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(54) Title: POLYMORPHIC FORMS OF SOFOSBUVIR

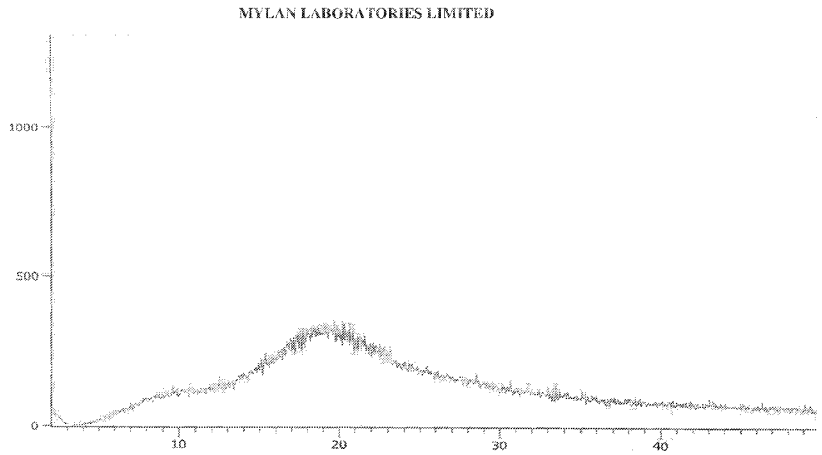


Figure 1-Powder X-ray diffraction pattern of amorphous sofosbuvir

(57) Abstract: The present disclosure provides crystalline sofosbuvir form-M1 and amorphous solid dispersion of sofosbuvir. The present disclosure also provides a process for the preparation of the amorphous form of sofosbuvir, the crystalline form of sofosbuvir, and amorphous solid dispersion of sofosbuvir and one or more pharmaceutically acceptable carriers.

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POLYMORPHIC FORMS OF SOFOSBUVIR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the earlier filing date of Indian Provisional Patent Application No. 4436/CHE/2014 filed on Sep 10, 2014.

BACKGROUND OF THE INVENTION

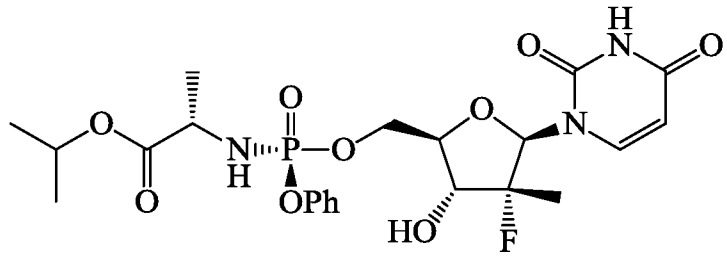
FIELD OF THE INVENTION

The present disclosure relates to crystalline forms of sofosbuvir, an amorphous form of sofosbuvir, amorphous solid dispersion of sofosbuvir with pharmaceutically acceptable carriers, as well as processes for preparation thereof.

BACKGROUND OF THE INVENTION

Nucleoside phosphoramidates are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and for treatment of hepatitis C infection in mammals.

Sofosbuvir is chemically named as (S)-isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)-(phenoxy)phosphorylamino)propanoate and is represented by the following chemical structure:



Sofosbuvir is marketed by Gilead Sciences under the brand name of SOVALDI®.

US Patent No. 7,964,580, which is hereby incorporated by reference, discloses sofosbuvir and a process for the preparation thereof. PCT Publication No.

WO2010135569A1, which is hereby incorporated by reference, discloses amorphous and crystalline forms of sofosbuvir.

Processing of an active pharmaceutical ingredient (API) and pharmaceutical excipients into a final dosage form may be simplified and facilitated by first preparing a solid dispersion of the API with excipients, which may then be supplied and utilized in final processing. The present disclosure provides a solid dispersion of sofosbuvir and pharmaceutical excipients as well as processes for their preparation. The present disclosure also provides crystalline and amorphous forms of sofosbuvir for inclusion in the solid dispersion as well as processes for their preparation.

SUMMARY OF THE INVENTION

One aspect of the present invention provides amorphous solid dispersion of sofosbuvir together with pharmaceutically acceptable carriers.

Yet another aspect of the present invention provides a process for the preparation of amorphous solid dispersion of sofosbuvir comprising:

a) dissolving sofosbuvir and pharmaceutically acceptable carriers in a mixture of water and organic solvent; and

b) removing the mixture of water and organic solvent to obtain amorphous solid dispersion of sofosbuvir.

