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(54) **Title:** CO-CRYSTAL OF SOFOSBUVIR AND AMINO ACID AND PROCESS FOR PREPARATION THEREOF

(57) **Abstract:** The present invention relates to co-crystals of sofosbuvir and amino acid and process for preparation thereof. The present invention also provides pharmaceutical composition comprising said co-crystals and one or more pharmaceutically acceptable carriers, excipients and diluents.



WO 2016/042576 A1

CO-CRYSTAL OF SOFOSBUVIR AND AMINO ACID AND PROCESS FOR PREPARATION THEREOF

FIELD OF THE INVENTION

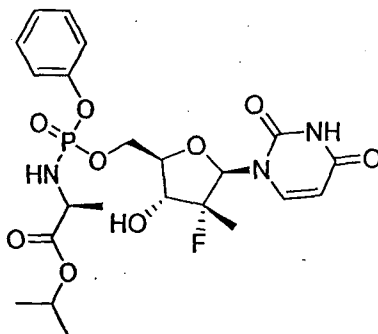
5 The present invention relates to co-crystal of sofosbuvir and amino acid and process for preparation thereof. The invention also relates to a pharmaceutical composition comprising said co-crystal and one or more pharmaceutically acceptable carriers, excipients and diluents for the treatment of hepatitis C.

10 BACKGROUND OF THE INVENTION

 The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely
15 known or forms part of common general knowledge in the field.

 Sofosbuvir (formerly PSI-7977 or GS-7977) is an approved drug for the treatment of hepatitis C. It was discovered at Pharmasset and then acquired for development by Gilead Sciences. Sofosbuvir is a prodrug that is metabolized to the active antiviral agent 2'-deoxy-2'- α -fluoro- β -C-methyluridine-5'-monophosphate. It is
20 a nucleotide analogue inhibitor of the hepatitis C virus (HCV) polymerase.

 Sofosbuvir is chemically known as Isopropyl (2S)-2-[[[(2R, 3R, 4R, 5R)-5-(2, 4-dioxypyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-yl] methoxy-phenoxy-phosphoryl]amino]propanoate of Formula (A).



U.S. Patent No. 7,964,580 B2, which corresponds to WO 2008/121634 A2, discloses sofosbuvir, and other novel nucleoside phosphoramidates and their preparations and use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals, which is herein incorporated by reference in its entirety.

International (PCT) Publication Nos. WO 2006/012440, WO 2008/045419, WO 2006/031725 and US Patent Nos. 7,601,820 and 8,492,539 discloses processes for the preparation of intermediates used for the preparation of sofosbuvir.

International (PCT) Publication No. WO 2010/135569 discloses various processes for the preparation of sofosbuvir and its intermediates.

International (PCT) Publication No. WO 2011/123645 discloses various crystalline forms and processes for the preparation of (S)-isopropyl 2-(S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1-(2H)-yl)-4-fluoro-3-hydroxy-4-methyl tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

U.S. PG-Pub No. US 2011/0251152 disclose crystalline forms 1 to 6 of sofosbuvir.

International (PCT) Publication No. WO 2014/08236 discloses processes for the preparation of diastereomerically enriched phosphoramidate derivatives.

CN 104447924 A discloses four crystalline forms of sofosbuvir viz. H₁, H₂, H₃ and H₄ and processes for their preparation.

International (PCT) Publication No. WO 2015/097605 discloses a process for the preparation of sofosbuvir or its pharmaceutically acceptable salt using novel intermediates.

CN 104558079 A discloses a process for the preparation of sofosbuvir and its impurity.

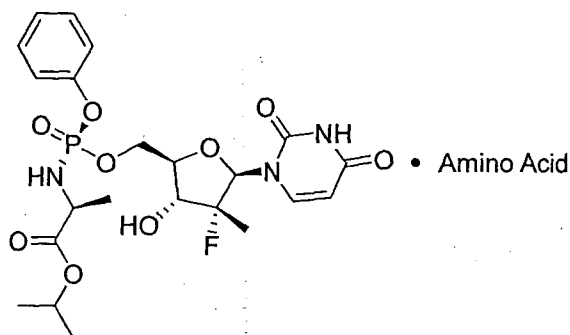
The processes disclosed in the prior art references provide the amorphous form and various crystalline forms of sofosbuvir but do not disclose co-crystals of sofosbuvir or processes for their preparations. The amorphous forms quickly convert into the thermodynamically more stable crystalline form. They can be stabilized by

incorporation in a solid dispersion matrix which results in large volume dosage forms since large amount of matrix material is required to obtain a stable solid dispersion. Crystalline forms are often disadvantageous due to poor solubility, hygroscopicity, dissolution rate, and other associated performance characteristics.

5 It is desirable to provide drug substances in co-crystalline forms as these can offer an alternative approach to modify or control the physicochemical properties of a drug substance. Co-crystallization can also be used to isolate or purify a drug substance during manufacturing.

10 SUMMARY OF THE INVENTION

In one general aspect, there is provided a co-crystal of sofosbuvir and amino acid of Formula (B).



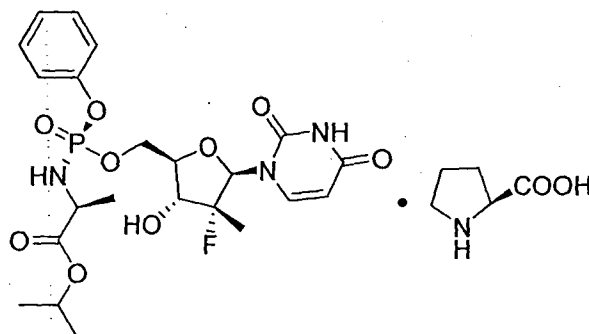
15 In another aspect, there is provided a process for the preparation of co-crystal of sofosbuvir and amino acid, the process comprising:

- (a) dissolving sofosbuvir and amino acid in one or more solvents to obtain a solution;
- (b) optionally warming the solution for complete dissolution;
- (c) cooling the solution; and

20 (d) removing the solvent or optionally adding an antisolvent to solution to obtain the co-crystal of sofosbuvir and amino acid.

