circ$ ;

$\gamma = 90.0^\circ$ .

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150. The process of any of embodiments 89 to 149, wherein the crystalline form of sofos-  
buvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection  
at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the  
range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419  
20 nm, has a melting point in the range of from 122 to 126 °C when measured via differen-  
tial scanning calorimetry at a heating rate of 10 K/min at a pressure in the range of from  
0.95 to 1.05 bar, in particular as described in Reference Example 1.3 herein.

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151. The process of any of embodiments 89 to 150, wherein the crystalline form of sofos-  
25 buvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form, as determined via thermogravimetric analysis, in particular as described in  
30 Reference Example 1.4 herein.

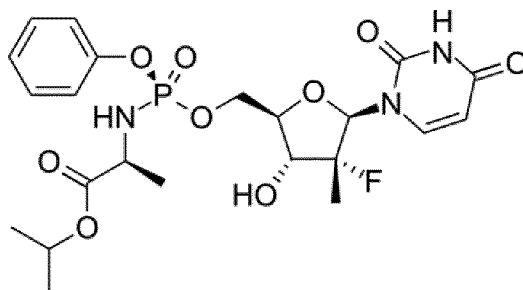
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152. The process of any of embodiments 89 to 151, wherein the crystalline form of sofos-  
buvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection  
at 2-theta angles in the range of from 2.0 to 7.8 °, when measured at a temperature in the  
range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419  
35 nm, comprises at most 0.4 weight-% of water based on the weight of the crystalline  
form as determined via gravimetric moisture sorption / desorption analysis at a tempera-  
ture of  $(25.0 \pm 0.1)^\circ\text{C}$  and a relative humidity of from 0 to 95 %, in particular as de-  
scribed in Reference Example 1.5 herein.

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153. The process of any of embodiments 89 to 152, wherein the crystalline form of sofosbuvir of formula (I) in the composition has a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b).

154. A composition comprising a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

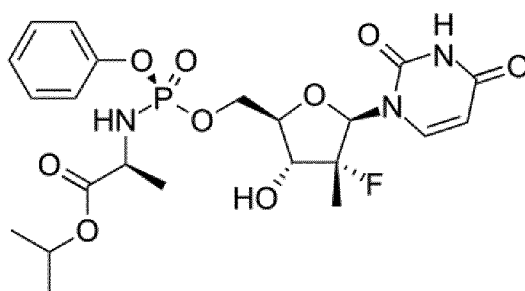
having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein and

at least one ketone having from 4 to 8 carbon atoms, preferably having from 5 to 7 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

and wherein in case the at least one ketone having from 4 to 8 carbon atoms, preferably having from 5 to 7 carbon atoms, is more than one ketone having from 4 to 8 carbon atoms, preferably having from 5 to 7 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms, preferably having from 5 to 7 carbon atoms.

155. The composition of embodiment 154, wherein the at least one ketone is according to any of embodiments 106 to 114, preferably according to embodiment 114.

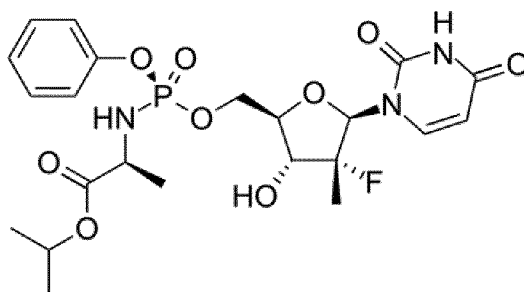
156. The composition of embodiment 154 or 155, wherein the at least one ketone comprises, preferably consists of, methyl isobutyl ketone.
157. The composition of any of embodiments 154 to 156, wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the crystalline form of sofosbuvir of formula (I) and of the at least one ketone.
158. The composition of any of embodiments 154 to 158, which is obtained or obtainable by a process according to embodiments 89 to 153.
159. The composition of any of embodiments 154 to 158, wherein the crystalline form of sofosbuvir of formula (I) has a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b).
160. A solid crystalline form of sofosbuvir of formula (I)



(I),

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, obtainable or obtained by a process according to any of embodiments 1 to 88, preferably according to any of embodiments 68 to 88 more preferably according to any of embodiments 79 to 88.
161. Use of the crystalline form of sofosbuvir according to embodiment 160 or of the composition according to any of embodiments 154 to 159 for the preparation of a pharmaceutical composition.

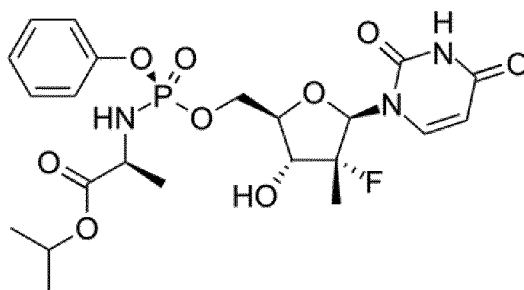
162. A method of using the crystalline form of sofosbuvir according to embodiment 160 or of the composition according to any of embodiments 154 to 159 for the preparation of a pharmaceutical composition.
- 5 163. A pharmaceutical composition, comprising the crystalline form of sofosbuvir according to embodiment 160 and at least one pharmaceutically acceptable excipient.
164. The pharmaceutical composition of embodiment 163, for use in a method for treating hepatitis C in a human.
- 10 165. Use of the pharmaceutical composition of embodiment 164 for treating hepatitis C in a human.
- 15 166. A method of treating hepatitis C in a human comprising administering the pharmaceutical composition of embodiment 164 to a human.
167. Use of the crystalline form of sofosbuvir according to embodiment 160 for preparing a medicament for the treatment of hepatitis C in a human.
- 20 168. Use of the crystalline form of sofosbuvir according to embodiment 160 for the treatment of hepatitis C in a human.
169. The crystalline form of sofosbuvir according to embodiment 160 for use in the treatment of hepatitis C in a human.
- 25 170. The crystalline form of sofosbuvir according to embodiment 160 for the treatment of hepatitis C in a human.
171. The crystalline form of sofosbuvir according to embodiment 160 for the treatment of hepatitis C in a human.
- 30 172. A method of treating hepatitis C in a human comprising administering the crystalline form of sofosbuvir according to embodiment 160 to a human.
- 35 173. Use of a ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

174. Use of a combination of at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more aromatic compounds, one or more ether compounds, one or more ester compounds, or a mixture of one two or more thereof, as medium for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)

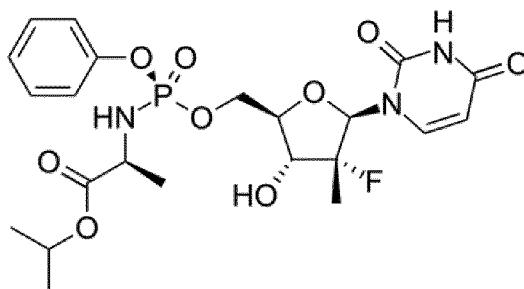


(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

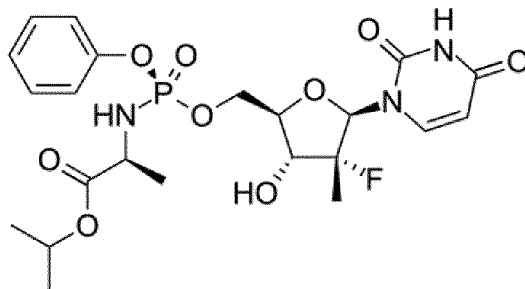
175. The use of embodiment 173 or 174, wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.

176. The use of any of embodiments 173 to 175, preferably of embodiment 175, wherein the solvent mediated transformation of sofosbuvir is carried out in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 600 g/mol, preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 1000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 2000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 3000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 6000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 300 to 7000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 200 to 8000 g/mol, more preferably in the absence of a polyethylene glycol.
177. Use of a ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably the ketone being methyl isobutyl ketone for stabilizing, for physically stabilizing the polymorphic form of sofosbuvir of formula (I)



(I)

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.
178. The use of embodiment 177, wherein the use comprises preparing a composition according to any of embodiments 89 to 153.
179. A mixture comprising sofosbuvir of formula (I)



(I),

and a solvent system comprising at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, and optionally at least one aprotic non-ketonic organic solvent.

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180. The mixture of embodiment 179, wherein the sofosbuvir of formula (I) comprises a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.
181. The mixture of embodiment 180, wherein in the mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, relative to the total content of solid crystalline sofosbuvir is at least 99% preferably at least 99.5 %, more preferably at least 99.9 %.
182. The mixture of any of embodiments 179 to 181, wherein the mixture is a mother liquor comprising solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, said mother liquor being obtainable or obtained by step (iii) of the process according to any of embodiments 1 to 67.

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183. The mixture of any of embodiments 179 to 182, wherein at least one ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms is present in an amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the mixture.

184. The mixture of any of embodiments 179 to 183, wherein the at least one ketone is according to any of embodiments 106 to 114, preferably according to embodiment 114.

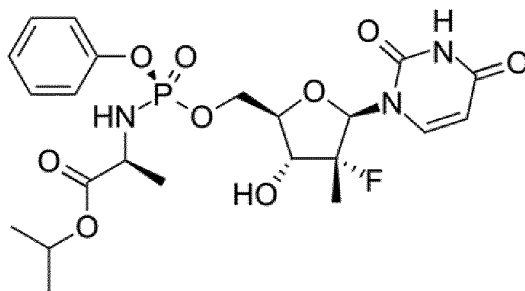
185. The mixture of embodiment 183 or 184, wherein the at least one ketone consists of methyl isobutyl ketone.

186. The mixture of any of embodiments 179 to 185, wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the crystalline form of sofosbuvir of formula (I) and of the residual solvent.

187. The mixture of any of embodiments 183 to 186, which is obtained or obtainable by a process according to embodiments 89 to 141.

188. The mixture of any of embodiments 182 to 187, wherein the crystalline form of sofosbuvir of formula (I) has a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill as described in Reference Example 1.7 b).

189. A solid crystalline form of sofosbuvir of formula (I)



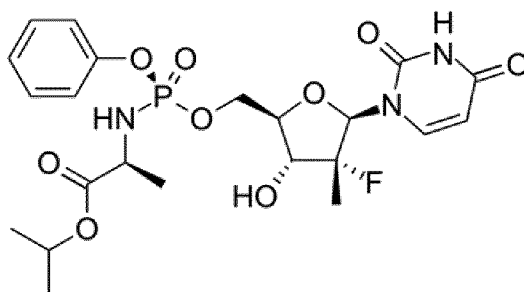
(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said solid crystalline form of sofosbuvir of formula (I) preferably being obtainable or obtained by a process according to any of embodiments 1 to 87, having a mechanical stress resistance of at least 1 min at 20 Hz and at least 1 min at 10 Hz, preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 5 min at 10 Hz, more preferably in the range of from 1 to 2 min at 20 Hz and in the range of from 1 to 8 min at 10 Hz, as determined in an oscillatory ball mill as described in Reference Example 1.7.

190. The solid crystalline form of embodiment 189, comprised in its mother liquor as obtainable or obtained by a process according to any of embodiments 1 to 67 and any of embodiments 83 to 88 insofar as embodiments 83 to 88 are dependent on any of embodiments 1 to 67.

191. The solid crystalline form of embodiment 189 as obtainable or obtained by a process according to any of embodiments 68 to 82 and any of embodiments 83 to 88 insofar as embodiments 83 to 88 are dependent on any of embodiments 68 to 82.

192. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

- (x) providing sofosbuvir according to formula (I) in a crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in a solvent;
- (xx) carrying out the workup of (x) with a solvent system comprising, preferably consisting of at least one ketone having from 4 to 8 carbon atoms, wherein preferably the at least one ketone having from 4 to 8 carbon atoms is according to any of embodiments 106 to 130, more preferably according to any of embodiments 106 to 114 and obtaining said solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1,

wherein said solid crystalline form of (xx) is dry or comprises less than 0.5 weight-%, preferably less than 0.3 weight-%, more preferably less than 0.1 weight-%, more preferably less than 0.05 weight-%, more preferably less than 0.01 weight-% of the solvent of (x) and/or of the solvent system of (xx) based on the total amount of said solid crystalline form and the solvent of (x) and/or of the solvent system of (xx).

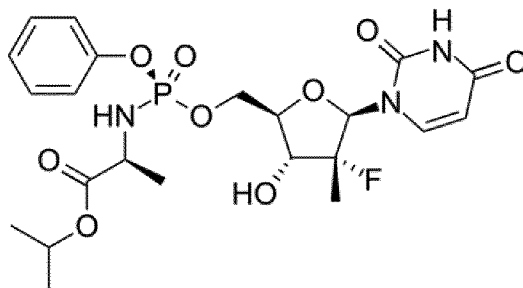
193. The process of embodiment 192 wherein the solvent of (x) is not the solvent system according (xx).

194. The process of embodiment 192 or 193, wherein the solvent of (x) is according to any of embodiments 93 to 99, preferably the solvent is selected from the group consisting of n-butanol, cyclohexane, and a mixture n-butanol and n-heptane.

195. The process of any of embodiments 192 to 194, wherein the solvent system of (xx) is according to any of embodiments 106 to 114.

196. The process of any of embodiments 192 to 195, wherein after (x) and before (xx) the crystalline form is separated from the solvent of (x), wherein preferably the separation is carried out without mechanical stress.

197. The process of any of embodiments 192 to 196, wherein the workup of (xx) comprises separating the crystalline form from the solvent system of (xx) and wherein preferably the separating comprises a filtering step and a drying step.
198. The process of embodiments 197, wherein the separating is according to any of embodiments 132 to 137.
199. A solid crystalline form of sofosbuvir of formula (I) obtained or obtainable by a process according to any of embodiments 192 to 198.
200. The solid crystalline form of embodiment 199 obtained or obtainable by a process according to any of embodiments 192 to 198 wherein said solid crystalline form of (xx) is dry or comprises less than 0.05 weight-%, more preferably less than 0.01 weight-% of the solvent of x) and/or of the solvent system of xx) based on the total amount of said solid crystalline form and the solvent of x) and/or of the solvent system of (xx).
201. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

- (i') providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
- (iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from

2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  in its mother liquor.

202. The process of embodiment 1, wherein according to (i'), the sofosbuvir is provided in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms, preferably in crystalline form 1.

203. The process of embodiment 201 or 202, wherein according to (ii'), the at least one ketone is a compound of formula  $R_1-(C=O)-R_2$  wherein  $R_1$  and  $R_2$  are independently alkyl or together form an alkanediyl group forming a ring with the carbonyl group (C=O).

204. The process of any of embodiments 201 to 203, wherein the at least one ketone is one or more of diisobutyl ketone, di-n-butyl ketone, di-tert-butyl ketone, 2-methyl-4-octanone, 2-nonanone, 3-nonanone, and 5-nonanone.