Another aspect of the present invention provides a process for the preparation of amorphous sofosbuvir comprising:

a) dissolving sofosbuvir in a mixture of water and organic solvent;

b) removing the mixture of water and organic solvent;

c) adding a hydrocarbon solvent;

d) isolating amorphous sofosbuvir.

In another embodiment of the present invention, amorphous sofosbuvir comprising:

a) dissolving sofosbuvir in a mixture of water and organic solvent;

b) removing the mixture of water and organic solvent to obtain amorphous sofosbuvir.

Another aspect of the present invention provides crystalline sofosbuvir form-M1.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be characterized by a powder X-ray diffraction (PXRD) pattern having characteristic peaks at about 5.44, 13.77, 14.45 and 19.06 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be further characterized by a PXRD pattern having characteristic peaks at about 2.69, 5.44, 8.22, 9.70, 11.00, 12.44, 13.77, 14.45, 16.58, 17.02, 17.97, 19.06, 19.51, 20.27, 21.51, 21.83, 22.19, 22.73, 23.39, 24.59, 24.99, 25.50, 26.22, 26.41, 26.82, 28.47, 28.94, 29.44, 30.68, 32.96, 34.94, 36.33 and 38.85 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be further characterized by the PXRD pattern in FIGURE 2.

Another aspect of the present disclosure provides a process for the preparation of crystalline sofosbuvir form-M1.

In one embodiment, crystalline sofosbuvir form-M1 may be prepared by the following steps:

a) dissolving sofosbuvir in an organic solvent;

b) adding an anti-solvent; and

c) isolating crystalline sofosbuvir form-M1.

Another aspect of the present invention provides crystalline sofosbuvir form-M2.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be characterized by a PXRD pattern having characteristic peaks at about 8.09, 12.42, 19.39, 19.98 and 20.84 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be further characterized by a PXRD pattern having characteristic peaks at about 8.09, 10.38, 12.09, 12.42, 13.47, 16.21, 16.80, 17.22, 18.00, 18.67, 19.39, 19.98, 20.17, 20.84, 21.41, 21.77, 22.02, 23.03, 23.32, 24.38, 24.94, 25.31, 25.55, 26.88, 27.15, 28.16, 28.58, 29.04, 29.59, 31.28, 31.97, 32.33, 32.74, 33.12, 33.45, 34.71, 35.20, 35.90, 36.47, 36.77, 37.25,

37.87, 38.22, 39.14, 39.39, 40.59, 40.99, 41.27, 42.02, 42.44, 43.59, 44.46, 45.08, 46.10, 46.56, 47.03, 47.33, 47.68 and 48.90 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be further characterized by the PXRD pattern in FIGURE 3.

Another aspect of the present disclosure provides a process for the preparation of crystalline sofosbuvir form-M2.

In one embodiment, crystalline sofosbuvir form-M2 may be prepared by the following steps:

a) dissolving sofosbuvir in an organic solvent;

b) adding an anti-solvent;

c) optionally seeding with crystalline sofosbuvir form-M2; and

d) isolating crystalline sofosbuvir form-M2.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

FIGURE 1 is a powder X-ray diffraction pattern of amorphous sofosbuvir;

FIGURE 2 is a powder X-ray diffraction pattern of crystalline sofosbuvir form-M1; and

FIGURE 3 is a powder X-ray diffraction pattern of crystalline sofosbuvir form-M2.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the description of the present invention has been simplified to illustrate elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that may be well known.

The present disclosure provides amorphous and crystalline forms sofosbuvir, as well as processes for the preparation thereof. The present disclosure also provides

amorphous solid dispersion of sofosbuvir in one or more pharmaceutically acceptable carriers as well as as a process for the preparation thereof.

One aspect of the present invention provides amorphous solid dispersion of sofosbuvir together with pharmaceutically acceptable carriers.

Another aspect of the present invention encompasses a process for the preparation of amorphous solid dispersion of sofosbuvir in one or more pharmaceutically acceptable carriers which may include the following steps:

a) dissolving sofosbuvir and pharmaceutically acceptable carriers in a mixture of water and organic solvent; and

b) removing the mixture of water and organic solvent to obtain amorphous solid dispersion of sofosbuvir.