In another aspect, there is provided a pharmaceutical composition comprising a co-crystal of sofosbuvir and amino acid having one or more pharmaceutically acceptable carriers, excipients and diluents for the treatment of hepatitis C.

In another aspect, there is provided a process for the preparation of co-crystal of sofosbuvir and L-proline of Formula (C),



the process comprising:

- (a) dissolving sofosbuvir and L-proline in one or more solvents to obtain the solution;
- (b) optionally warming the solution for complete dissolution;
- (c) cooling the solution; and
- (d) removing the solvent or optionally adding an antisolvent to the solution to obtain

the co-crystal of sofosbuvir and L-proline.

In an another aspect, there is provided co-crystal of sofosbuvir and L-proline characterized by x-ray powder diffraction pattern substantially as depicted in FIG.1, differential scanning thermogram (DSC) substantially as depicted in FIG.3, IR spectrum substantially as depicted in FIG.4 and ^1H NMR spectrum substantially as depicted in FIG.5.

In another aspect, there is provided a pharmaceutical composition comprising co-crystal of sofosbuvir and L-proline having one or more pharmaceutically acceptable carriers, excipients and diluents for the treatment of hepatitis C.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a powder x-ray diffraction pattern of the co-crystal of sofosbuvir and L-proline.

FIG. 2 shows comparison among powder x-ray diffraction pattern of the co-crystal of sofosbuvir and L-proline with sofosbuvir and L-proline.

FIG. 3 shows results of DSC analysis of the co-crystal of sofosbuvir and L-proline.

FIG. 4 shows IR spectrum of the co-crystal of sofosbuvir and L-proline.

FIG. 5 shows ^1H NMR spectrum of the co-crystal of sofosbuvir and L-proline.

DETAILED DESCRIPTION OF THE INVENTION

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As used herein the term “obtaining” may include filtration, filtration under vacuum, centrifugation, and decantation for isolation of the product. The product may be preceded for further reaction with or without isolation and with or without drying in case of the product was isolated.

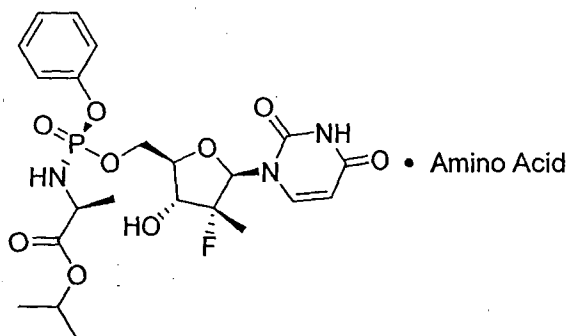
10

As used herein, unless indicated otherwise, the term “isolated” or “isolation” refer to the subject compound as physically separated from the reaction mixture in which it is formed.

The term “ambient temperature” and “room temperature” means a temperature range between 20°C to 40°C.

15

In one general aspect, there is provided a co-crystal of sofosbuvir and amino acid of Formula (B).



The said co-crystal can be characterized by its physicochemical parameters, for example those presented hereinafter.

20

Pharmaceutical co-crystals are crystalline molecular complexes that contain the drug substance along with an additional molecule present in the same crystal structure. The additional molecule or guest has been described in the literature as a co-crystal former. A co-crystal can thus be seen to be a multiple component crystal in which the drug substance and the co-crystal former are arranged in a three dimensional repetitive structure, wherein non-covalent and non-ion pair interactions exist between the drug substance and the co-crystal former, such as hydrogen

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bonding, pi-stacking, and van der Waals interactions. Co-crystalline forms show different physicochemical properties compared to the drug substance alone, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture a drug substance and the corresponding finalized dosage forms, as well as an effect on drug product stability, dissolution, and bioavailability.

In another aspect, there is provided a process for the preparation of co-crystal of sofosbuvir and amino acid, the process comprising:

- (a) dissolving sofosbuvir and amino acid in one or more solvents to obtain a solution;
- (b) optionally warming the solution to complete dissolution;
- (c) cooling the solution; and
- (d) removing the solvent or optionally adding antisolvent to solution to obtain the co-crystal of sofosbuvir and amino acid.

Sofosbuvir can be prepared by any of the method described in the literature mentioned herein above. The formation of co-crystals of sofosbuvir and amino acid can be carried out by using amino acids selected from the group comprising glycine, L-proline, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid, L-lysine, L-arginine, L-histidine, L-serine, L-threonine, L-cysteine, L-methionine, L-phenylalanine, L-tyrosine, L-tryptophan, L-alanine, L-valine, L-leusine, L-isoleusine, D-asparagine, D-aspartic acid, D-glutamine, D-glutamic acid, D-arginine, D-serine, D-threonine, D-methionine, D-phenylalanine, D-alanine, D-valine, D-leusine, D-isoleusine and D-proline.

During the process, sofosbuvir and amino acid can be dissolved in one or more solvents. Both the ingredients may be dissolved in the same solvent, either together or separately in a different solvent. In case of separate dissolution of both ingredients, the two solutions are mixed.