205. The process of embodiment 204, wherein the at least one ketone is diisobutyl ketone.

206. The process of any of embodiments 201 to 205, said process comprising

(i') providing sofosbuvir according to formula (I) in crystalline form 1 having an X-ray powder diffraction pattern with reflections at 2-theta angles of  $(5.0 \pm 0.2)^\circ$ ,  $(7.3 \pm 0.2)^\circ$ ,  $(9.4 \pm 0.2)^\circ$ ,  $(16.6 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(18.1 \pm 0.2)^\circ$ ,  $(22.0 \pm 0.2)^\circ$ ,  $(25.0 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular determined according to Reference Example 1.1; or in amorphous form; or as a mixture of these forms; preferably in crystalline form 1;

(ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising a at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;

(iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  in its mother liquor; wherein according to (ii'), the at least one ketone is diisobutyl ketone.

207. The process of any of embodiments 201 to 206, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent consists of carbon, hydrogen, and optionally oxygen.

208. The process of any of embodiments 201 to 207, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, one or more ether compounds, one or more ester compounds, or a mixture of one two or more thereof.

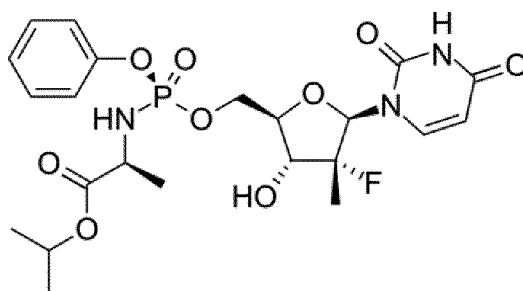
209. The process of any of embodiments 201 to 208, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, preferably is one or more aromatic compounds.

210. The process of any of embodiments 201 to 208, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent comprises one or more ether compounds, preferably is one or more ether compounds.

211. The process of any of embodiments 201 to 208, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent comprises one or more ester compounds, preferably is one or more ester compounds.

212. The process of embodiment 211, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, 1-methyl ethyl acetate.

213. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a

wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, preferably the process of any of embodiments 1 to 8, said process comprising

(i') providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;

(ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent comprises 1-methyl ethyl acetate;

(iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  in its mother liquor.

214. The process of embodiment 213, wherein according to (ii'), the solvent system consists of at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent comprises 1-methyl ethyl acetate.

215. The process of embodiment 213 or 214, wherein the at least one aprotic non-ketonic organic solvent is 1-methyl ethyl acetate.

216. The process of any of embodiments 213 to 215, wherein the at least one ketone comprises diisobutyl ketone.

217. The process of any of embodiments 213 to 216, wherein the at least one ketone is diisobutyl ketone.

218. The process of any of embodiments 213 to 217, wherein according to (ii'), the solvent system consists of diisobutyl ketone and 1-methyl ethyl acetate.

219. The process of any of embodiments 213 to 218, wherein the mixture prepared according to (ii') does not comprise toluene.

220. The process of any of embodiments 201 to 219, wherein the mixture prepared according to (ii') does not comprise a ketone having 5 or 6 carbon atoms, preferably from 5 to 7 carbon atoms.

221. The process of any of embodiments 201 to 220, wherein the mixture prepared according to (ii') does not comprise a ketone having from 4 to 8 carbon atoms.
222. The process of any of embodiments 201 to 221, wherein the mixture according to (ii') does not comprise ethanol.
223. The process of any of embodiments 201 to 222, wherein the mixture according to (ii') does not comprise one or more of methanol, ethanol, acetone, butanone, and acetonitrile.
224. The process of any of embodiments 201 to 223, wherein the mixture according to (ii') does not comprise n-butanol.
225. The process of any of embodiments 201 to 224, wherein the mixture according to (ii') does not comprise one or more of n-propanol, n-butanol, and n-pentanol.
226. The process of any of embodiments 201 to 225, wherein the mixture according to (ii') does not comprise one or more of a C<sub>3</sub> alcohol, a C<sub>4</sub> alcohol, and a C<sub>5</sub> alcohol.
227. The process of any of embodiments 201 to 226, wherein the mixture according to (ii') does not comprise an aliphatic alcohol.
228. The process of any of embodiments 201 to 227, wherein the mixture according to (ii') does not comprise n-heptane.
229. The process of any of embodiments 201 to 228, wherein the mixture according to (ii') does not comprise one or more of hexane, n-pentane, cyclohexane, and n-heptane.
230. The process of any of embodiments 201 to 229, wherein the mixture according to (ii') does not comprise a C<sub>7</sub> alkane.
231. The process of any of embodiments 201 to 229, wherein the mixture according to (ii') does not comprise one or more of a C<sub>5</sub> alkane, a C<sub>6</sub> alkane, a C<sub>7</sub> alkane, a C<sub>8</sub> alkane, or a mixture of two or more thereof, more preferably a C<sub>7</sub> alkane.
232. The process of any of embodiments 201 to 231, wherein the mixture according to (ii') does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 600 g/mol.

233. The process of any of embodiments 201 to 232, wherein the mixture according to (ii') does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 1000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 2000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 3000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 400 to 6000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 300 to 7000 g/mol, more preferably does not comprise a polyethylene glycol having an average molecular weight in the range of from 200 to 8000 g/mol, more preferably does not comprise a polyethylene glycol.
234. The process of any of embodiments 201 to 233, wherein in the mixture according to (ii'), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.1:1 to 10:1, preferably of from 0.2: 1 to 5:1, more preferably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably of from 0.9:1 to 1.1:1.
235. The process of any of embodiments 201 to 234, wherein the mixture according to (ii') contains the sofosbuvir according to formula (I), relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 100 to 500 mg/mL, preferably of from 125 to 400 mg/mL, more preferably of from 150 to 250 mg/mL.
236. The process of any of embodiments 201 to 235, wherein the mixture according to (ii') contains the sofosbuvir according to formula (I), relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 175 to 225 mg/mL.
237. The process of any of embodiments 201 to 236, wherein preparing the mixture according to (ii') comprises preparing a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.
238. The process of any of embodiments 201 to 237, wherein preparing the mixture according to (ii') comprises suspending the sofosbuvir provided in (i') in at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent.
239. The process of embodiment 238, wherein suspending the sofosbuvir provided in (i') in

at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent is carried out at a temperature of the at least a portion of the solvent system in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.

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240. The process of embodiment 238 or 239, wherein preparing the mixture according to (ii') comprises suspending the sofosbuvir provided in (i') in at least a portion of the solvent system comprising the at least one ketone and the at least one aprotic non-ketonic organic solvent, and heating the obtained suspension, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

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241. The process of embodiment 240, wherein the obtained suspension is heated to a temperature of at least 40 °C, preferably to a temperature in the range of from 40 °C to less than the boiling point of the component of the solvent system having the lowest boiling point.

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242. The process of any of embodiments 201 to 237, wherein preparing the mixture according to (ii') comprises dissolving the sofosbuvir provided in (i') in at least a portion of one or more of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I).

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243. The process of embodiment 242, wherein preparing the mixture according to (ii') comprises dissolving the sofosbuvir provided in (i') in at least a portion of the at least one ketone, obtaining a solution comprising dissolved sofosbuvir of formula (I).

25

244. The process of embodiment 242 or 243, further comprising adding at least a portion of one or more of the at least one aprotic non-ketonic organic solvent, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

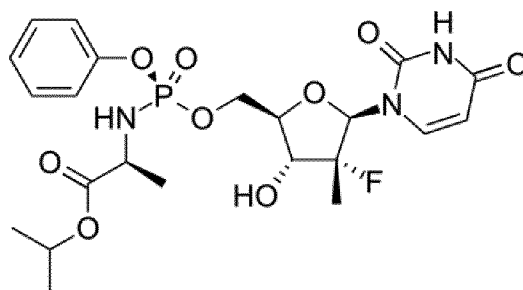
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245. The process of embodiment 244, comprising adding at least a portion of the at least one aprotic non-ketonic organic solvent, obtaining a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.

35

246. The process of any of embodiments 201 to 245, wherein preparing the mixture according to (ii') comprises agitation, preferably mechanical agitation, more preferably stirring.

247. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein, said process comprising

- (i') providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
- (iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° in its mother liquor;

preferably the process of any of embodiments 201 to 246,

wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

248. The process of embodiment 247, wherein according to (ii'), the solvent system consists of at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably consists of, 1-methyl ethyl acetate, the at least one ketone preferably comprising, more preferably consisting of, diisobutyl ketone, wherein the solvent system more preferably consists of diisobutyl ketone and 1-methyl ethyl acetate.

249. The process of embodiment 247 or 248, wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.

250. The process of any of embodiments 247 to 249, wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out for a period of time of less than 3 h, preferably at most 2.5 h, more preferably in the range of from 0.25 to 2.5 h, more preferably in the range of from 0.5 to 2 h, more preferably in the range of from 0.5 to 1.5 h.

251. The process of any of embodiments 201 to 250, preferably of embodiment 240 or 241, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises cooling the mixture, preferably to a temperature in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.

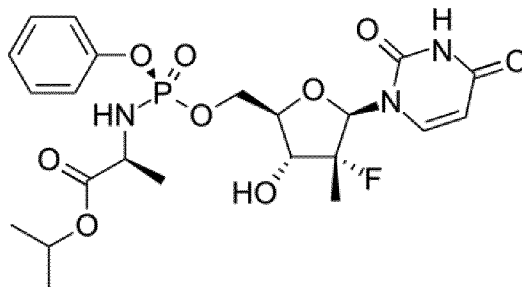
252. The process of embodiment 250 or 251, wherein cooling the mixture comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

253. The process of any of embodiments 201 to 252, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises seeding the mixture.

254. The process of embodiment 253, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises seeding the solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system obtained according to the process of embodiment 237, preferably of embodiment 240 or 241, or of any of embodiments 242 to 245.

255. The process of embodiment 253 or 254, wherein seeding the mixture comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.

256. The process of any of embodiments 253 to 255, wherein the mixture is seeded with seed crystals of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.

257. The process of embodiment 256, wherein, based on the amount of sofosbuvir contained in the mixture, seed crystals in an amount in the range of from 1 to 15 weight-%, preferably of from 5 to 12 weight-%, more preferably of from 8 to 10 weight-%, are added to the mixture.

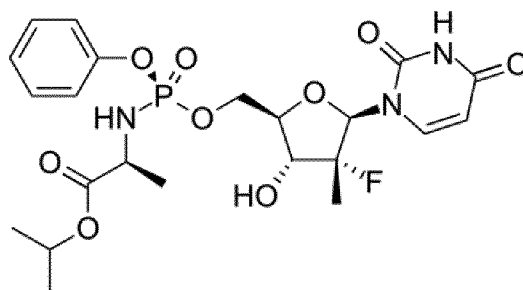
258. The process of any of embodiments 253 to 257, wherein seeding the mixture is carried out at a temperature of the mixture in the range of from 10 to 35 °C, preferably in the range of from 15 to 30 °C.

259. The process of any of embodiments 253 to 258, wherein after seeding, the mixture is agitating, preferably mechanically agitating, more preferably stirring.

260. The process of embodiment 259, wherein after seeding, the mixture is agitated, preferably mechanically agitated, more preferably stirred, for a period of time in the range of from 0.1 to 48 h, preferably of from 0.2 to 24 h, more preferably of from 0.5 to 12 h.

261. The process of embodiment 259 or 260, wherein after seeding, the mixture is agitated, preferably mechanically agitated, more preferably stirred, at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.

262. The process of any of embodiments 201 to 261, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') does not comprise adding seed crystals of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.

263. The process of any of embodiments 201 to 262, further comprising

(iv') separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° from its mother liquor;

(v') drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °.

264. The process of any of embodiments 256 to 261, wherein the seed crystals of sofosbuvir of formula (I) are prepared by a process according to embodiment 262, preferably by a process according to embodiment 263 insofar as embodiment 263 is dependent on embodiment 262.

265. The process of embodiment 263 or 264, wherein (iv') comprises

(iv'.1) diluting the mother liquor comprising the solid crystalline form of sofosbuvir.

266. The process of embodiment 265, wherein diluting comprises adding at least one ketone having 9 carbon atoms to the mother liquor comprising the solid crystalline form of sofosbuvir, preferably the at least one ketone comprised in the mixture according to (ii').

267. The process of embodiment 266, wherein in addition to the at least one ketone having 9 carbon atoms, at least one aprotic non-ketonic organic solvent is added to the mother liquor comprising the solid crystalline form of sofosbuvir, preferably the at least one aprotic non-ketonic organic solvent comprised in the mixture according to (ii').

268. The process of embodiment 267, wherein the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is in the range of from 0.1:1 to 10:1, preferably of from 0.2:1 to 5:1, more preferably of from 0.5:1 to 2:1, more preferably of from 0.8:1 to 1.2:1, more preferably from 0.9:1 to 1.1:1.

269. The process of embodiment 267 or 268, wherein the volume ratio of the at least one ketone added to the mother liquor relative to the at least aprotic non-ketonic organic solvent added to the mother liquor is the volume ratio of the at least one ketone comprised in the mixture according to (ii') relative to the at least aprotic non-ketonic organic solvent comprised in the mixture according to (ii').

270. The process of any of embodiments 263 to 269, wherein separating according to (iv') comprises

(iv'.2) subjecting the mother liquor comprising the solid crystalline form of sofosbuvir, optionally the mother liquor comprising the solid crystalline form of sofosbuvir diluted according to any of embodiments 265 to 269, to a solid-liquid separation process, preferably to filtration.

271. The process of embodiment 270, wherein separating according to (iv') comprises

(iv'.3) washing the solid crystalline form of sofosbuvir separated from its mother liquor.

272. The process of embodiment 271, wherein washing according to (iv'.3) is carried out with at least one aprotic organic compound, optionally the at least one aprotic non-ketonic organic solvent as defined in any of embodiments 207 to 212, preferably with one or more of isopropyl acetate and diethyl ether, wherein the at least one aprotic organic compound is optionally used in combination with at least one ketone, preferably the at least one ketone as defined in any of embodiments 201 to 205.

273. The process of embodiment 271 or 272, wherein washing according to (iv'.3) is carried out at a temperature in the range of from 0 to 30 °C, preferably of from 15 to 30 °C.