According to the present invention, sofosbuvir and one or more pharmaceutical acceptable carriers are dissolved in a mixture of water and organic solvent. Within the context of the present invention, this may be carried out at a temperature of about 25 °C to about 30 °C. The input sofosbuvir may be crystalline or amorphous and may be prepared by any prior-art process. A wide range of pharmaceutically acceptable carriers may be employed. In some embodiments, the pharmaceutically acceptable carriers are soluble in the water and organic solvent mixture. Examples of suitable pharmaceutically acceptable carriers include PLASDONE™ S-630 or polyvinylpyrrolidine K-30. The organic solvent employed may be, for example, a polar solvent. In some embodiments of the present invention, the organic solvent and water are miscible. Suitable polar solvents include, for example, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, dimethylformamide, and mixtures thereof.

Next, the mixture of water and organic solvent may be removed, resulting in amorphous solid dispersion of sofosbuvir in one or more pharmaceutically acceptable carriers. Within the context of the present invention, the mixture of water and organic solvent may be removed according to well-known techniques in the art, for example, distillation, spray drying, freeze drying, or by agitated thin film drier.

Another aspect of the present invention provides a process for the preparation of amorphous sofosbuvir, which may include the following steps:

a) dissolving sofosbuvir in a mixture of water and organic solvent;

b) removing the mixture of water and organic solvent;

c) adding a hydrocarbon solvent; and

d) isolating amorphous sofosbuvir.

According to the present invention, sofosbuvir may be dissolved in a mixture of water and organic solvent. Within the context of the invention, this step may occur at about 55 °C to about 75 °C. The input sofosbuvir may be crystalline or amorphous and may be prepared by any prior-art process. The organic solvent employed may be, for example, a polar solvent. In some embodiments of the present invention, the organic solvent and water are miscible. Examples of suitable polar solvents include methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, tetrahydrofuran, and mixtures thereof.

Next, the mixture of water and organic solvent may be removed. This may be performed by methods well known in the art, for example, by distilling the solution under vacuum, distillation, evaporation, freeze drying, spray drying, or by agitated thin film drier (ATFD).

According to the present invention, a hydrocarbon solvent may then be added. The hydrocarbon solvent may be, for example, hexane, cyclohexane, methylcyclohexane, heptane, pentane, or a mixture thereof. Amorphous sofosbuvir may then be isolated. Isolation of the amorphous sofosbuvir may be carried out according to routine methods well known in the art, for example, by filtering and drying the resulting solid.

In another embodiment of the present invention, amorphous sofosbuvir may be prepared by the process which may include the following steps:

a) dissolving sofosbuvir in a mixture of water and organic solvent; and

b) removing the mixture of water and organic solvent to obtain amorphous sofosbuvir.

According to the present disclosure, sofosbuvir may be dissolved in a mixture of water and organic solvent. Within the context of the present invention, this step may be carried out at about 55 °C to about 70 °C. The input sofosbuvir may be crystalline or amorphous and may be prepared by any prior-art process. The organic solvent employed may be, for example, a polar solvent. In some embodiments of the present invention, the organic solvent and water are miscible. Examples of suitable polar solvents include methanol, ethanol, propanol, isopropanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof. In some embodiments of the present invention, the solution may then be filtered.

According to the present invention, the mixture of water and organic solvent may then be removed to produce amorphous sofosbuvir. This may be carried out according to methods well known in the art, for example, distillation, evaporation, freeze drying, spray drying, or by agitated thin film drier.

The present invention provides several polymorphic forms of sofosbuvir. These forms may be characterized by powder X-ray diffraction ("PXRD"). Thus, the PXRD patterns of each of the polymorphic forms of sofosbuvir provided by the present disclosure were measured.

The PXRD patterns were measured on a BRUKER D-8 DISCOVER powder diffractometer equipped with goniometer of θ/2θ configuration and LYNX EYE detector. The Cu-anode X-ray tube was operated at 40 kV and 30 mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 0.4 seconds step time.

Another aspect of the present disclosure provides crystalline sofosbuvir form-M1.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be characterized by a PXRD pattern having characteristic peaks at about 5.44, 13.77, 14.45 and 19.06 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be further characterized by a PXRD pattern having characteristic peaks at about 2.69, 5.44, 8.22, 9.70, 11.00, 12.44, 13.77, 14.45, 16.58, 17.02, 17.97, 19.06, 19.51, 20.27, 21.51,

21.83, 22.19, 22.73, 23.39, 24.59, 24.99, 25.50, 26.22, 26.41, 26.82, 28.47, 28.94, 29.44, 30.68, 32.96, 34.94, 36.33 and 38.85 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M1 may be further characterized by the PXRD pattern shown in FIGURE 2.