In general, the sofosbuvir is dissolved in one or more solvents whereupon the amino acid is added. The obtained reaction mixture is warmed until complete dissolution is observed to obtain the solution. The solution is allowed to cool to room temperature as the co-crystal precipitates or antisolvent may be added for the

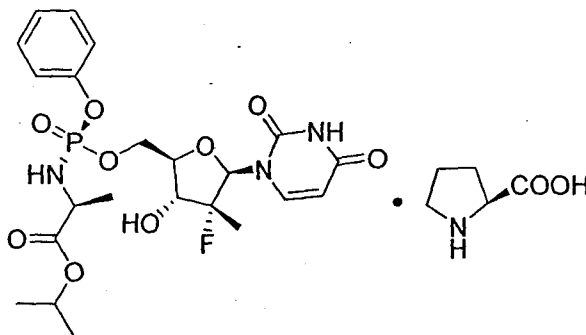
crystallization. The co-crystal thus formed is filtered and optionally washed and dried.

In general, the solvents is selected from one or more of water, C₁-C₆alcohols comprises of methanol, ethanol, isopropanol, n-butanol, and t-butyl alcohol or
5 mixture thereof. In particular, the solvents are methanol and ethanol.

After the completion of the reaction, the solvent is removed by evaporation or distillation or may be concentrated and then one or more anti-solvent is added to obtain the co-crystal. The anti-solvents is selected from one or more of water, hexane, n-heptane, n-pentane, cyclohexane, and methylcyclohexane; aromatic hydrocarbons
10 selected from toluene, xylene, and ethylbenzene; ethers selected from diethyl ether, diisopropyl ether, methyl-terbutyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, and 2-methoxyethanol; ketones selected from acetone, butanone, methyl butyl ketone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, and t-butyl acetate; chlorinated hydrocarbons selected from methylene dichloride,
15 ethylene dichloride, and chlorobenzene, acetonitrile, and mixtures thereof. In particular, the anti-solvents is selected from methyl-terbutyl ether, toluene, hexane, and cyclohexane.

In another aspect, there is provided a pharmaceutical composition comprising co-crystal of sofosbuvir and amino acid having one or more pharmaceutically
20 acceptable carriers, excipients and diluents for the treatment of hepatitis C.

In another aspect, there is provided a co-crystal of sofosbuvir and amino acid of Formula (C),

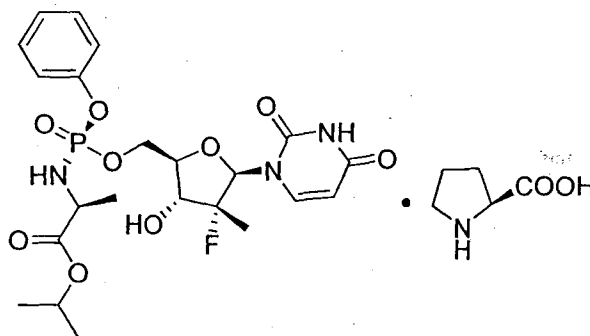


Co-crystalline forms of a drug substance are characterized by a number of methods including, for example, x-ray powder diffraction, microscopy, thermal analysis (e.g. differential scanning calorimetry, thermal gravimetric analysis and hot-stage microscopy), spectroscopy (e.g., infrared (IR) and near infrared (NIR), Raman, solid-state nuclear magnetic resonance (SSNMR)), and in particular by single crystal X-ray diffraction.

The co-crystal of sofosbuvir and L-proline is characterized by a powder X-ray diffraction pattern having peaks at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.24, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and 34.9° $2\theta \pm 0.2^\circ 2\theta$. The co-crystal of sofosbuvir and L-proline is further characterized by a powder X-ray diffraction pattern having peaks at about 7.2, 8.9, 9.7, 13.7, 14.6, 16.6, 18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and 38.0° $2\theta \pm 0.2^\circ 2\theta$.

The DSC thermogram shows an endothermic event at 177.2°C and then an exothermic event at 244.3°C.

In another aspect, there is provided a process for the preparation of co-crystal of sofosbuvir and L-proline of Formula (C),



the process comprising:

- (a) dissolving sofosbuvir and L-proline in one or more solvents to obtain the solution;
- (b) optionally warming the solution for complete dissolution;
- (c) cooling the solution; and
- (d) removing the solvent or optionally adding an antisolvent to the solution to obtain the co-crystal of sofosbuvir and L-proline.

In general, the sofosbuvir and L-proline are dissolved in one or more solvents, if desired the reaction mixture may be warmed to obtain complete dissolution. Both the ingredients may be dissolved in the same solvent, either together or separately in a different solvent. In case of separate dissolution of both ingredients, the two solutions
5 are mixed.

In general, the solvent comprises one or more of water, C₁-C₆-alcohols selected from methanol, ethanol, isopropanol, n-butanol, and t-butyl alcohol or mixture thereof. In particular, the solvents are methanol and ethanol.

The precipitation of the co-crystal occurs upon cooling a solution of
10 sofosbuvir and L-proline, for example a solution at higher temperatures, may be allowed to cool at room temperature or much lower temperatures, and if desired, the solvent may be evaporated by distillation under reduced pressure or by introducing a stream of inert gas.

In general, the sofosbuvir may be dissolved in a one or more solvent
15 whereupon L-proline is added. The obtained reaction mixture is warmed, for example to about 50°C-90°C until the complete dissolution is observed. The solution is allowed to cool to room temperature or lower temperatures as the co-crystal precipitates. The removal of the solvent is done either by filtration or by distillation under reduced pressure or the solution is concentrated and then anti-solvent may be
20 added for the crystallization. The co-crystal thus formed can be filtered and optionally washed and dried.