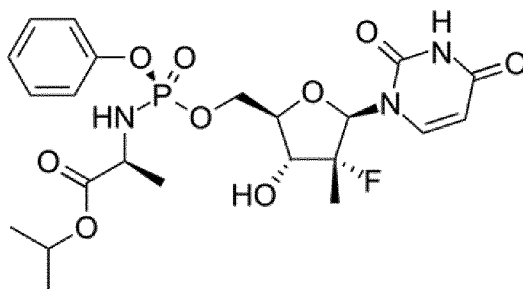
274. The process of any of embodiment 263 to 273, wherein according to (v'), drying is carried out at a temperature in the range of from 30 to 50 °C, preferably of from 35 to 45 °C.
- 5 275. The process of any of embodiments 263 to 274, wherein according to (v'), drying is carried out at an absolute pressure below 1 bar, preferably in the range of from 5 to 500 mbar, more preferably of from 5 to 100 mbar, more preferably of from 5 to 50 mbar.
- 10 276. The process of any of embodiment 263 to 275, wherein according to (v'), drying is carried out for a period of time in the range of from 1 to 48 hours, preferably of from 6 to 24 hours.
- 15 277. The process of any of embodiments 201 to 276, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° exhibits a Fourier transform infrared spectrum comprising peaks at wavenumbers of  $(3252 \pm 2) \text{ cm}^{-1}$ ,  $(2928 \pm 2) \text{ cm}^{-1}$ ,  $(1718 \pm 2) \text{ cm}^{-1}$ ,  $(1668 \pm 2) \text{ cm}^{-1}$ ,  $(1456 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, preferably comprising additional peaks at wavenumbers of  $(1494 \pm 2) \text{ cm}^{-1}$ ,  $(1373 \pm 2) \text{ cm}^{-1}$ ,  $(1265 \pm 2) \text{ cm}^{-1}$ ,  $(1223 \pm 2) \text{ cm}^{-1}$ ,  $(945 \pm 2) \text{ cm}^{-1}$ , when measured at a temperature in the range of from 15 to 25 °C using a ZnSe ATR cell, in particular as described in Reference Example 1.2 herein.
- 20 278. The process of any of embodiments 201 to 277, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° has the monoclinic space group symmetry  $P2_1$  and the following unit cell parameters as determined by an X-ray single-crystal structure analysis at 120 K:
- 25  $a = (5.16 \pm 0.04) \text{ Angstrom}$ ;  
 $b = (16.86 \pm 0.12) \text{ Angstrom}$ ;  
 $c = (14.44 \pm 0.10) \text{ Angstrom}$ ;  
 $\alpha = 90.0^\circ$ ;  
 $\beta = (100.2 \pm 0.8)^\circ$ ;  
 $\gamma = 90.0^\circ$ .
- 30 279. The process of any of embodiments 201 to 278, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° has a melting point in the range of from 122 to 126 °C when measured via differential scanning calorimetry at a heating

rate of 10 K/min at a pressure in the range of from 0.95 to 1.05 bar, in particular as described in Reference Example 1.3 herein.

280. The process of any of embodiments 201 to 279, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° comprises at most 0.5 weight-% of organic solvent, based on the weight of the crystalline form, as determined via thermogravimetric analysis, in particular as described in Reference Example 1.4 herein.

281. The process of any of embodiments 201 to 280, wherein the crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° comprises at most 0.4 weight-% of water based on the weight of the crystalline form as determined via gravimetric moisture sorption / desorption analysis at a temperature of  $(25.0 \pm 0.1) ^\circ\text{C}$  and a relative humidity of from 0 to 95 %, in particular as described in Reference Example 1.5 herein.

282. A solid crystalline form of sofosbuvir of formula (I)



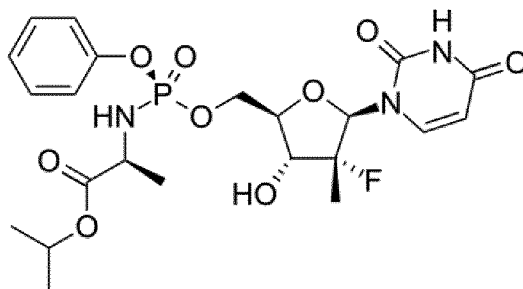
(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2) ^\circ$ ,  $(10.4 \pm 0.2) ^\circ$ ,  $(12.4 \pm 0.2) ^\circ$ ,  $(17.3 \pm 0.2) ^\circ$ ,  $(19.4 \pm 0.2) ^\circ$ , obtainable or obtained by a process according to any of embodiments 201 to 276, preferably according to any of embodiments 263 to 276, more preferably according to any of embodiments 274 to 276.

283. Use of the crystalline form of sofosbuvir according to embodiment 282 for the preparation of a pharmaceutical composition.

284. A method of using the crystalline form of sofosbuvir according to embodiment 282 for the preparation of a pharmaceutical composition.

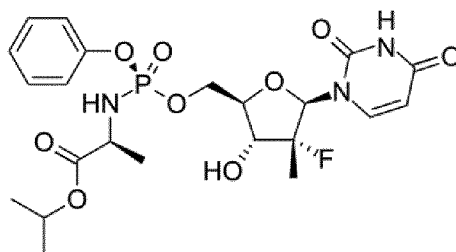
285. A pharmaceutical composition, comprising the crystalline form of sofosbuvir according to embodiment 282 and at least one pharmaceutically acceptable excipient.
286. The pharmaceutical composition of embodiment 285 for use in a method for treating hepatitis C in a human.
287. Use of the pharmaceutical composition of embodiment 286 for treating hepatitis C in a human.
288. A method of treating hepatitis C in a human comprising administering the pharmaceutical composition of embodiment 286 to a human.
289. Use of the crystalline form of sofosbuvir according to embodiment 282 for preparing a medicament for the treatment of hepatitis C in a human.
290. Use of the crystalline form of sofosbuvir according to embodiment 282 for the treatment of hepatitis C in a human.
291. The crystalline form of sofosbuvir according to embodiment 282 for use in the treatment of hepatitis C in a human.
292. The crystalline form of sofosbuvir according to embodiment 282 for the treatment of hepatitis C in a human.
293. A method of treating hepatitis C in a human comprising administering the crystalline form of sofosbuvir according to embodiment 282 to a human.
294. Use of a ketone having 9 carbon atoms for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

295. Use of a combination of at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more ester compounds, more preferably comprising 1-methyl ethyl acetate, more preferably being 1-methyl ethyl acetate, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, as medium for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



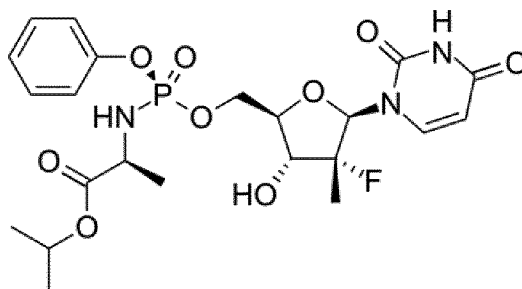
(I)

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm.
296. The use of embodiment 294 or 295, wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.
297. The use of any of embodiments 294 to 296, preferably of embodiment 296, wherein the solvent mediated transformation of sofosbuvir is carried out in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 600 g/mol, preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 1000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 2000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400 to 3000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 400

to 6000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 300 to 7000 g/mol, more preferably in the absence of a polyethylene glycol having an average molecular weight in the range of from 200 to 8000 g/mol, more preferably in the absence of a polyethylene glycol.

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298. Use of a ketone having 9 carbon atoms for reducing the crystallization time of the solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

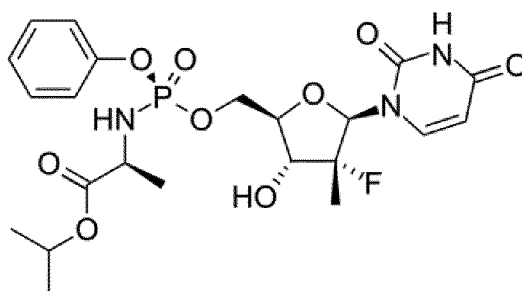
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having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.

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299. Use of a combination of at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, preferably consisting of carbon, hydrogen, and optionally oxygen, more preferably comprising one or more ester compounds, more preferably comprising 1-methyl ethyl acetate, more preferably being 1-methyl ethyl acetate, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, for reducing the crystallization time of the solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)

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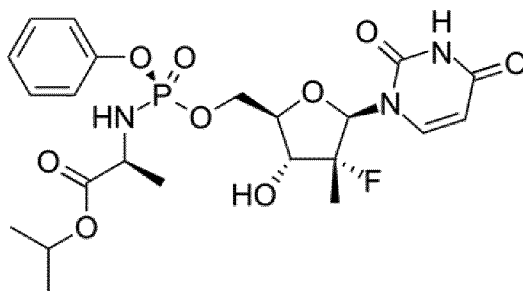


(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of

$(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.

- 5 300. A mixture comprising sofosbuvir of formula (I)



(I),

- and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, and wherein the at least one aprotic non-ketonic solvent preferably comprises, more preferably is, 1-methyl ethyl acetate.
- 10

301. The mixture of embodiment 300, wherein the sofosbuvir of formula (I) comprises a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.
- 15

302. The mixture of embodiment 301, wherein in the mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  relative to the total content of solid crystalline sofosbuvir is at least 99 %, preferably at least 99.5 %, more preferably at least 99.9 %.
- 25

303. The mixture of any of embodiments 300 to 302, wherein the mixture is a mother liquor comprising solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.
- 30

0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, said mother liquor being obtainable or obtained by step (iii') of the process according to any of embodiments 201 to 262.

The present invention is further illustrated by the following reference examples, examples, and comparative examples.

## Examples

### Crystalline Form 7 of Sofosbuvir

In this Example section, reference is made to crystalline form 7 of sofosbuvir. This crystalline form 7 is the crystalline form described throughout this invention as the crystalline form of sofosbuvir having an X-ray powder diffraction pattern which comprises no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, which preferably comprises reflections at 2-theta angles of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, and which more preferably comprises additional reflections at 2-theta angles of (12.1 ± 0.2) °, (13.5 ± 0.2) °, (16.2 ± 0.2) °, (16.8 ± 0.2) °, (18.0 ± 0.2) °, (18.7 ± 0.2) °, (20.2 ± 0.2) °, (20.9 ± 0.2) °, (22.1 ± 0.2) °, (23.4 ± 0.2) °, (25.4 ± 0.29 °, (28.0 ± 0.2)°, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in particular as described in Reference Example 1.1 herein.

### Abbreviations used in the Example section

|      |                                            |
|------|--------------------------------------------|
| ACP  | acetophenone                               |
| CYH  | cyclohexanone                              |
| DEK  | diethyl ketone                             |
| DIBK | diisobutyl ketone                          |
| DIPK | diisopropyl ketone                         |
| IPA  | isopropyl acetate (1-methyl ethyl acetate) |
| MEK  | methyl ethyl ketone                        |
| MIBK | methyl isobutyl ketone                     |
| MIPK | methyl-isopropyl ketone                    |
| MPK  | methyl n-propyl ketone                     |
| MTBE | methyl tert-butyl ether                    |
| TOL  | toluene                                    |

r.t. room temperature

r.p.m. revolutions per minute



Differential scanning calorimetry (DSC) was performed with a DSC 7 (Perkin-Elmer, Norwalk, Ct., USA) using a Pyris 2.0 software and with a DSC 204F1 (Netzsch GmbH & Co. Holding AG, Selb, Germany). Approximately  $(1 \text{ to } 5 \pm 0.005)$  mg sample (using a UM3 ultramicrobalance, Mettler, Greifensee, CH) was weighed into an Al-pan (30 microL), sealed with a cover, which was perforated by a needle and heated from 25 to 150 °C at a rate of 10 K/min. Dry nitrogen was used as the purge gas (purge: 20 mL/min).

#### 1.4. Organic solvent content

Thermogravimetric analysis (TGA) was performed using the following equipment/conditions: Thermogravimetric-system TGA-7, Pyris-Software for Windows NT, (Perkin-Elmer, Norwalk, Ct., USA), Platinum-sample holder (50 microL), nitrogen as the purge gas (sample purge: 20 mL/min, balance purge: 40 mL/min). Heating rate: 10 K/min; heating range: 25-145 °C.

##### 1.4.2 Quantitative determination of the residual solvent

Residual solvents were quantified by GC using an internal standard solution of 0.50 g *n*-decane in 500 mL isopropanol. An accurately weighed sample of MIBK or *n*-butanol (7-10 mg) was dissolved in 10 mL of the standard solution and injected twice into the GC (see method below). The peak area for each solvent was normalized with the internal standard and the calculated response factor was averaged over 2 injections. Residual solvent in mechanically stressed samples of sofosbuvir was analyzed by dissolving accurately weighed samples of the solid (50 -60 mg) in 10 mL of the internal standard solution. The peak area was normalized with the standard and quantified with the corresponding response factor for each solvent.

GC Method: HP5 (Agilent, 5% phenyl methyl siloxane) column, 45 °C for 5 min, then 20 °C/min to 200 °C for 3 min, 1 ml/min H<sub>2</sub>. T<sub>r</sub> (MIBK) = 5.6 min, T<sub>r</sub> (*n*-butanol) = 4.3 min, T<sub>r</sub> (*n*-decane) = 9.7 min.

#### 1.5 Water content

The moisture sorption desorption isotherms were acquired using a SPS-11 moisture sorption analyzer (MD Messtechnik, Ulm, D). The samples were weighed into Aluminium sample holders. The measurement cycles for the novel crystalline form according to the present invention were started at 43 % RH, decreased to 40 % RH (relative humidity), further decreased in 10 % steps to 10 % RH, decreased in 5 % steps to 0 % RH, increased in 5 % steps to 10 % RH, further increased in 10 % steps to 90 % RH and subsequently increased to 95 % RH, decreased again to 90 % RH, decreased in 10 % steps to 10 % RH, further decreased in 5 %

steps to 0 % RH, again increased in 5 % steps to 10 %, subsequently increased in 10 % steps to 40 % RH and finally increased to 43 % RH. The measurement cycles for form 1 were started at 43 % RH, decreased to 40 % RH, further decreased in 10 % steps to 10 % RH, decreased in 5 % steps to 0 % RH, increased in 5 % steps to 10 % RH, further increased in 10 % steps to 90 % RH and subsequently increased to 91 % RH, decreased again to 90 % RH, decreased in 10 % steps to 10 % RH, further decreased in 5 % steps to 0 % RH, again increased in 5 % steps to 10 %, subsequently increased in 10 % steps to 40 % RH and finally increased to 43 % RH. The equilibrium condition for each step was set to a mass constancy of  $\pm 0.005$  % over 60 min. The temperature was  $(25 \pm 0.1)$  °C. The water content of the samples was determined after the moisture sorption/ desorption experiments with a TGA 7 system (Perkin Elmer, Norwalk, Ct., USA) using the Pyris 2.0 software. The samples were weighed into Aluminium pans (50 microL). Dry nitrogen was used as purge gas (purge rate: 20 mL/min). The samples were heated from 25 to 200 °C using a heating rate of 10 K/min.

## 1.6 Unit cell

Intensity data for the crystal structure were recorded at 120 K on a Rigaku AFC12 goniometer driven by the CrystalClear-SM Expert 3.1 b27 software (Rigaku, 2012) and equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ Super Bright Mo rotating anode generator ( $\lambda = 0.71075$  Angstrom) with HFVarimax optics. The structure was solved using the direct methods procedure in SHELXS97 and refined by full-matrix least squares on  $F^2$  using SHELXL97. All non-hydrogen atoms were refined anisotropically.