The X-ray powder diffraction pattern was measured under the following experimental conditions:

Instrument	:	X-Ray Diffractometer, D/Max-2200/PC,
25 Make	:	Rigaku, Japan or PANanalytical or Equivalent
X- Ray	:	Cu/40kv/40mA
Diverging Slit	:	1°
Scattering Slit	:	1°
Receiving Slit	:	0.15 mm
30 Monochromator RS	:	0.8 mm
Counter	:	Scintillation Counter

Scan Mode : Continuous
Scan Speed : 3.000° /min
Sampling Width : 0.020°
Scan Axes : Two Theta vs cps
5 Scan Range : 2° to 40.0°
Theta Offset : 0.000°

Differential scanning calorimetric analysis may be performed using a Perkin Elmer Diamond DSC control unit or an equivalent differential scanning calorimeter. 2-5 mg samples were placed in crimped aluminum pans and heated from 50° C to
10 300°C in a liquid nitrogen atmosphere at a heating rate of 10° C/minute.

The IR spectrum was measured by the KBr method. The ¹H NMR spectrum was measured by Bruker 300 MHz spectrometer wherein samples were dissolved in MeOD for analysis. The cocrystal of sofosbuvir and L-proline was found to be 1:1 by the analysis described herein before.

15 In an another aspect, there is provided co-crystal of sofosbuvir and L-proline characterized by X-ray powder diffraction pattern substantially as depicted in FIG.1, differential scanning thermogram (DSC) substantially as depicted in FIG.3, IR spectrum substantially as depicted in FIG.4 and ¹H NMR spectrum substantially as depicted in FIG.5.

20 In another aspect, there is provided a pharmaceutical composition comprising co-crystal of sofosbuvir and L-proline having one or more pharmaceutically acceptable carriers, excipients and diluents for the treatment of hepatitis C. These drug products are different because the active ingredient is present in a lower energy, crystalline form that has desirable intrinsic properties. The co-crystal has better flow
25 properties, is easier to prepare, shows better physical stability, and has a dissolution profile comparable to the current drug product. The pharmaceutically acceptable excipients comprises one or more of surfactants, solubilizers, disintegrants, microcrystalline cellulose, starch, sodium starch glycolate, crosslinked carboxy methyl cellulose sodium, crosslinked PVP, pigments, flavors, fillers, lubricants,
30 glidants, preservatives, thickening agents, buffering agents and pH modifiers.

The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to; limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

EXAMPLES:

Example-1: Co-crystal of sofosbuvir and L-proline

In a 100 mL round bottom flask, 1.0 gm sofosbuvir was dissolved in 3.0 mL ethanol at 25±3°C. To this solution, 0.21 gm L-Proline was added and the reaction mixture was warmed to 55-65°C to obtain a clear solution. The reaction mixture was stirred for 15 minutes and cooled to ambient temperature. The reaction mixture was further stirred for an hour at 25-30°C to get precipitate. The precipitated mass was stirred for another one hour at 25-30°C then filtered under vacuum. The precipitate then washed with 3.0 mL ethanol and then dried at 45°C for 12 hours in an oven to get 0.6 gm of co-crystal of sofosbuvir and L-proline.

Example-2: Co-crystal of sofosbuvir and L-proline

In a 100 mL round bottom flask, 1.0 gm sofosbuvir was dissolved in 5.0 mL methanol at room temperature. To this solution, 0.21 gm L-Proline was added and the reaction mixture was warmed to 60°C to obtain a clear solution. The reaction mixture was stirred for 10 minutes and cooled to ambient temperature. The reaction mixture was further stirred for an hour at room temperature to get precipitate. The precipitated mass was stirred for another one hour at room temperature then filtered under vacuum. The precipitate then washed with 10 mL methanol and then dried in an oven to get 0.5 gm of co-crystal of sofosbuvir and L-proline.

Example-3: Co-crystal of sofosbuvir and L-proline

In a 100 mL round bottom flask, 1.0 g sofosbuvir was dissolved in 5.0 mL ethanol at room temperature. To this solution, 0.21 gm L-Proline was added and the reaction mixture was warmed to 60°C to obtain a clear solution. The reaction mixture

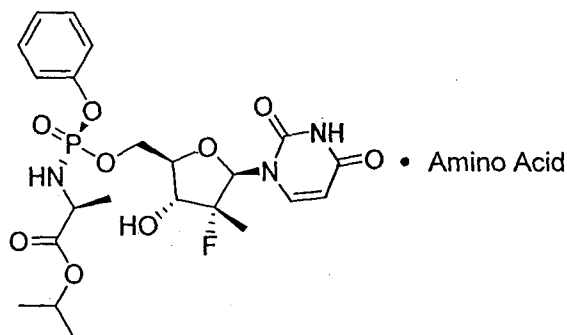
was concentrated and cooled to ambient temperature. 10 mL methyl tertiary butyl ether was added into the reaction mixture and stir 30 minutes at ambient temperature. The precipitated mass was then filtered under vacuum and wet solid was washed with 10 mL methyl tertiary butyl ether and then dried in an oven to get 1.2 gm of co-crystal of sofosbuvir and L-proline.

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

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We claim:

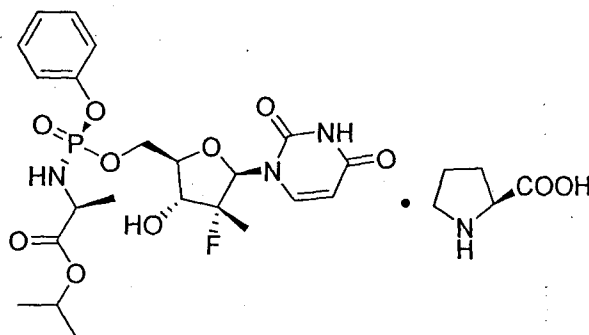
1. A co-crystal of sofosbuvir and amino acid of Formula (B)



2. The co-crystal according to claim 1, wherein the amino acid is selected from the group comprising glycine, L-proline, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid, L-lysine, L-arginine, L-histidine, L-serine, L-threonine, L-cysteine, L-methionine, L-phenylalanine, L-tyrosine, L-tryptophan, L-alanine, L-valine, L-leucine, L-isoleucine, D-asparagine, D-aspartic acid, D-glutamine, D-glutamic acid, D-arginine, D-serine, D-threonine, D-methionine, D-phenylalanine, D-alanine, D-valine, D-leucine, D-isoleucine and D-proline.
3. A process for the preparation of co-crystal of sofosbuvir and amino acid, the process comprising:
- dissolving sofosbuvir and amino acid in one or more solvents to obtain a solution;
 - optionally warming the solution to complete dissolution;
 - cooling the solution; and
 - removing the solvent or optionally adding antisolvent to solution to obtain the co-crystal of sofosbuvir and amino acid.
4. The process according to claim 3, wherein the solvent in step (a) is selected from water, methanol, ethanol, isopropanol, n-butanol, and t-butyl alcohol or mixture thereof.

5. The process according to claim 3, wherein the anti-solvent in step (d) is selected from water, hexane, n-heptane, n-pentane, cyclohexane, and methylcyclohexane; aromatic hydrocarbons selected from toluene, xylene, and ethylbenzene; ethers selected from diethyl ether, diisopropyl ether, methyl-
 5 terbutyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, and 2-methoxyethanol; ketones selected from acetone, butanone, methyl butyl ketone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, and t-butyl acetate; chlorinated hydrocarbons selected from methylene dichloride, ethylene dichloride, and chlorobenzene, acetonitrile,
 10 and mixtures thereof.

6. A co-crystal of sofosbuvir and amino acid of Formula (C),



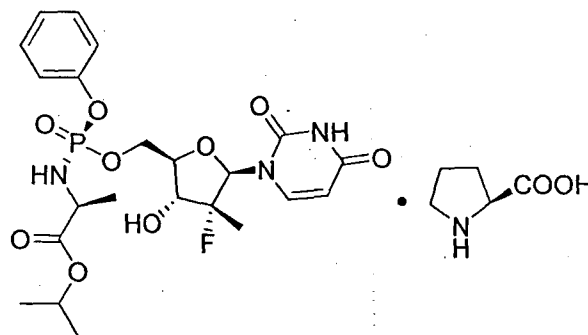
- 15 7. A co-crystal of sofosbuvir and L-proline, characterized by a powder x-ray diffraction pattern having peaks expressed as 2θ at about 5.7, 9.3, 10.6, 11.5, 12.4, 17.0, 17.2, 17.9, 18.1, 19.8, 20.8, 22.0, 23.8, 24.0, 26.6, 26.8, 33.5 and $34.9^\circ 2\theta \pm 0.2^\circ 2\theta$.
- 20 8. The co-crystal of sofosbuvir and L-proline according to claim 7 is further characterized by a powder x-ray diffraction pattern having peaks expressed as 2θ at about 7.2, 8.9, 9.7, 13.9, 14.6, 16.6, 18.6, 19.1, 19.6, 20.1, 21.4, 24.4, 25.1, 25.7, 27.7, 28.6, 28.9, 29.6, 30.0, 30.5, 31.5, 32.3, 33.1, 34.0, 36.5 and $38.0^\circ 2\theta \pm 0.2^\circ 2\theta$.

9. The co-crystal of sofosbuvir and L-proline according to claim 7 is further characterized by a differential scanning calorimetry (DSC) having an endothermic event at about 177.2°C and an exothermic event at 244.3°C.

5 10. The co-crystal of sofosbuvir and L-proline according to claim 7, having a powder x-ray diffraction pattern substantially as depicted in Fig 1, differential scanning thermogram (DSC) substantially as depicted in FIG.3, IR spectrum substantially as depicted in FIG.4 and ¹H NMR substantially spectrum as depicted in FIG.5.

10

11. A process for the preparation of co-crystal of sofosbuvir and L-proline of Formula (C),



the process comprising:

15

- (a) dissolving sofosbuvir and L-proline in one or more solvents to obtain the solution;
- (b) optionally warming the solution to complete dissolution;
- (c) cooling the solution; and
- (d) removing the solvent or optionally adding an antisolvent to the solution to obtain the co-crystal of sofosbuvir and L-proline.

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12. The process according to claim 11, wherein the solvent in step (a) is selected from water, methanol, ethanol, isopropanol, n-butanol, and t-butyl alcohol or mixture thereof.

13. The process according to claim 11, wherein the anti-solvent in step (d) is selected from water, hexane, n-heptane, n-pentane, cyclohexane, and methylcyclohexane; aromatic hydrocarbons selected from toluene, xylene, and ethylbenzene; ethers selected from diethyl ether, diisopropyl ether, methyl-
5 terbutyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, and 2-methoxyethanol; ketones selected from acetone, butanone, methyl butyl ketone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, and t-butyl acetate; chlorinated hydrocarbons selected from methylene dichloride, ethylene dichloride, and chlorobenzene, acetonitrile,
10 and mixtures thereof.
14. A pharmaceutical composition comprising a pharmaceutical composition comprising co-crystal of sofosbuvir and L-proline having one or more pharmaceutically acceptable carriers, excipients and diluents.
- 15 15. The pharmaceutical composition according to claim 14, wherein the pharmaceutically acceptable excipients comprises one or more of surfactants, solubilizers, disintegrants, microcrystalline cellulose, starch, sodium starch glycolate, crosslinked carboxy methyl cellulose sodium, crosslinked PVP,
20 pigments, flavors, fillers, lubricants, glidants, preservatives, thickening agents, buffering agents and pH modifiers.
- 25