## 1.7 Ball milling

a) The stability of crystalline form 7 of sofosbuvir under mechanical stress was tested using a Retsch® oscillatory ball mill MM 301 equipped with grinding jars of 1.5 mL containing 2 balls of 5 mm of diameter. 100-200 mg of sample were introduced in the jar and grinded for 1 minute at a frequency of 20 Hz, followed by 4 minutes at a frequency of 10 Hz. Afterwards the jar was opened and the sample was scratched with a spatula inside the jar to remove material from the jar wall and the surface of the milling balls before grinding it further at a frequency of 20 Hz for 1 minute and 10 Hz for 4 minutes. The remaining material was removed from the jar and analyzed by XRPD.

b) The stability of crystalline form 7 of sofosbuvir with residual amount of solvent under mechanical stress was tested using a Retsch® ball mill MM 301 equipped with grinding jars of 1.5 mL containing 2 balls of 5 mm of diameter. For this stability test various samples of sofosbuvir form 7 containing defined amount of residual solvent were tested. Sofosbuvir form

7 (100-150 mg) was introduced in the jar and ball milled at a frequency of 10 Hz for defined periods of time (0, 10, 30, 60, 120 min). The stability of the crystalline form 7 was determined by XRPD.

**Reference Example 2: Preparation of seed crystals of the crystalline form of sofosbuvir according to the present invention**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was suspended in a 1:1 mixture of MIBK and toluene (2 mL) and warmed up above 50 °C until a clear solution was obtained. The solution was allowed to stand without stirring for 2 h, whereby a thick crystal suspension formed. The suspension was filtered through a G3 Nutsche filter washing with diethyl ether, and dried for 17 h at 40 °C/7 mbar to obtain 171 mg (86 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Examples 1: Preparation of the crystalline form of sofosbuvir according to the present invention (starting from suspension)**

**Example 1.1: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of MIBK and TOL)**

**Example 1.1.1: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir (0.99 g) in a mixture of MIBK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (0.99 g) was suspended in a mixture of MIBK (2.5 mL) and TOL (2.5 mL) and heated to a temperature of at least 50 °C until a clear solution was obtained. The solution was allowed to cool to r.t. over 30 min under stirring and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.5) (8 mg) after which increasing turbidity was observed. The suspension was stirred for 2 h at r.t., 2.5 h in an ice bath and 4 h at r.t. and 1 h in an ice bath (total stirring time = 9.5 h). The solid was filtered through a G3 Nutsche filter, washed with diethyl ether, and dried for 17 h at 40 °C/7 mbar to obtain 870 mg (88 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir (see Figure 1).

**Example 1.1.2: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir (200 mg) in a mixture of MIBK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was suspended in a 1:1 mixture of MIBK and TOL (2 mL) and warmed up above 50 °C until a clear solution was obtained. The solution was allowed to stand without stirring for 2 h, whereby a thick crystal suspension formed. The suspension was filtered through a G3 Nutsche filter washing with diethyl ether, and dried for 17 h at 40 °C/7 mbar to obtain 171 mg (86 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 1.2: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of MIBK and IPA) –**

**Example 1.2.1: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of MIBK and IPA) – non-lab scale (12 g)**

A 100 mL Schmizo reactor equipped with a Teflon stirrer, a thermostat, a thermometer and a nitrogen inlet/outlet was charged with sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (11.79 g) and a 1:1 mixture of MIBK and IPA (60 mL). The suspension was warmed to 50 °C with stirring (110 rpm) until a clear solution was obtained. The solution was cooled to 25 °C over about 30 min with stirring (110 r.p.m) and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.1) (100.1 mg), upon which increasing turbidity was immediately observed. The suspension was stirred at 110 r.p.m. for a total of 20 h, whereby crystal samples of ca. 150 mg were taken after 4 h, 6 h, 8 h and 20 h for analysis. After 20 h, the thick suspension was diluted with 10 mL of cooled MIBK/IPA (1:1), filtered through a G3 Nutsche filter washing with 10 mL of ice-cold MIBK/IPA (1:1) and diethyl ether (2 x 10 mL) and dried for 3 h at 40 °C/7 mbar. Samples from earlier time points were filtered, washed and dried in the same way. XRPD analysis of samples from all time points showed pure crystalline form 7 of sofosbuvir. The combined yield of all samples was 10.14 g (86 %).

**Example 1.2.2: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of MIBK and IPA) – non-lab scale (20 g)**

A 100 mL Schmizo reactor equipped with a Teflon stirrer, a thermostat, a thermometer and a nitrogen inlet/outlet was charged with sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (20 g) and a 1:1 mixture of MIBK and IPA (100 mL). The suspension was warmed to 48 °C with stirring (110 rpm) until a clear solution was obtained. The solution was cooled to 21 °C over about 30 min with stirring (110 r.p.m) and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.1) (200

mg), upon which increasing turbidity was immediately observed. The suspension was stirred at 110 r.p.m. for a total of 17 h. After this time, the thick suspension was directly filtered through a G3 Nutsche filter washing with 20 mL of the mother liquor, followed by 10 mL of ice-cold MIBK/IPA (1:1) and diethyl ether (1 x 20 mL). Drying for 3 h at 40 °C/7 mbar afforded 17.84 g (89%) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 1.3: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of MIBK and MTBE)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (500 mg) was suspended in a 1:1 mixture of in methyl MIBK and MTBE (2.5 mL) and heated to a temperature of at least 50 °C until a clear, slightly opalescent solution was obtained. The solution was allowed to cool to r.t. under stirring for 1h and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (4 mg) after which increasing turbidity was observed. The suspension was stirred for a 3 h at r.t., diluted with 1 mL of a cooled MIBK/MTBE (1:1) solution and filtered through a G3 Nutsche filter washing with diethyl ether. Drying for 16 h at 40 °C/10 mbar gave 423 mg (85 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 1.4: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in MIBK)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (201.95 mg) was suspended in MIBK (1 mL) and warmed up above 50 °C until a clear solution was obtained. The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2), after which increasing turbidity was observed. The suspension was stirred for a 2 h at r.t and in an ice bath for 30 min, filtered through a G3 Nutsche filter washing with diethyl ether. Drying for 16 h at 40 °C/8 mbar gave 84.6 mg (42 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Examples 2: Preparation of the crystalline form of sofosbuvir according to the present invention (starting from solution)**

**Example 2.1: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in CYH, crystallizing in a mixture of CYH and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (205.7 mg) was dissolved in CYH (0.5 mL) and charged with TOL (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 4 h at r.t. and filtered through a G3 Nutsche filter washing with TOL. Drying for 16 h at 40 °C/8 mbar gave 147.9 mg (72 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 2.2: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in MIPK, crystallizing in a mixture of MIPK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was dissolved in MIPK (0.5 mL) and charged with TOL (0.5 mL). The solution was stirred for 30 min at r.t and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 4 h at r.t., diluted with 0.5 mL MIPK/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 169.9 mg (85 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 2.3: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in DEK, crystallizing in a mixture of DEK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was dissolved in DEK (0.5 mL) and charged with TOL (0.5 mL). The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 4 h at r.t., diluted with 0.5 mL DEK/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 157.5 mg (79 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir.

**Example 2.4: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in MPK, crystallizing in a mixture of MPK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (206 mg) was dissolved in methyl MPK (0.5 mL) and charged with TOL (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example

1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 1 h at r.t., diluted with 0.5 mL MPK/TOL (1:1), stirred for additional 3 h at r.t. and filtered through a G3 Nutsche filter washing with TOL. Drying for 16 h at 40 °C/8 mbar gave 125.0 mg (61 %) of crystalline solid. XRPD analysis showed pure crystal form 7 of sofosbuvir.

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**Example 2.5: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in MIPK, crystallizing in a mixture of MIPK and IPA)**

10 Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (208.3 mg) was dissolved in MIPK (0.5 mL) and charged with IPA (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 1 h at r.t., diluted with 0.5 mL MIPK/TOL (1:1), stirred for additional 3 h at r.t. and filtered through  
15 a G3 Nutsche filter washing with TOL. Drying for 16 h at 40 °C/8 mbar gave 132.5 mg (64 %) of crystalline solid. XRPD analysis showed pure crystal form 7 of sofosbuvir.

**Example 2.6: Preparation of the crystalline form of sofosbuvir according to the present invention (dissolving sofosbuvir in MIPK, crystallizing in a mixture of MIPK and MTBE)**

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Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (203 mg) was dissolved in MIPK (0.5 mL) and charged with MTBE (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2  
25 mg) after which increasing turbidity was observed. The suspension was stirred for a 1 h at r.t., diluted with 0.5 mL MIPK/MTBE (1:1), stirred for additional 3 h at r.t. and filtered through a G3 Nutsche filter. Drying for 17 h at 40 °C/8 mbar gave 151.4 mg (74 %) of crystalline solid. XRPD analysis showed pure crystal form 7 of sofosbuvir.

30 **Comparative Examples 1: Preparation of a crystalline form of sofosbuvir (starting from suspension)**

**Comparative Example 1.1: Preparation of a crystalline form of sofosbuvir (suspending sofosbuvir in a mixture of DIBK and TOL)**

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Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was suspended in a mixture of DIBK (0.5 mL) and TOL (0.75 mL) and warmed to a temperature of at least 50 °C until a clear solution was obtained. The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (prepared according to

Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was left to stand for 17 h, resulting in partial crystallization. Scratching the reaction vessel wall resulted in complete crystallization. The solid was diluted with 0.5 mL DIBK/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 170.7 mg (86 %) of crystalline solid. XRPD analysis showed pure crystal form 1 of sofosbuvir (see Figure 3).

**Comparative Examples 2: Preparation of a crystalline form of sofosbuvir (starting from solution)**

**Comparative Example 2.1: Preparation of a crystalline form of sofosbuvir (dissolving sofosbuvir in MEK, crystallizing in a mixture of MEK and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (204.5 mg) was dissolved in MEK (0.5 mL) and charged with TOL (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 1 h, diluted with 0.5 mL MEK/TOL (1:1), stirred for additional 3 h at r.t. and filtered through a G3 Nutsche filter washing with TOL. Drying for 16 h at 40 °C/8 mbar gave 163.2 mg (80 %) of crystalline solid. XRPD analysis showed the presence of crystalline forms 7 and 6 of sofosbuvir (see Figure 2).

**Comparative Example 2.2: Preparation of a crystalline form of sofosbuvir (dissolving sofosbuvir in MEK, crystallizing in a mixture of MEK and MTBE)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (205.4 mg) was dissolved in MEK (0.5 mL) and charged with MTBE (0.5 mL). The solution was seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 1 h at r.t., diluted with 0.5 mL MEK/MTBE (1:1), stirred for additional 3 h at r.t. and filtered through a G3 Nutsche filter. Drying for 17 h at 40 °C/8 mbar gave 122.5 mg (60 %) of crystalline solid. XRPD analysis shows the presence of crystalline forms 7 and 6 of sofosbuvir.

**Comparative Example 2.3: Preparation of a crystalline form of sofosbuvir (dissolving sofosbuvir in ACP, crystallizing in a mixture of ACP and TOL)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was dissolved in ACP (0.5 mL) and charged with TOL (0.5 mL). The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 4 h at r.t., diluted with 0.5 mL ACP/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 149.2 mg (75 %) of crystalline solid. XRPD analysis showed the presence of crystalline forms 7 and 6 of sofosbuvir.

### Summary of the Results of the Examples and the Comparative Examples above

In the following Table 2, the results of the Examples and Comparative Examples are shown:

**Table 2**

Summary of the Results of the Examples and the Comparative Examples

| E# / CE# <sup>1)</sup>    |         |         | aprotic non-ketonic organic solvent |                    |       |      |
|---------------------------|---------|---------|-------------------------------------|--------------------|-------|------|
|                           | ketone  |         | TOL                                 | IPA                | MTBE  | none |
|                           | abbrev. | C atoms | crystalline form(s) obtained        |                    |       |      |
| CE2.1 / CE2.2             | MEK     | 4       | 6 + 7                               | n.d. <sup>2)</sup> | 6 + 7 | n.d. |
| E2.3                      | DEK     | 5       | 7                                   | n.d.               | n.d.  | n.d. |
| E2.4                      | MPK     | 5       | 7                                   | n.d.               | n.d.  | n.d. |
| E2.2 / E2.5 / E2.6        | MIPK    | 5       | 7                                   | 7                  | 7     | n.d. |
| E1.1 / E1.2 / E1.3 / E1.4 | MIBK    | 6       | 7                                   | 7                  | 7     | 7    |
| E2.1                      | CYH     | 6       | 7                                   | n.d.               | n.d.  | n.d. |
| CE2.3                     | ACP     | 8       | 6 + 7                               | n.d.               | n.d.  | n.d. |
| CE1.1                     | DIBK    | 9       | 1                                   | n.d.               | n.d.  | n.d. |

<sup>1)</sup> E = Example; CE = Comparative Example

<sup>2)</sup> n.d. = not determined

As shown in the examples and comparative examples above, the use of a ketone having 9 carbon atoms employed according to the recipe as outlined in CE1.1 above, did not lead to crystalline form 7, and the starting material, crystalline form 1, was not transformed, although DIBK was employed in combination with toluene and toluene was found to be an especially preferable aprotic non-ketonic organic solvent when used with ketones having from 5 to 7, in particular 5 or 6 carbon atoms. In contrast to CE1.1, the use of ketones having 4 or 8 carbon atoms allow for preparing crystalline form 7 of sofosbuvir; however, crystalline form 7 was

obtained not in pure form but as a mixture of forms 6 and 7. Reference is made to CE2.1, CE2.2, and CE2.3. As for CE1.1, these examples were carried out in the presence of toluene was found to be an especially preferable aprotic non-ketonic organic solvent when used with ketones having from 5 to 7, in particular 5 or 6 carbon atom.

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According to E1.4 wherein a ketone having 6 carbon atoms was employed alone, i.e. not in combination with a non-ketonic aprotic solvent, pure crystalline form 7 was obtained. The yield was found to be 42 %. In the other examples according to the invention, ketones having from 5 to 7, in particular 5 or 6 carbon atoms were used in combination with non-ketonic aprotic solvents. For all tested combinations, pure crystalline form 7 was obtained, wherein in each case, the yield was (significantly) higher than the yield obtained when using the ketone alone (up to 88 % (E1.1)). This holds true for the lab-scale processes as well as for an up-scaled process as shown in E1.2. Irrespective whether the process was carried out via an initial solution of the starting material or an initial suspension of the starting material, pure form 7 was obtained in each example of the invention. As shown by the results according to Table 2 above, the specific choice of the ketones allows using a variety of aprotic non-ketonic organic solvents. It is very important to note that in all examples of the invention, it was possible to stir the reaction mixture from which crystalline form 7 was obtained in its mother liquor.

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Therefore, the use of ketones having from 5 to 7, in particular 5 or 6 carbon atoms in the process of the invention was shown to allow for realizing an extremely robust process for preparing pure crystalline form 7, wherein the process, allowing stirring during solvent-mediated transformation, can be used for preparing crystalline form 7 in an industrial and economically advantageous manner.