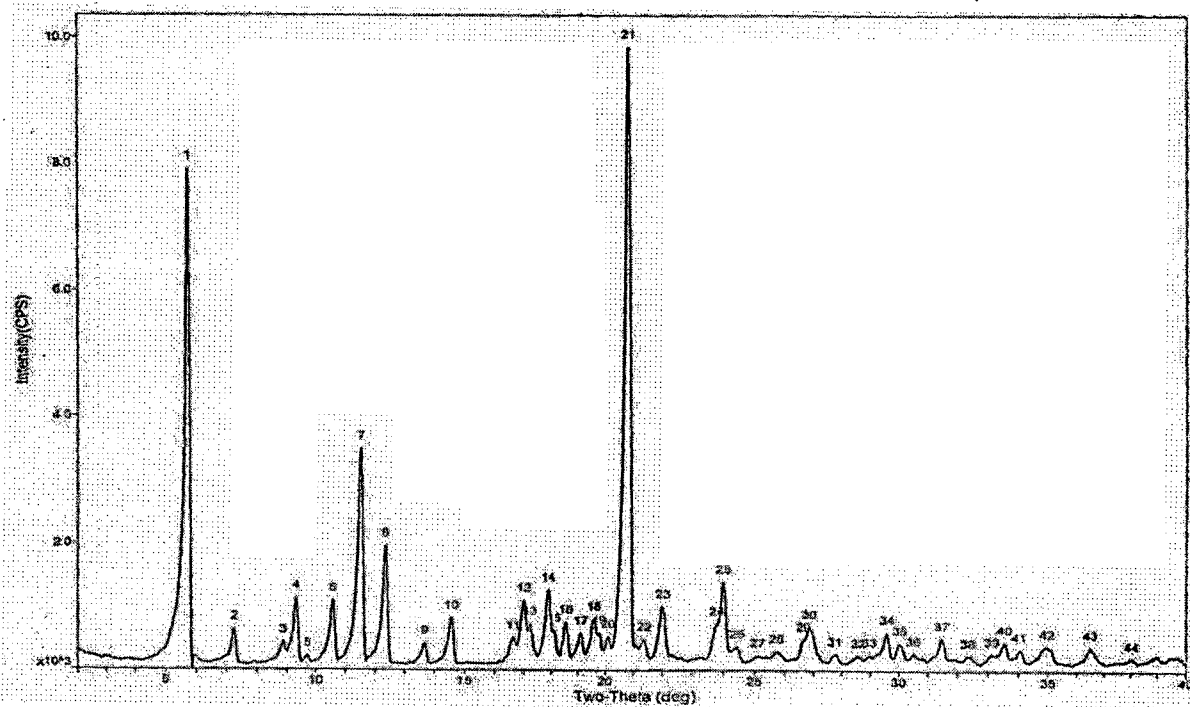


Figure-1

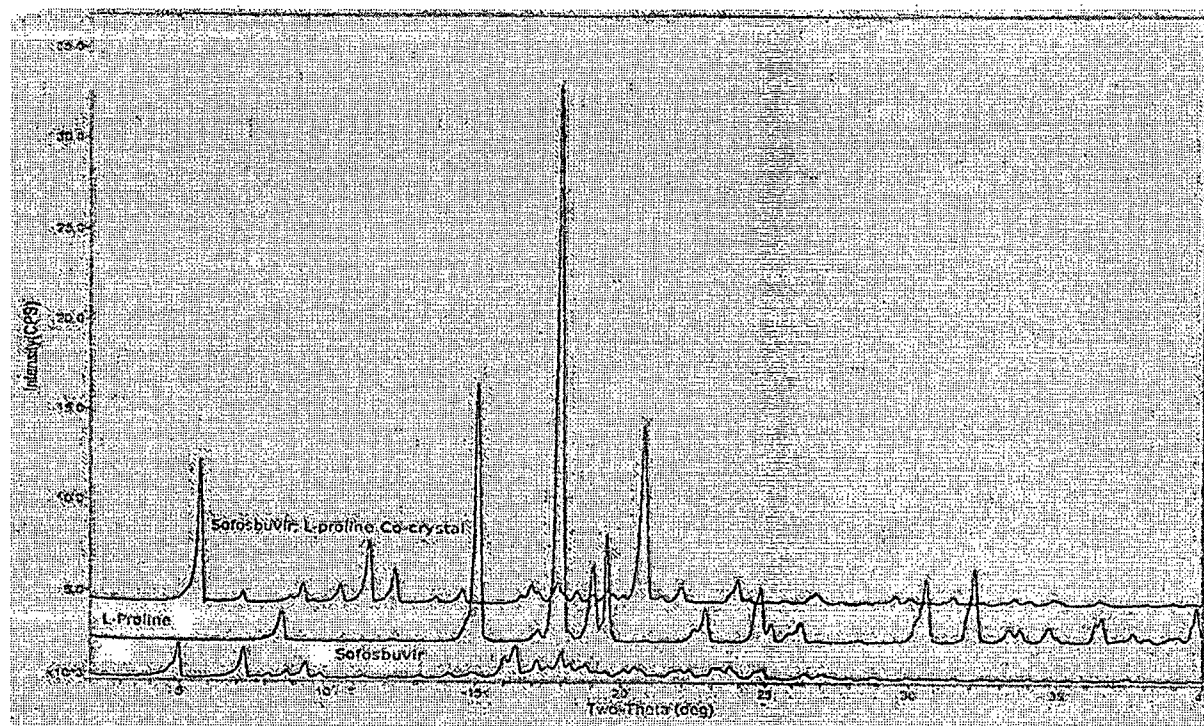


Figure-2

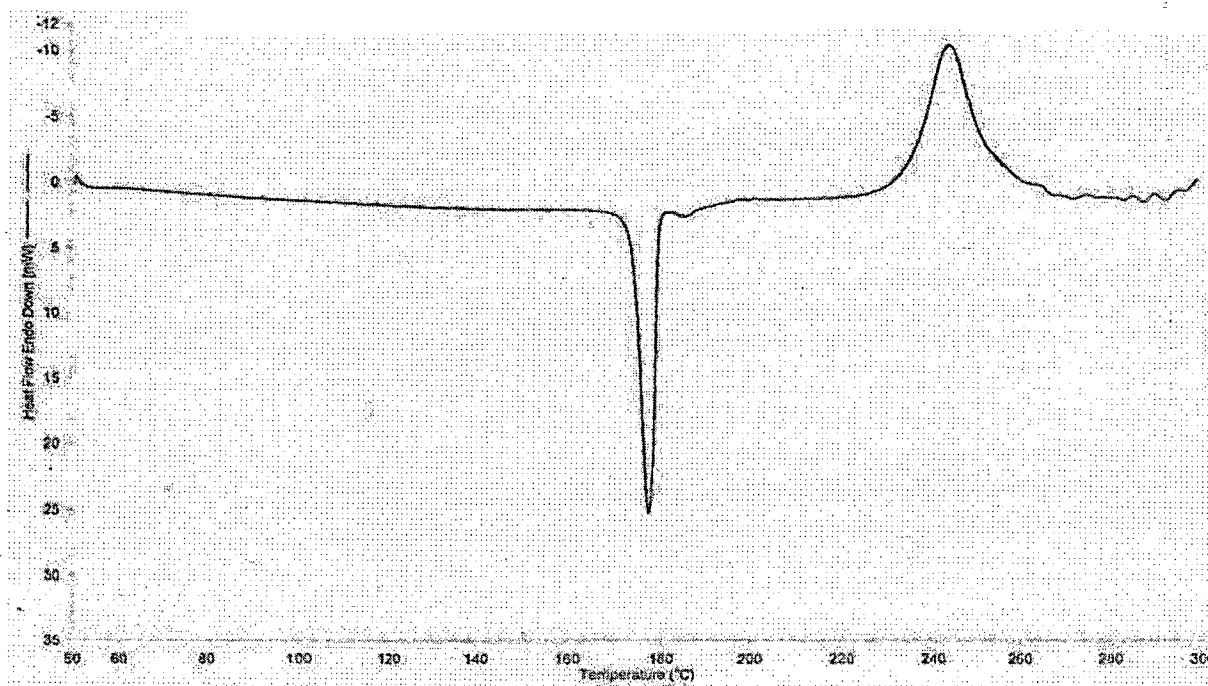


Figure-3

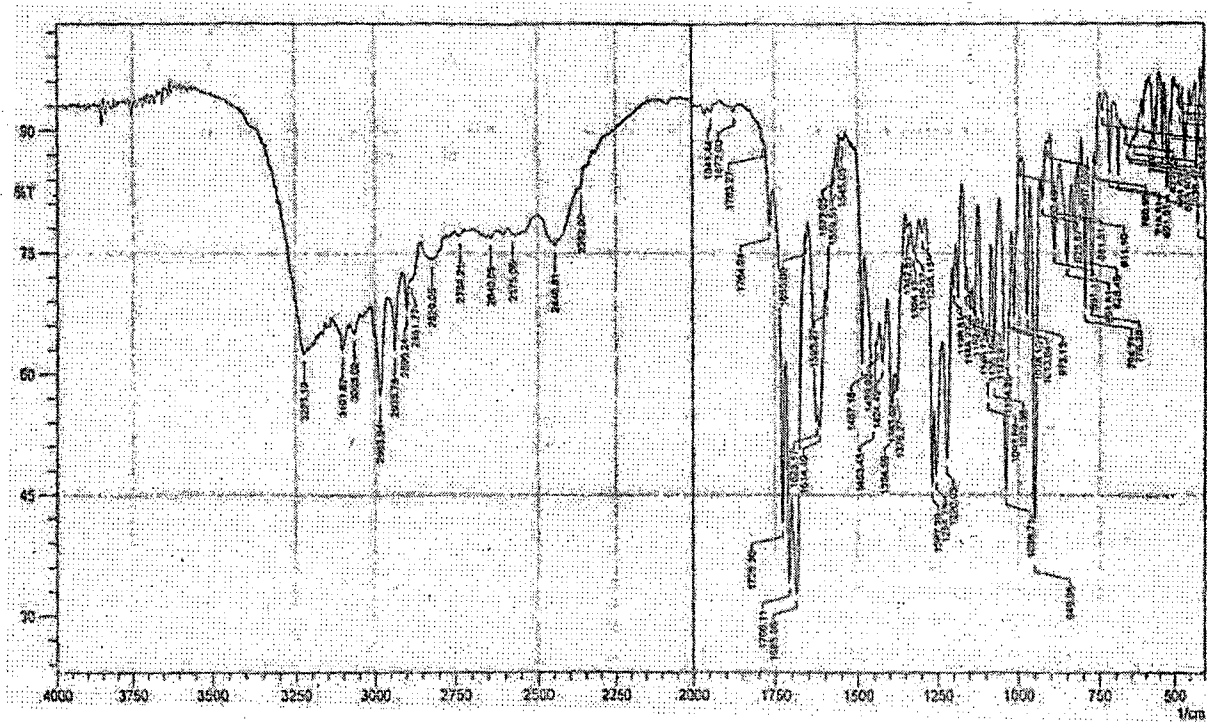


Figure-4

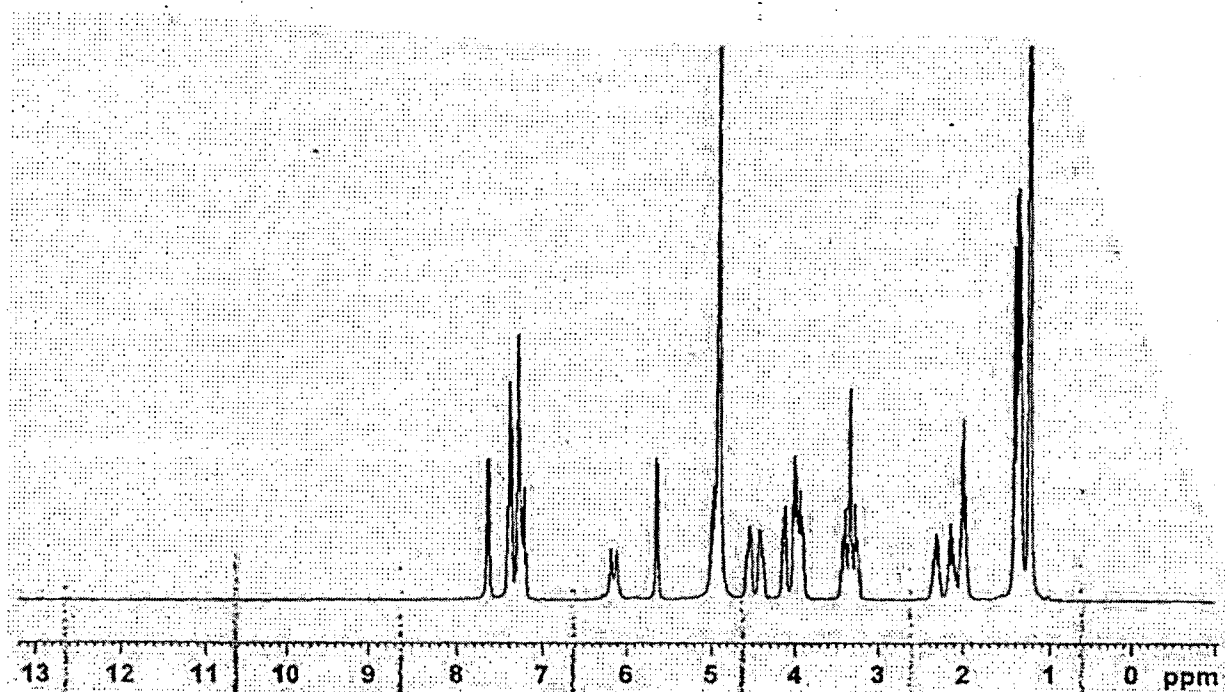


Figure-5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000361A. CLASSIFICATION OF SUBJECT MATTER
INV. C07H19/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/123645 A2 (PHARMASSET INC [US]; ROSS BRUCE S [US]; SOFIA MICHAEL JOSEPH [US]; PAM) 6 October 2011 (2011-10-06) page 7 - page 8; compound 4 page 13	1-15
Y	WO 2014/033617 A1 (NOVARTIS AG [CH]; ANANDAN SAMPATH-KUMAR [US]; AULAKH VIRENDER SINGH [U]) 6 March 2014 (2014-03-06) page 18 claim 10	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2016