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**Example 3                      Preparation of the sofosbuvir samples containing MIBK according to the present invention (for stress test)**

**30      Example 3.1-3.5:      Preparation of the sofosbuvir samples containing 26.6%, 23.8%, 12.7%, 5.3% and 0.2% weight MIBK**

In a G3-Nutsche filter, sofosbuvir crystalline form 7 (0.5 g) was suspended in 5 mL of MIBK. The slurry was filtered applying vacuum. Three different vacuum pressures were applied to obtain residual MIBK content of 26.6% (example 3.1), 23.8 % (example 3.2) and 0.2% (example 3.5) in the filter cake (see Reference example 1.4.2 herein for analytical method). Residual MIBK content of 12.7% (example 3.3) was achieved by suspending sofosbuvir crystalline form 7 (0.5 g) in a mixture of MIBK/diethyl ether (1:1) in a G3-Nutsche filter, filtering

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the slurry and drying the sample for 10 min at 100 mbar and room temperature. GC analytics indicated no residual diethyl ether in this sample. Residual MIBK content of 5.3% (example 3.4) was achieved by suspending sofosbuvir crystalline form 7 (0.5 g) in a mixture of MIBK/diethyl ether (1:2) in a G3-Nutsche filter, filtering the slurry and drying the sample for 10 min at 100 mbar and room temperature. GC analytics indicated no residual diethyl ether in this sample.

### Comparative Examples 3.1-3.3: Preparation of sofosbuvir samples containing n-butanol

In a G3-Nutsche filter, sofosbuvir crystalline form 7 (0.5 g) was washed with a mixture of n-butanol and diethyl ether without stirring. The following ratios were used:

| Example | n-butanol/diethyl ether | Residual n-butanol content |
|---------|-------------------------|----------------------------|
| CE 3.1  | 1:2                     | 22.0%                      |
| CE 3.2  | 1:5                     | 9.9%                       |
| CE 3.3  | 1:10                    | 5.3%                       |

Each slurry was filtered and the solid was dried for 10 min at 100 mbar and room temperature. GC analytics indicated no residual diethyl ether any of the samples, and residual amounts of n-butanol as shown.

### Examples 4: Mechanical stress of crystalline form 7 of sofosbuvir by ball milling

#### Example 4.1: Stability of dried crystalline form 7 of sofosbuvir

Sofosbuvir of crystalline form 7 (prepared according to Example 1.2.1) (100-200 mg) was ground in a ball mill as described in Reference Example 1.7 a) herein. The XRPD pattern of the resulting solid material showed pure crystalline form 7 of sofosbuvir.

#### Example 4.2: Stability of wet crystalline form 7 of sofosbuvir

Sofosbuvir of crystalline form 7 (prepared according to Example 1.2.1) (100-200 mg) was suspended in 1.5 mL of a MIBK/IPA mixture (1:1). The mixture was stirred at 500-700 r.p.m. for 10 minutes and filtered on a medium-porosity glass fritted funnel. About 150-200 mg of the wet filter cake ground in a ball mill as described in Reference Example 1.7 herein. The XRPD pattern of the resulting solid material showed pure crystalline form 7 of sofosbuvir.

### Examples 4.3-4.7: Stability of Form 7 of sofosbuvir — containing MIBK as residual solvent — under mechanical stress

120-150 mg of crystalline form 7 of sofosbuvir (prepared according to Examples 3.1-3.5 herein) was ball milled at 10 Hz according to Reference Example 1.7 b). After a total milling time of 10 min, 30 min, 60 min and 120 min a sample was taken and analyzed by XRPD. The results of the XRPD analyses are presented in Table 3:

**Table 3:** Stress stability (ball milling) of crystalline form 7 of sofosbuvir containing MIBK as residual solvent

| Example     | MIBK content in the starting material | Sofosbuvir physical form* after ball milling at 10 Hz for a total time of |        |              |        |         |
|-------------|---------------------------------------|---------------------------------------------------------------------------|--------|--------------|--------|---------|
|             |                                       | 0 min                                                                     | 10 min | 30 min       | 60 min | 120 min |
| Example 4.3 | 26.6%<br>(Example 3.1)                | 7                                                                         | 7      | 7 + little 6 | 6      | 6       |
| Example 4.4 | 23.9%<br>(Example 3.2)                | 7                                                                         | 7      | 7            | 6      | 6       |
| Example 4.5 | 12.7%<br>(Example 3.3)                | 7                                                                         | 7      | 7            | 7      | 6 + 7   |
| Example 4.6 | 5.3%<br>(Example 3.4)                 | 7                                                                         | 7      | 7            | 7      | 7       |
| Example 4.7 | 0.2%<br>(Example 3.5)                 | 7                                                                         | 7      | 7            | 7      | 7       |

\*"7" means that the XRPD pattern of the resulting solid material corresponds to pure crystalline form 7 of sofosbuvir. "6" means that the XRPD pattern of the resulting solid material corresponds to pure crystalline form 6 of sofosbuvir. "6 + 7" means that the XRPD pattern of the resulting solid material corresponds to a mixture of form 6 and form 7 of sofosbuvir with a higher amount of form 6 than form 7 in the sample. "7 + little 6" means that the XRPD pattern of the resulting solid material corresponds to a mixture of form 7 and form 6 of sofosbuvir with mainly form 7 and a little amount of form 6 in the sample.

### Comparative Examples 4.1-4.3: Stability of Form 7 of sofosbuvir — containing n-butanol as residual solvent — under mechanical stress

110-130 mg of crystalline form 7 of sofosbuvir (prepared according to Comparative Examples 3.1-3.3 herein) were ball milled at 10 Hz according to Reference Example 1.7 b). After a total milling time of 10 min, 30 min, 60 min and 120 min a sample was taken and analyzed by XRPD. The results of the XRPD analyses are presented in Table 4:

**Table 4:** Stress stability (ball milling) of crystalline form 7 of sofosbuvir containing n-butanol as residual solvent

| Comparative examples (CE) | n-BuOH content in the starting material | Sofosbuvir physical form* after ball milling at 10 Hz for a total time of |        |        |        |         |
|---------------------------|-----------------------------------------|---------------------------------------------------------------------------|--------|--------|--------|---------|
|                           |                                         | 0 min                                                                     | 10 min | 30 min | 60 min | 120 min |
| CE4.1                     | 22.0% (CE 3.1)                          | 7                                                                         | 6 + 7  | 6      | 6      | 6       |
| CE4.2                     | 9.9% (CE 3.2)                           | 7                                                                         | 6 + 7  | 6 + 7  | 6      | 6       |
| CE4.3                     | 5.3% (CE 3.3)                           | 7                                                                         | 7 + 6  | 7 + 6  | 6 + 7  | 6       |

\*"7" means that the XRPD pattern of the resulting solid material corresponds to pure crystal line form 7 of sofosbuvir. "6" means that the XRPD pattern of the resulting solid material corresponds to pure crystalline form 6 of sofosbuvir. "6 + 7" means that the XRPD pattern of the resulting solid material corresponds to a mixture of form 6 and form 7 of sofosbuvir with a higher amount of form 6 than form 7 in the sample. "7 + 6" means that the XRPD pattern of the resulting solid material corresponds to a mixture of form 7 and form 6 of sofosbuvir with a higher amount form 7 than form 6 in the sample.

As shown in the examples E 4.3 to E 4.7 and comparative examples CE4.1 to CE4.3 above, the use of n-butanol employed according to the recipe as outlined in CE4.1 to CE4.3 above, did not lead to a physically stable crystalline form 7. The starting material, crystalline form 7, transformed into polymorphic form 6 under mechanical stress. In contrast to CE4.1-CE4.3, the use of ketones having 6 carbon atoms (MIBK) stabilized polymorphic form 7 of sofosbuvir and allows the preparation and isolation of pure crystalline form 7 of sofosbuvir.

As shown in examples E4.3 to E4.7 the residual amount of MIBK influence the stability of the crystalline form 7. According to E4.3 wherein a ketone having 6 carbon atoms was present in an amount of 26.6 weight-% crystalline form 7 started to convert into crystalline form 6

after 30 minutes of ball milling. In example E4.5 wherein the residual amount of MIBK was of 12.7 weight-% the crystalline form 7 started to convert into crystalline form 6 only after 120 minutes of ball milling. In examples E4.6 and E4.7 with a residual amount of MIBK of 5.5 and 0.2 weight-%, respectively, no polymorphic transformation of form 7 into form 6 was observed.

Therefore, the use of ketones according to the present invention, such as MIBK present in a residual amount of equal or less than 27 weight-%, was shown to stabilize crystalline form 7. Hence, ketones according to the present invention such as MIBK can be used for preparing crystalline form 7 in an industrial and economically advantageous manner.

**Example 5: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of DIBK and IPA)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (1.00 g) was suspended in a mixture of DIBK (2.5 mL) and IPA (3.75 mL) and heated to a temperature of at least 50 °C until a clear solution was obtained. The solution was allowed to cool to r.t. over 30 min under stirring and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Reference Example 2) (10 mg). The suspension was stirred for 1 h and cooled to 0 °C after which viscous material collected on the reaction vessel floor. The suspension was warmed to a temperature of at least 50 °C whereby a large amount of precipitate was formed which was insoluble at this temperature. The suspension was allowed to cool to room temperature, diluted with 1.5 mL DIBK/IPA (2:3) and filtered through a G3 Nutsche filter, washing with 1.5 mL DIBK/IPA (2:3) and diethyl ether (5 mL). The solid was dried for 17 h at 45 °C/4 mbar to obtain 0.934 g (93 %) of crystalline solid. XRPD analysis showed pure crystalline form 7 of sofosbuvir (see Figure 4).

**Example 6: Preparation of the crystalline form of sofosbuvir according to the present invention (suspending sofosbuvir in a mixture of DIBK and IPA)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (991.85 mg) was suspended in a mixture of DIBK (2.5 mL) and IPA (3.75 mL) and heated to a temperature of at least 50 °C until a clear solution was obtained. The solution was allowed to cool to r.t. over 30 min under stirring and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 5) (8 mg) after which increasing turbidity was observed. The suspension was stirred for 2.5 h at r.t. and 0.5 h at 0 °C. The solid was filtered through a G3 Nutsche filter, washed with 1 mL DIBK/IPA (2:3) and diethyl ether (10 mL), and dried for 17 h at 40 °C/7 mbar to obtain 883.7 mg (89 %) of crystalline solid. XRPD analysis showed crystalline form 7 of sofosbuvir with traces of form 6.

**Comparative Example 5: Preparation of a crystalline form of sofosbuvir by suspending sofosbuvir in a mixture of DIBK and TOL)**

5 Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was suspended in a mixture of DIBK (0.5 mL) and TOL (0.75 mL) and warmed to a temperature of at least 50 °C until a clear solution was obtained. The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (2 mg) after which increasing turbidity was observed. The suspension was left to stand for 17 h, resulting in oiling out and crystal-liked particles. Scratching the reaction vessel wall resulted in complete crystallization. The solid was diluted with 0.5 mL DIBK/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 170.7 mg (86 %) of crystalline solid. XRPD analysis showed pure crystal form 1 of sofosbuvir (see Figure 5).

15 **Comparative Example 6: Preparation of a crystalline form of sofosbuvir by dissolving sofosbuvir in ACP, crystallizing in a mixture of ACP and TOL**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200 mg) was dissolved in ACP (0.5 mL) and charged with TOL (0.5 mL). The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (2 mg) after which increasing turbidity was observed. The suspension was stirred for a 4 h at r.t., diluted with 0.5 mL ACP/TOL (1:1), filtered through a G3 Nutsche filter and dried for 20 h at 40 °C/7 mbar to obtain 149.2 mg (75 %) of crystalline solid. XRPD analysis showed the presence of crystalline forms 7 and 6 of sofosbuvir (see Figure 6).

**Comparative Example 7: Preparation of a crystalline form of sofosbuvir by suspending sofosbuvir in mixture of DIBK and TOL (crystallization without stirring)**

30 Sofosbuvir of crystalline form 1 prepared according to WO 2011/123645 A1, Example 10 (200 mg) was suspended in DIBK (1.5 mL) and toluene (0.5 mL) and warmed up above 50 °C until a clear solution was obtained. The solution was allowed to cool to room temperature, whereby it oiled out. The heterogeneous oil mixture was seeded with form 7 crystals prepared according to Example 1.2 and left to stand for 17 hours, whereby it fully crystallized. The crystals were diluted with a 1:1 DIBK/TOL mixture (0.5 mL) and filtered through a G3-suction filter. Drying for 16 h at 40 °C/8 mbar gave 153.3 mg (77 %) of crystalline solid. XRD analysis showed a mixture of a non-stoichiometric solvate, amorphous form and only traces of form 7 sofosbuvir.

**Comparative Example 8: Preparation of a crystalline form of sofosbuvir by suspending sofosbuvir in mixture of DIBK and TOL (crystallization without stirring)**

Sofosbuvir of crystalline form 1 (prepared according to WO 2011/123645 A1, Example 10) (200.9 mg) was suspended in a mixture of DIBK (0.5 mL) and TOL (0.75 mL) and warmed to a temperature of at least 50 °C until a clear solution was obtained. The solution was stirred for 30 min at r.t. and seeded with sofosbuvir crystalline form 7 crystals (prepared according to Example 1.2) (2 mg) after which the compound oiled out. The suspension was left to stand for 66 h, resulting in full crystallization. The solid was diluted with 1 mL DIBK/TOL (1:1), filtered through a G3 Nutsche filter washing with 1 mL DIBK/TOL (2:3) and ether, and dried for 20 h at 40 °C/7 mbar to obtain 163.8 mg (81.5 %) of crystalline solid. XRPD analysis showed pure crystal form 7 of sofosbuvir.

**Summary of the Results of the Examples and the Comparative Examples**

In the following Table 5, the results of the Examples and Comparative Examples are shown:

**Table 5**

Summary of the Results of the Examples and the Comparative Examples

| <b>E# / CE# <sup>1)</sup></b> | <b>ketone /<br/>C atoms</b> | <b>aprotic non-<br/>ketonic solvent</b> | <b>crystalline form<br/>obtained</b> | <b>stirring</b> | <b>crystalliz.<br/>time / h</b> |
|-------------------------------|-----------------------------|-----------------------------------------|--------------------------------------|-----------------|---------------------------------|
| E5                            | DIBK / 9                    | IPA                                     | 7                                    | yes             | 1                               |
| E6                            | DIBK / 9                    | IPA                                     | 7 + traces 6                         | yes             | 3                               |
| CE5                           | DIBK / 9                    | TOL                                     | 1                                    | no              | 17                              |
| CE6                           | ACP / 8                     | TOL                                     | 6+7                                  | yes             | 4                               |
| CE7                           | DIBK / 9                    | TOL                                     | solvate + amorphous                  | no              | 17                              |
| CE8                           | DIBK / 9                    | TOL                                     | 7                                    | no              | 66                              |

<sup>1)</sup> E = Example; CE = Comparative Example

As shown in the examples and comparative examples above, the use of a ketone having 9 carbon atoms with toluene as aprotic non-ketonic organic, as shown in CE5 and CE7, did not lead to pure crystalline form 7. However, the use of a ketone having 9 carbon atoms, together with an aprotic non-ketonic organic which was not toluene but, in particular, 1-methyl ethyl acetate (IPA), crystalline form 7 of sofosbuvir was obtained in pure form. Further, as shown

in CE6, toluene as aprotic non-ketonic organic solvent in combination with a ketonic compound having 8 instead of 9 carbon atoms did not lead to pure crystalline form 7 of sofosbuvir but to a mixture of forms 6 and 7. Further, as shown in CE8, the combination of a ketone having 9 carbon atoms and an aprotic non-ketonic organic which was toluene may result in pure crystalline form 7; however, these conditions initially give an oil which must undergo very slow crystallization (66 hours) in the absence of any agitation. Shorter crystallization times (17 hours) from the initial oily material in the absence of stirring irreproducibly give Form 1 (see CE5), or a mixture of non-stoichiometric solvates and traces of Form 7 (see CE7). This is in contrast to the process of the invention, which gives Form 7 after short crystallization times (E5: 1 hour, E6: 3 hours)

As shown by the results according to Table 5 above, the specific choice of a ketone having 9 carbon atoms in combination with an aprotic non-ketonic organic which does not comprise toluene and, in particular, comprises 1-methyl ethyl acetate, allows to prepare crystalline form 7 of sofosbuvir wherein it was possible to stir the reaction mixture and to achieve very advantageous crystallization times. In particular, as shown by the comparison of Examples E5 and E6, it was found that by decreasing the crystallization time, it was even possible to eliminate the presence of minor traces of crystalline form 6 which means that the shorter the crystallization time, the better the results are for the inventive combination of a ketone having 9 carbon atoms and an aprotic non-ketonic organic which does not comprise toluene and, in particular, comprises 1-methyl ethyl acetate, for preparing crystalline form 7 of sofosbuvir.