Date of mailing of the international search report

28/01/2016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2015/000361

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011123645	A2	06-10-2011	AR 080819 A1 09-05-2012
			AR 080870 A1 16-05-2012
			AU 2011235044 A1 22-11-2012
			AU 2011235112 B2 09-07-2015
			CA 2794671 A1 06-10-2011
			CN 102858790 A 02-01-2013
			CN 102906102 A 30-01-2013
			CN 104017020 A 03-09-2014
			CO 6630166 A2 01-03-2013
			CO 6630167 A2 01-03-2013
			CR 20120532 A 05-02-2013
			CR 20120534 A 05-02-2013
			DK 2552930 T3 07-12-2015
			EA 201290988 A1 30-04-2013
			EA 201290993 A1 30-04-2013
			EC SP12012282 A 31-05-2013
			EP 2552930 A2 06-02-2013
			EP 2552931 A2 06-02-2013
			ES 2516466 T3 30-10-2014
			ES 2551944 T3 24-11-2015
			HK 1181775 A1 19-06-2015
			HK 1199645 A1 10-07-2015
			HR P20151075 T1 04-12-2015
			JP 2013523767 A 17-06-2013
			JP 2013527145 A 27-06-2013
			JP 2015205903 A 19-11-2015
			KR 20120138242 A 24-12-2012
			KR 20130064064 A 17-06-2013
			NZ 603232 A 27-02-2015
			PE 01512013 A1 21-02-2013
			PE 01832013 A1 21-02-2013
			PT 2552930 E 17-11-2015
			SG 184323 A1 29-11-2012
			SG 184324 A1 29-11-2012
			SM T201500285 B 08-01-2016
			TW 201136593 A 01-11-2011
			TW 201139457 A 16-11-2011
			US 2011245484 A1 06-10-2011
			UY 33311 A 31-10-2011
			WO 2011123645 A2 06-10-2011
			WO 2011123668 A2 06-10-2011
WO 2014033617	A1	06-03-2014	EP 2890704 A1 08-07-2015
			US 2015232501 A1 20-08-2015
			UY 34998 A 31-03-2014
			WO 2014033617 A1 06-03-2014