### Short Description of the Figures

Fig. 1 shows the X-ray powder diffraction (XRPD) pattern of the crystalline form 7 as prepared according to Example 1.1 of to the present invention, as determined according to Reference Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 1000, 2000, 3000.

Fig. 2 shows the X-ray powder diffraction (XRPD) pattern of the product mixture of the crystalline forms 6 and 7 as prepared according to Example 1.1 of to the present invention as prepared according to Comparative Example 2.1 and as determined according to Reference Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 500, 1000.

Fig. 3 shows the X-ray powder diffraction (XRPD) pattern of the crystalline form 1 as prepared according to Comparative Example 1.1 and as determined according to Refer-

ence Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 2000, 4000.

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Fig. 4 shows the X-ray powder diffraction (XRPD) pattern of the crystalline form 7 as prepared according to Example 5 of to the present invention, as determined according to Reference Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 1000, 2000, 3000.

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Fig. 5 shows the X-ray powder diffraction (XRPD) pattern of the crystalline form 1 as prepared according to Comparative Example 5 and as determined according to Reference Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 2000, 4000.

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Fig. 6 shows the X-ray powder diffraction (XRPD) pattern of the product mixture of the crystalline forms 6 and 7 as prepared according to Comparative Example 6 and as determined according to Reference Example 1.1. The x-axis shows the 2-theta angle / °, with tick marks, from left to right, at 10, 20, 30 ° 2-theta. The y-axis shows the intensity / counts, with tick marks, from bottom to top, at 0, 500, 1000.

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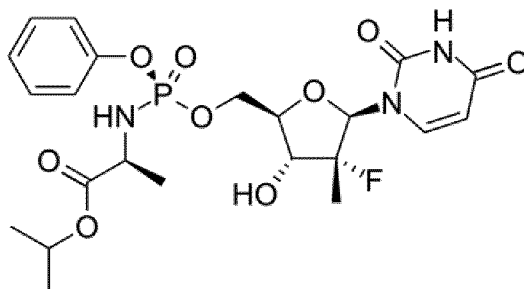
#### Cited Prior Art

- WO 2010/135569 A1
- WO 2011/123645 A1
- CN 104130302 A

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## Claims

1. A process for preparing a solid crystalline form of sofosbuvir of formula (I)

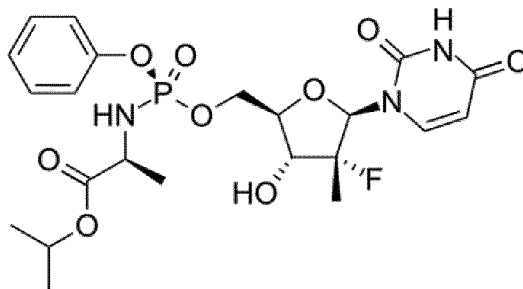


(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, said process comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and
  - a solvent system comprising at least one ketone having from 5 to 7 carbon atoms and optionally at least one aprotic non-ketonic organic solvent or
  - a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, in its mother liquor.

2. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



(I)

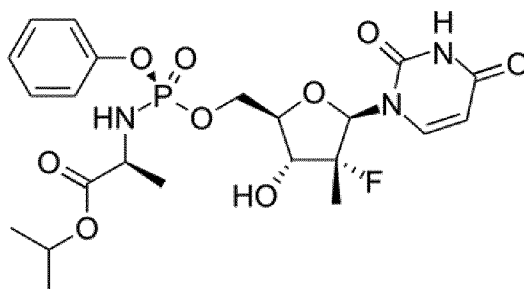
having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, said process comprising

- (i) providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
- (ii) preparing a mixture comprising the sofosbuvir provided in (i) and a solvent system comprising at least one ketone having from 5 to 7 carbon atoms and optionally at least one aprotic non-ketonic organic solvent;
- (iii) subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in its mother liquor.

3. The process of claim 2, wherein according to (i), the sofosbuvir is provided in crystalline form 1.
4. The process of claim 2 or 3, wherein according to (ii), the at least one ketone has 5 or 6 carbon atoms.
5. The process of any of claims 2 to 4, wherein the at least one ketone is one or more of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone.
6. The process of any of claims 2 to 5, wherein the solvent system according to (ii) further comprises at least one aprotic non-ketonic organic solvent.

7. The process of any of claims 2 to 6, wherein the solvent system according to (ii) further comprises at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent comprises one or more aromatic compounds, one or more ether compounds, one or more ester compounds, or a mixture of one or more thereof.
8. The process of claim 7, wherein the at least one aprotic non-ketonic organic solvent is one or more of toluene, methyl tert-butyl ether, and 1-methyl ethyl acetate.
9. The process of any of claims 2 to 8, wherein in the mixture according to (ii), the volume ratio of the at least one ketone relative to the at least one aprotic non-ketonic organic solvent is in the range of from 0.1:1 to 10:1, preferably of from 0.9:1 to 1.1:1.
10. The process of any of claims 2 to 9, wherein the mixture according to (ii) contains the sofosbuvir according to formula (I), relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 100 to 500 mg/mL, preferably of from 175 to 225 mg/mL.
11. The process of any of claims 2 to 10, wherein preparing the mixture according to (ii) comprises preparing a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.
12. The process of any of claims 2 to 11, wherein preparing the mixture according to (ii) comprises agitation, preferably mechanical agitation, more preferably stirring.
13. The process of any of claims 2 to 12, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises stirring the mixture.
14. The process of claim 13, wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.
15. The process of any of claims 2 to 14, wherein subjecting the mixture obtained in (ii) to solvent-mediated transformation conditions according to (iii) comprises seeding the mixture.

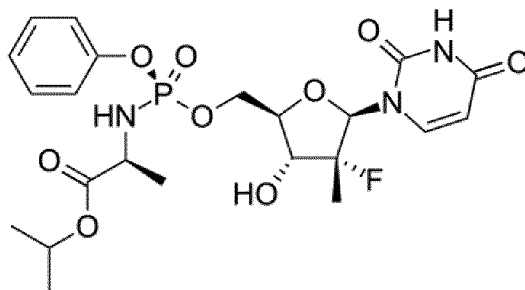
16. The process of claim 15, wherein seeding the mixture comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.
17. The process of any of claims 2 to 16, further comprising
- 5 (iv) separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, from its mother liquor;
- 10 (v) drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.
- 15
18. Use of a ketone having from 7 to 9 carbon atoms, optionally in combination with at least one aprotic non-ketonic organic solvent, for solvent-mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)
- 20



(I)

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm.
- 25
19. The use of claim 18, wherein the solvent-mediated transformation of sofosbuvir comprises agitation, preferably mechanical agitation, more preferably stirring.
- 30

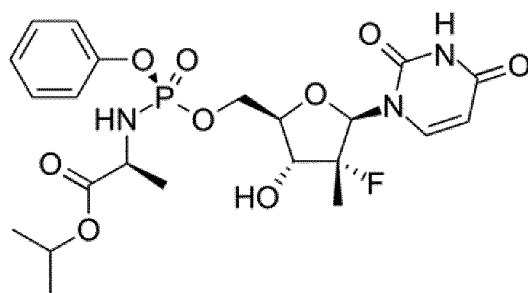
20. A mixture comprising solid crystalline sofosbuvir of formula (I)



(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and a solvent system comprising at least one ketone having from 5 to 7 carbon atoms, and optionally at least one aprotic non-ketonic organic solvent, wherein in the mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, relative to the total content of solid crystalline sofosbuvir is at least 99.9 %.

21. A composition comprising crystalline sofosbuvir of formula (I)



(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm,

and at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the  
5 range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

10 22. The composition of claim 21, wherein at least 99 weight-%, preferably at least 99.5 weight-%, preferably at least 99.7 weight-%, more preferably at least 99.9 weight-% of the composition consists of the crystalline form of sofosbuvir according to claim 21 and the at least one ketone having from 4 to 8 carbon atoms.

15 23. The composition of claim 21 or 22, wherein the residual amount is in the range of from 12 to 0.2 weight-%, preferably in the range of from 6 to 0.2 weight-% based on the total weight of the composition.

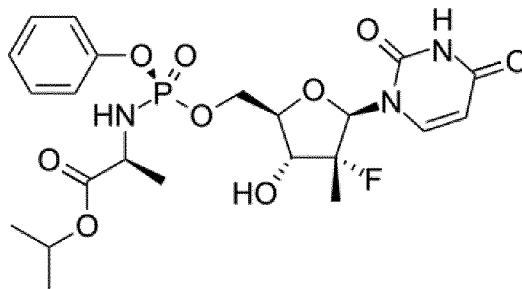
20 24. The composition of any of claims 21 to 23, wherein the ketone is selected from the group consisting of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably the solvent is methyl isobutyl ketone.

25 25. The composition of any of claims 21 to 24, wherein the ketone is methyl isobutyl ketone.

26. The composition of any of claims 21 to 25, wherein the ketone is methyl isobutyl ketone in a residual amount in the range of from 5.5 to 0.2 weight-%, based on the total  
30 amount of the composition.

27. The composition of any of claims 21 to 26, wherein the solid crystalline form of sofosbuvir of formula (I) has a mechanical stress resistance of at least 10 min at 10 Hz, preferably at least 30 min at 10 Hz, more preferably at least 60 min at 10 Hz, more preferably 120 min at 10 Hz as determined in an oscillatory ball mill.  
35

28. A process for preparing a composition comprising  
-a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

-at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms,

said process comprising

- 1) providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm;
- 2) preparing a mixture which is a suspension comprising, preferably consisting of, the sofosbuvir provided in 1) and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms; and
- 3) recovering from the mixture of 2) a composition comprising the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a

temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm and

the at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in a residual amount in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and

wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

29. The process of claim 28, wherein the ketone is selected from the group consisting of cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl isopropyl ketone, and methyl isobutyl ketone, preferably the solvent is methyl isobutyl ketone.

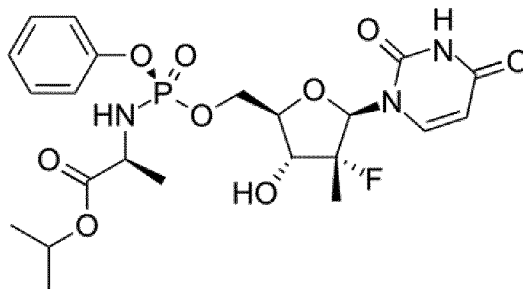
30. The process of claim 28 or 29, wherein the ketone is methyl isobutyl ketone.

31. The process of any of claims 28 to 30, wherein the ketone is methyl isobutyl ketone in a residual amount in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition.

32. Use of a ketone having from 4 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, more preferably 6 carbon atoms, more preferably the ketone being methyl isobutyl ketone for stabilizing crystalline sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha$ <sub>1,2</sub> radiation having a wavelength of 0.15419 nm.

33. The use of claim 32 wherein the ketone forms with the crystalline sofosbuvir a composition according to any of claims 21 to 27.

34. A process for preparing a solid crystalline form of sofosbuvir of formula (I)

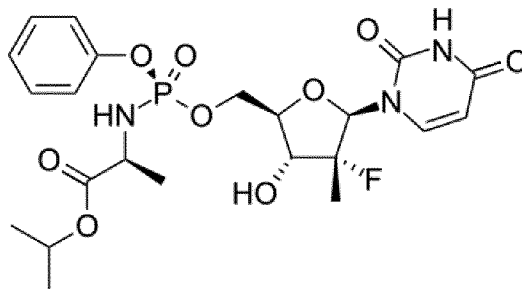


(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, said process comprising

- (x) providing sofosbuvir according to formula (I) in a crystalline form having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, in a solvent preferably selected from the group consisting of an alcohol, a mixture alcohol and alkane, and water; and
- (xx) carrying out the work-up of (x) with a solvent system comprising, preferably consisting of at least one ketone having from 4 to 8 carbon atoms and obtaining said solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, wherein said solid crystalline form is dry or comprises less than 0.5 weight-%, preferably less than 0.3 weight-%, more preferably less than 0.1 weight-%, more preferably less than 0.05 weight-%, more preferably less than 0.01 weight-% of the solvent of (x) and/or of the solvent system of (xx) based on the total amount of said solid crystalline form and the solvent of (x) and/or of the solvent system of (xx).

35. A process for preparing a composition comprising a solid crystalline form (form 7) of sofosbuvir of formula (I)



(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and

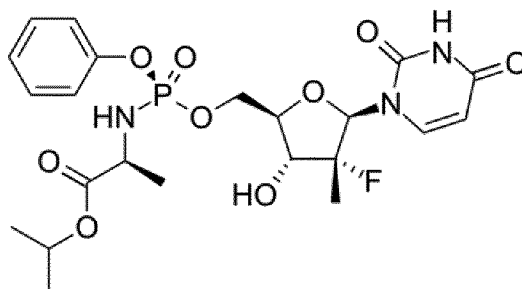
at least one ketone having from 4 to 8 carbon atoms, wherein the at least one ketone is present in a residual amount of equal or less than 27 weight-%, preferably in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition,

said process comprising

1') providing a solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and

2') preparing a mixture wherein the mixture is a composition comprising the sofosbuvir provided in 1') and a solvent system comprising, preferably consisting of, at least one ketone having from 4 to 8 carbon atoms wherein the at least one ketone is present in the composition in a residual amount which is equal or less than 27 weight-%, preferably in a residual amount which is in the range of from 27 to 0.2 weight-% or in the range of from 24 to 12 weight-% or in the range of from 24 to 6 weight-% or in the range of from 13 to 0.2 weight-% or in the range of from 12 to 6 weight-%, more preferably in the range of from 5.5 to 0.2 weight-%, based on the total amount of the composition, and wherein in case the at least one ketone having from 4 to 8 carbon atoms is more than one ketone having from 4 to 8 carbon atoms said residual amount relates to the total amount of ketones having from 4 to 8 carbon atoms.

36. A process for preparing a solid crystalline form of sofosbuvir of formula (I)



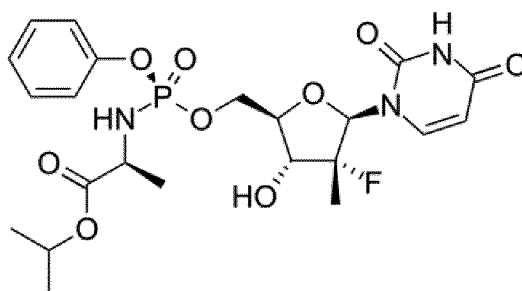
(I)

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, said process comprising

- (i') providing sofosbuvir according to formula (I) in crystalline form, pseudo-crystalline form, amorphous form, or as a mixture of two or more of these forms;
  - (ii') preparing a mixture comprising the sofosbuvir provided in (i') and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic organic solvent does not comprise toluene;
  - (iii') subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions, obtaining the solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° in its mother liquor.
37. The process of claim 36, wherein according to (i'), the sofosbuvir is provided in crystalline form 1.
38. The process of claim 36 or 37, wherein according to (ii'), the at least one ketone is diisobutyl ketone.
39. The process of any of claims 36 to 38, wherein according to (ii'), the at least one aprotic non-ketonic organic solvent comprises one or more ester compounds, preferably is one or more ester compounds.

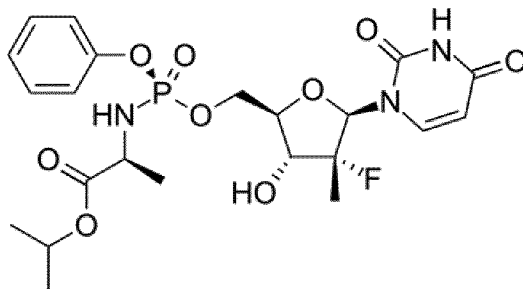
40. The process of claim 39, wherein the at least one aprotic non-ketonic organic solvent comprises, preferably is, 1-methyl ethyl acetate.
41. The process of any of claims 36 to 40, wherein in the mixture according to (ii'), the volume ratio of the at least one ketone relative to the at least aprotic non-ketonic organic solvent is in the range of from 0.1:1 to 10:1, preferably of from 0.9:1 to 1.1:1.
42. The process of any of claims 36 to 41, wherein the mixture according to (ii') contains the sofosbuvir according to formula (I), relative to the at least one ketone and the at least one aprotic non-ketonic organic solvent, in an amount in the range of from 100 to 500 mg/mL, preferably of from 175 to 225 mg/mL.
43. The process of any of claims 36 to 42, wherein preparing the mixture according to (ii') comprises preparing a solution comprising sofosbuvir of formula (I) dissolved in at least a portion of the solvent system.
44. The process of any of claims 36 to 43, wherein preparing the mixture according to (ii') comprises agitation, preferably mechanical agitation, more preferably stirring.
45. The process of any of claims 36 to 44, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture.
46. The process of claim 45 wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out at one or more temperatures of the mixture in the range of from -5 to 35 °C, preferably from 0 to 30 °C.
47. The process of claim 45 or 46, wherein agitating the mixture, preferably mechanically agitating the mixture, more preferably stirring the mixture is carried out for a period of time of less than 3 h, preferably at most 2.5 h, more preferably in the range of from 0.25 to 2.5 h, more preferably in the range of from 0.5 to 2 h, more preferably in the range of from 0.5 to 1.5 h.
48. The process of any of claims 36 to 47, wherein subjecting the mixture obtained in (ii') to solvent-mediated transformation conditions according to (iii') comprises seeding the mixture.
49. The process of any of claims 36 to 48, further comprising

- (iv') separating the solid crystalline form of sofosbuvir preferably having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$  from its mother liquor;
- (v') drying the separated solid crystalline form of sofosbuvir having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ .
50. Use of a ketone having from 9 carbon atoms, preferably in combination with at least one aprotic non-ketonic organic solvent wherein the at least one aprotic non-ketonic solvent does not comprise toluene, for solvent mediated transformation of sofosbuvir to obtain sofosbuvir of formula (I)



(I)

- having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of  $(8.1 \pm 0.2)^\circ$ ,  $(10.4 \pm 0.2)^\circ$ ,  $(12.4 \pm 0.2)^\circ$ ,  $(17.3 \pm 0.2)^\circ$ ,  $(19.4 \pm 0.2)^\circ$ , when measured at a temperature in the range of from 15 to 25 °C with Cu-K $\alpha_{1,2}$  radiation having a wavelength of 0.15419 nm, wherein the solvent mediated transformation of sofosbuvir preferably comprises agitation, more preferably mechanical agitation, more preferably stirring.
51. A mixture comprising solid crystalline sofosbuvir of formula (I)



(I),

having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 °, and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) °, when measured at a temperature in the range of from 15 to 25 °C with Cu-Kalpha<sub>1,2</sub> radiation having a wavelength of 0.15419 nm, and a solvent system comprising at least one ketone having 9 carbon atoms and at least one aprotic non-ketonic organic solvent, wherein the at least one aprotic non-ketonic solvent does not comprise toluene, and wherein the at least one aprotic non-ketonic solvent preferably comprises, more preferably is, 1-methyl ethyl acetate, wherein in the mixture, the molar ratio of the solid crystalline form of sofosbuvir of formula (I) having an X-ray powder diffraction pattern comprising no reflection at 2-theta angles in the range of from 2.0 to 7.8 ° and preferably comprising reflections at 2-theta values of (8.1 ± 0.2) °, (10.4 ± 0.2) °, (12.4 ± 0.2) °, (17.3 ± 0.2) °, (19.4 ± 0.2) ° relative to the total content of solid crystalline sofosbuvir is at least 99.9 %.

Figure 1

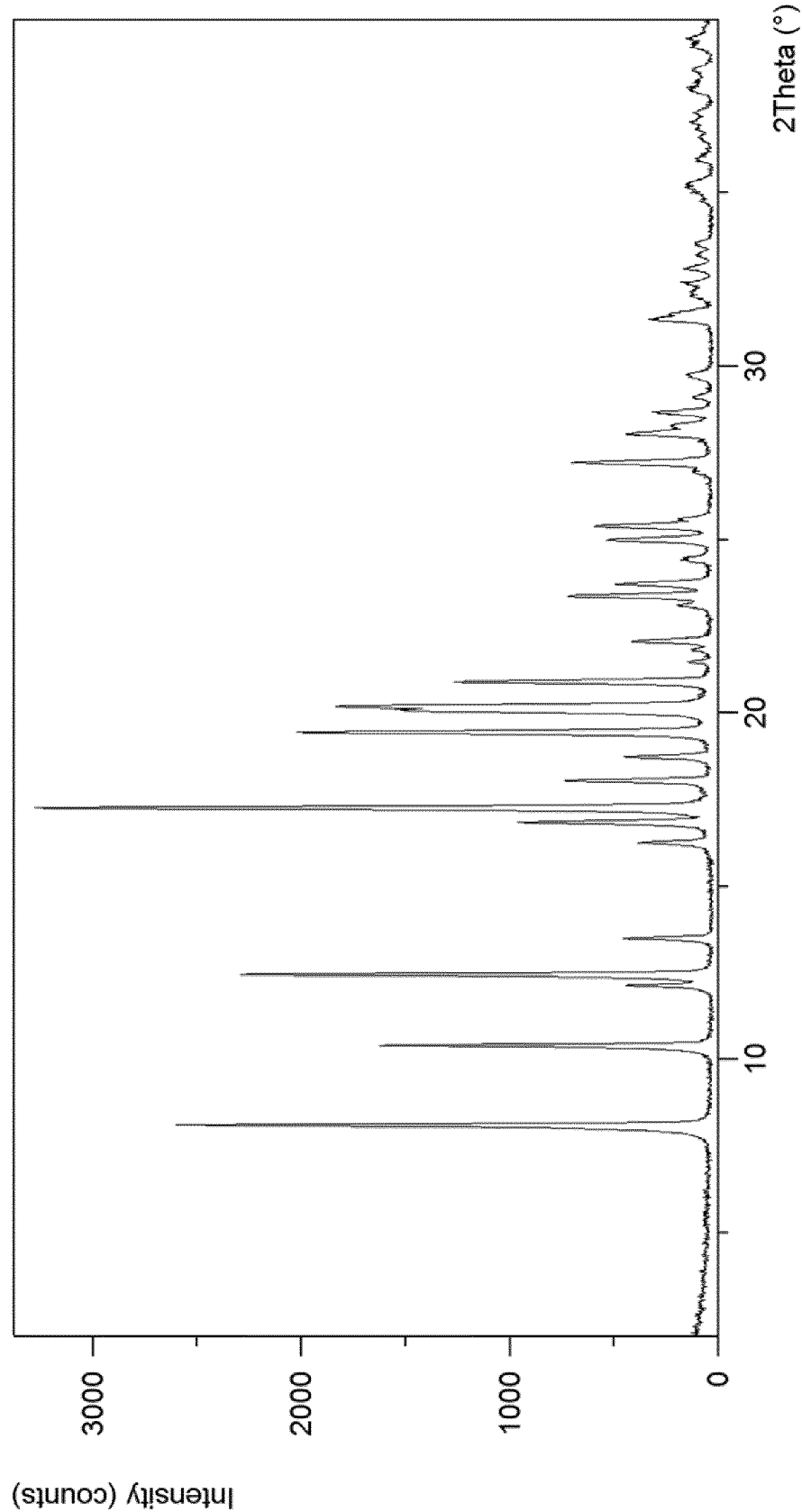


Figure 2

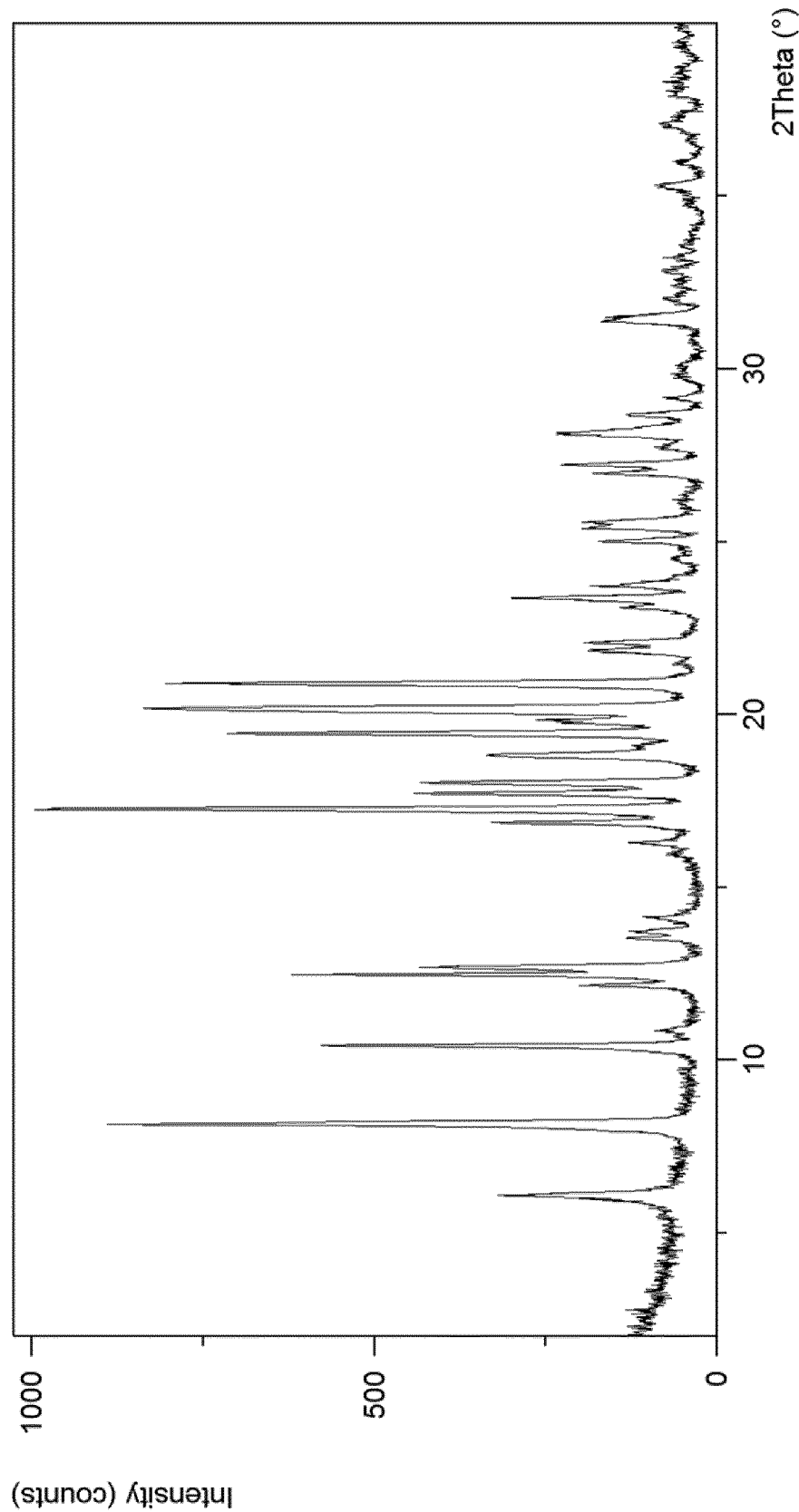
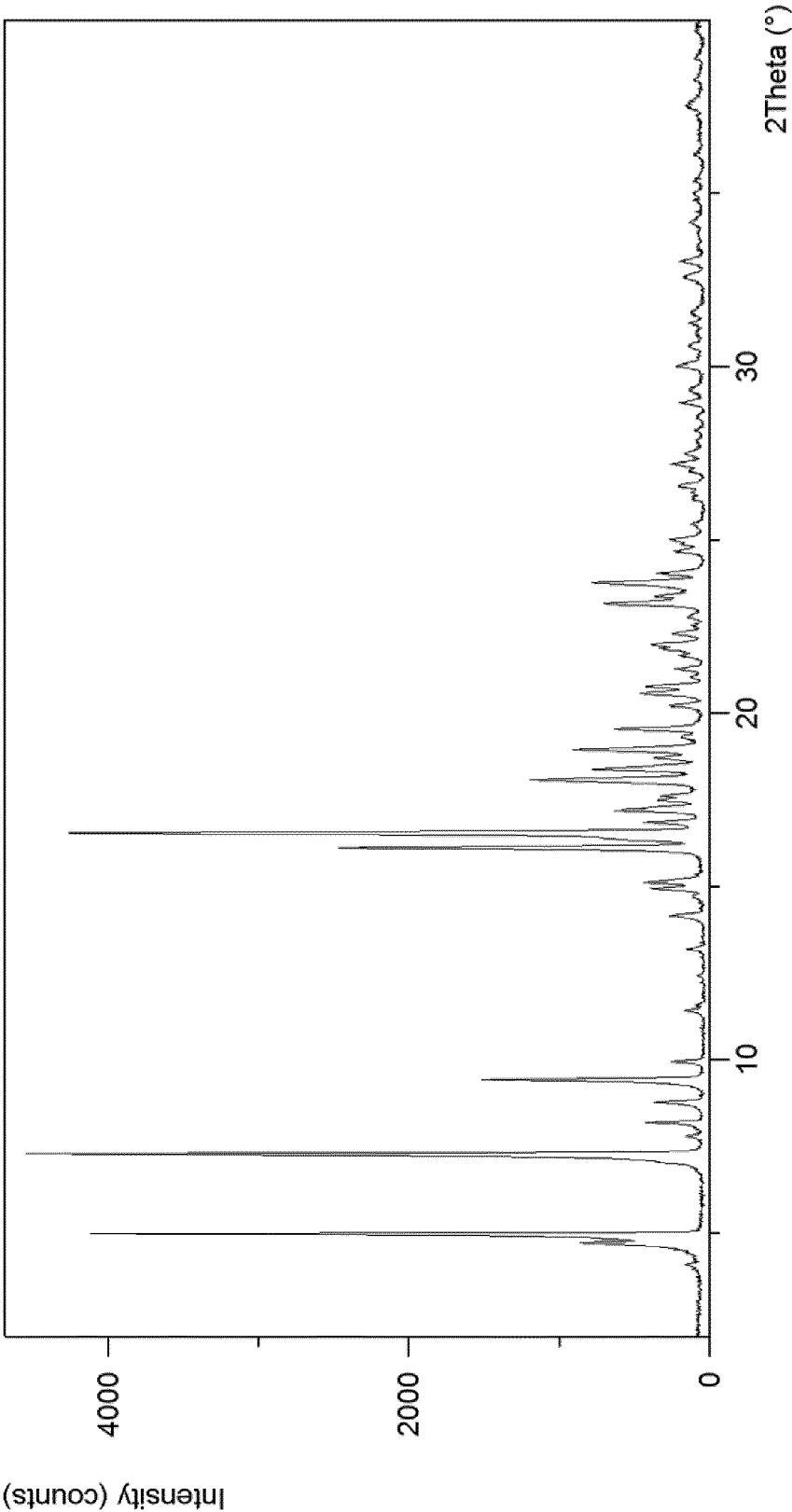
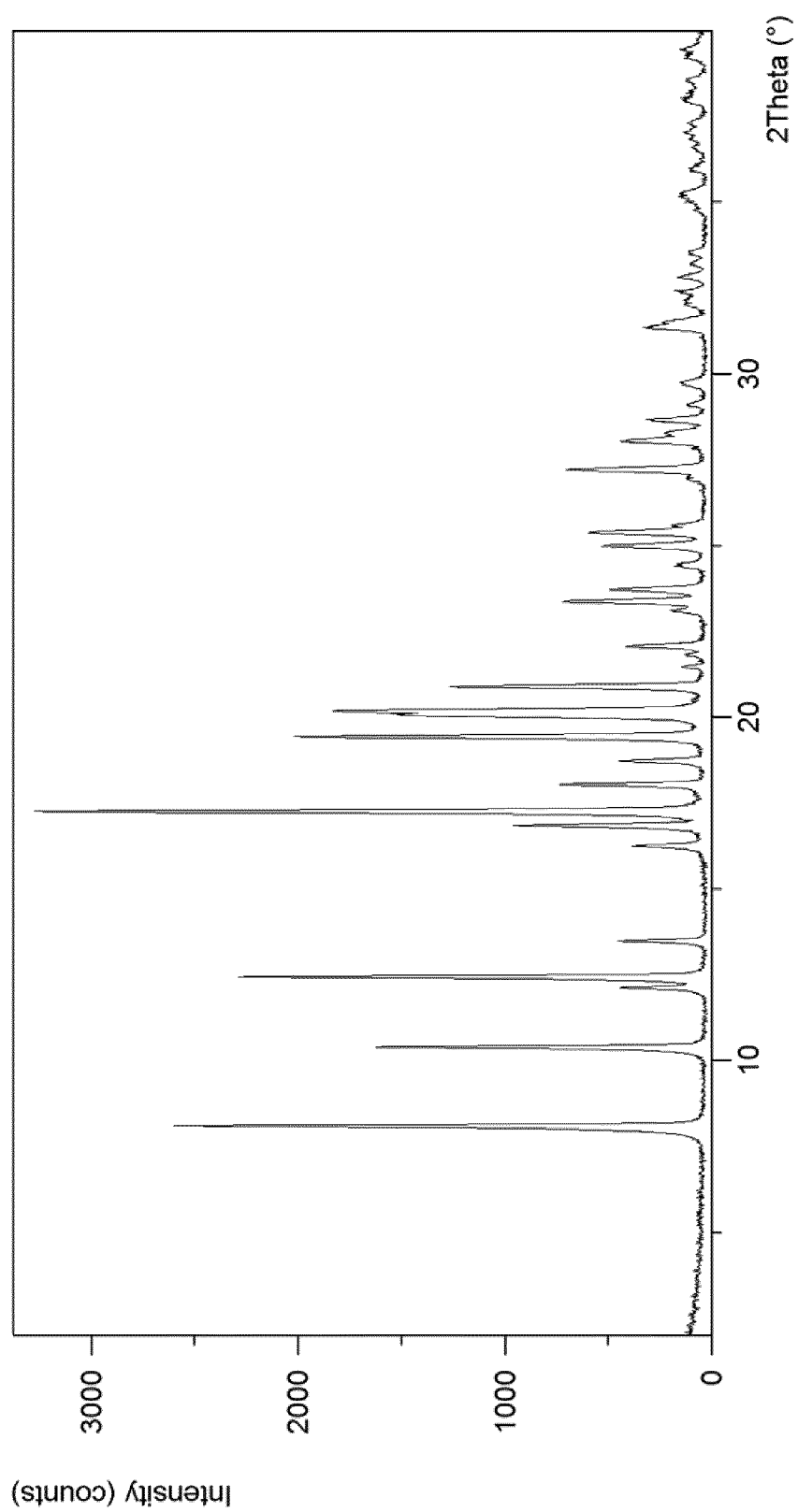


Figure 3



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Figure 4



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Figure 5

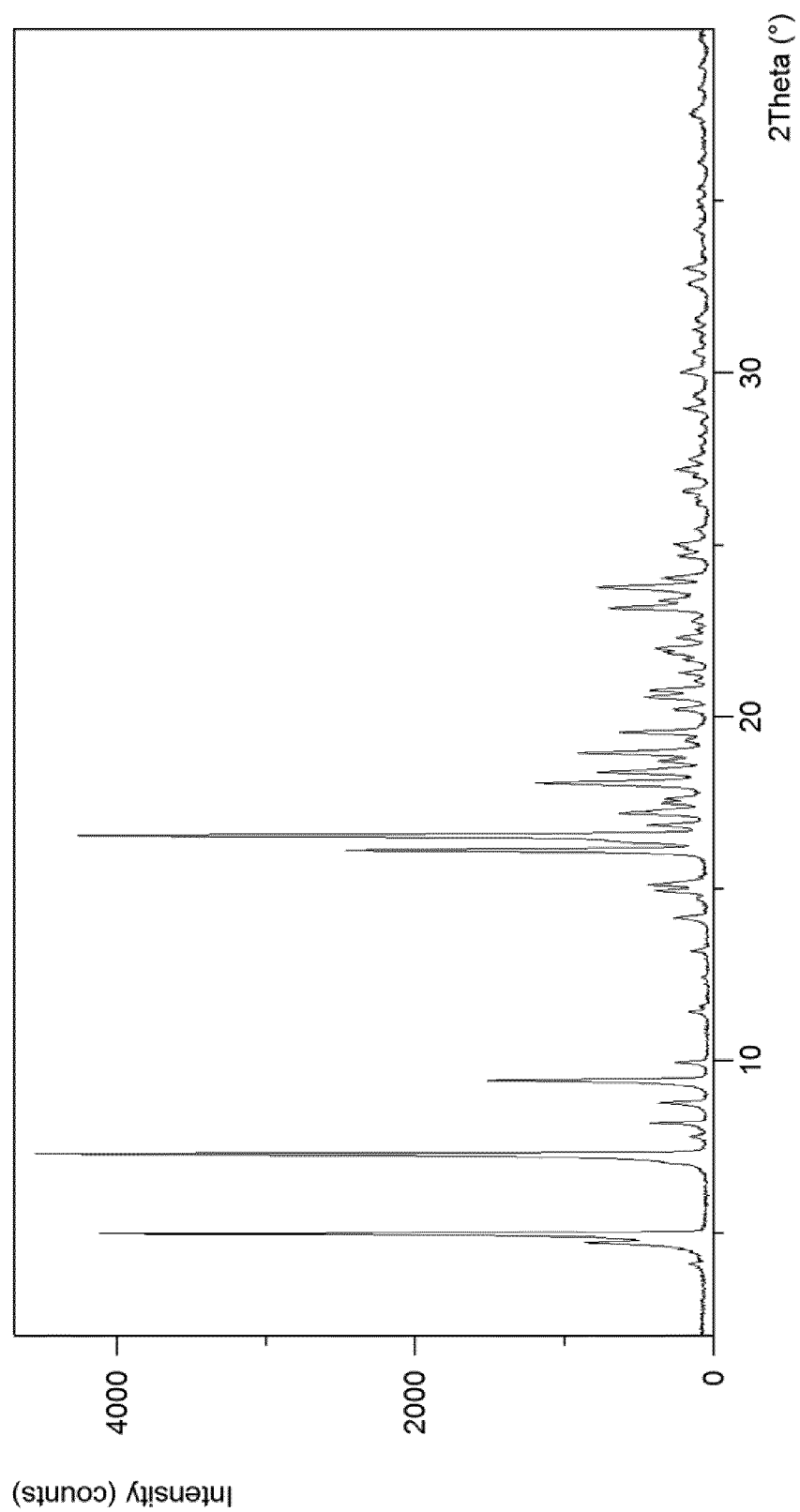
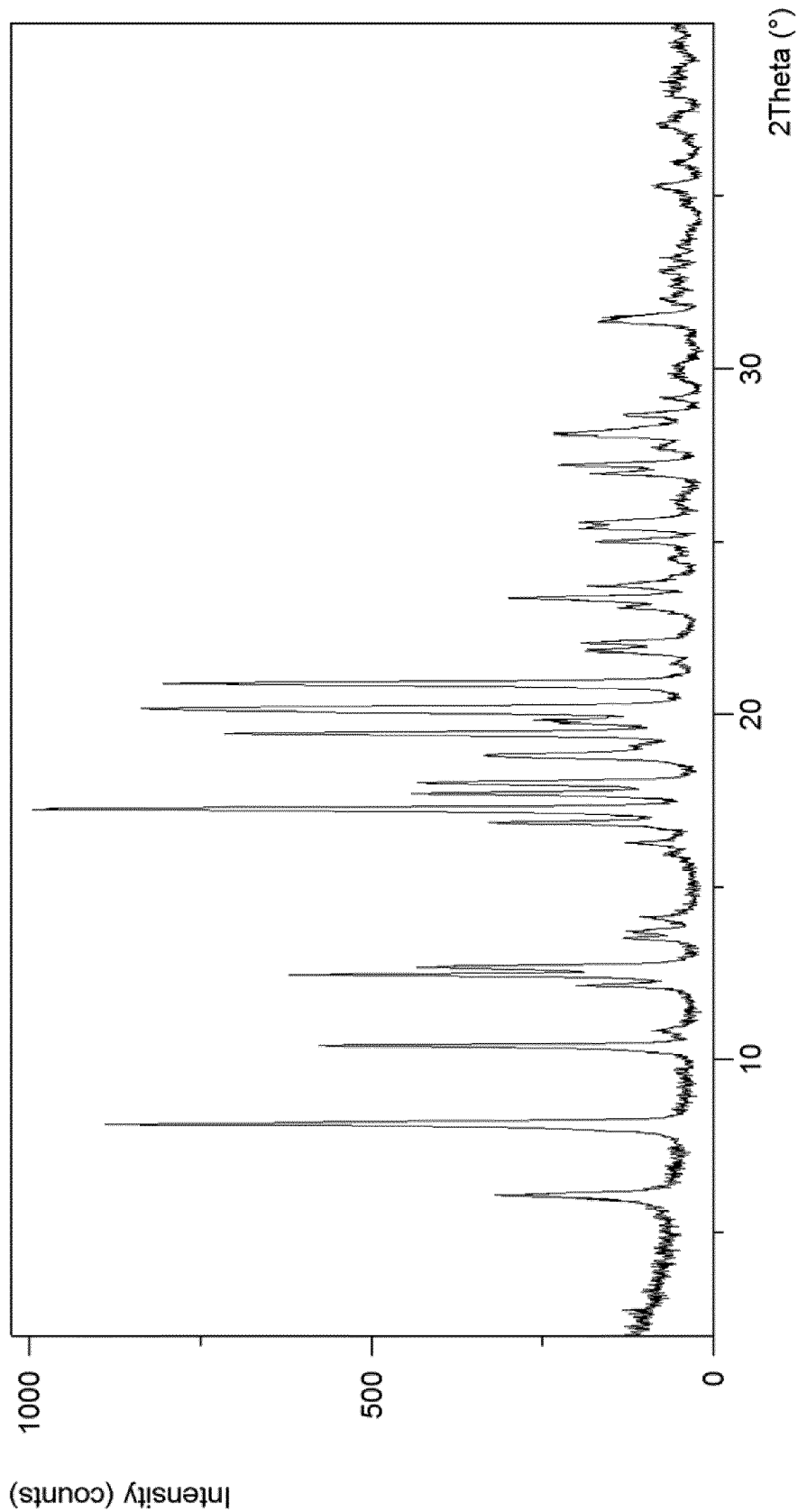


Figure 6



## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/057105

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. C07H1/00 C07H19/10 A61K31/7072<br>ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>C07H<br><br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br><br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                       | Relevant to claim No.                                                |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | CN 104 130 302 A (GUANGDONG HEC PHARMACEUTICAL)<br>5 November 2014 (2014-11-05)<br>cited in the application<br>Whole document, in particular figure 1 and claim 6<br><br>-----                                                                                                                                                                                                                           | 1-51                                                                 |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 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",<br>JOURNAL OF MEDICINAL CHEMISTRY,<br>vol. 53, no. 19,<br>16 September 2010 (2010-09-16), pages 7202-7218, XP055004442,<br>ISSN: 0022-2623, DOI: 10.1021/jm100863x<br>Preparation of compound 51 on page 7214<br><br>-----<br>-/- | 1-51                                                                 |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
| <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                      |
| Date of the actual completion of the international search<br><br>24 May 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                          | Date of mailing of the international search report<br><br>01/06/2016 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                          | Authorized officer<br><br>Lécaillon, Jennifer                        |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2016/057105

| C(Continuation). 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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