Another aspect of the present invention provides a process for the preparation of crystalline sofosbuvir form-M1, which may include the following steps:

a) dissolving sofosbuvir in an organic solvent;

b) adding an anti-solvent; and

c) isolating crystalline sofosbuvir form-M1.

According to the present invention, sofosbuvir may be dissolved in an organic solvent. Within the context of the present invention, this may be carried out at about 25 °C to about 30 °C. The organic solvent may be, for example, benzyl amine. The input sofosbuvir which is dissolved in the organic solvent may be crystalline or amorphous and may be prepared by any prior-art process.

Next, an anti-solvent may be added to result in formation of a solid. Within the context of the present invention, the anti-solvent employed may be, for example, an ether solvent. Examples of suitable ether solvents include diethyl ether, diisopropylether, methyl tert-butyl ether, and mixtures thereof.

Next, the crystalline sofosbuvir form-M1 may be isolated. Isolation of crystalline sofosbuvir form-M1 may be carried out according to methods well known in the art, for example, by filtering and drying under vacuum. In some embodiments of the invention, it has been found that drying at a temperature of about 35 °C to about 45 °C is particularly useful when isolating crystalline sofosbuvir form-M1.

Another aspect of the present invention provides crystalline sofosbuvir form-M2.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be characterized by a PXRD pattern having characteristic peaks at about 8.09, 12.42, 19.39, 19.98 and 20.84 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be further characterized by a PXRD pattern having characteristic peaks at about 8.09, 10.38, 12.09, 12.42, 13.47, 16.21, 16.80, 17.22, 18.00, 18.67, 19.39, 19.98, 20.17, 20.84, 21.41, 21.77, 22.02, 23.03, 23.32, 24.38, 24.94, 25.31, 25.55, 26.88, 27.15, 28.16, 28.58, 29.04, 29.59, 31.28, 31.97, 32.33, 32.74, 33.12, 33.45, 34.71, 35.20, 35.90, 36.47, 36.77, 37.25, 37.87, 38.22, 39.14, 39.39, 40.59, 40.99, 41.27, 42.02, 42.44, 43.59, 44.46, 45.08, 46.10, 46.56, 47.03, 47.33, 47.68 and 48.90 (±) 0.2° 2-theta.

Within the context of the present invention, crystalline sofosbuvir form-M2 may be further characterized by the PXRD pattern in FIGURE 3.

Another aspect of the present invention provides a method for the preparation of crystalline sofosbuvir form-M2 which may be carried out by the following steps:

a) dissolving sofosbuvir in an organic solvent;

b) adding an anti-solvent;

c) optionally seeding with crystalline sofosbuvir form-M2; and

d) isolating crystalline sofosbuvir form-M2.

According to this embodiment of the present invention, sofosbuvir may be dissolved in an organic solvent. In some embodiments, this step may be carried out at about 25 °C to about 30 °C. Within the context of the present disclosure, the solvent employed above may include, as examples, n-butyl acetate, isobutyl acetate, ethyl acetate, isopropyl alcohol, anisole, or a mixture thereof. The input sofosbuvir which is dissolved in the organic solvent may be crystalline or amorphous and may be prepared by any prior-art process.

Next, an anti-solvent may be added resulting in the formation of a solid. Within the context of the present disclosure, the anti-solvent employed above may include, as examples, n-heptane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, or a mixture thereof.

Next, the solution may be optionally seeded with crystalline sofosbuvir form-M2.

According to the present invention, crystalline sofosbuvir form-M2 may then be isolated. Isolation may be carried out according to methods well known in the art, for example, by filtering and drying under vacuum.

The polymorphs of sofosbuvir and solid dispersions prepared by the methods disclosed herein may be used to formulate an oral dosage form, such as a tablet. When administered to patients, the sofosbuvir of the present invention may be useful treatment of individuals infected with hepatitis C, as sofosbuvir has been demonstrated to be an effective HCV NS5B (hepatitis C virus nonstructural protein 5B) polymerase inhibitor. Sofosbuvir may be used singly or in combination with other drugs, such as ledipasvir, ribavirin, or pegylated interferon.

The sofosbuvir and solid dispersions of sofosbuvir of the present invention may be formulated into a tablet which may contain inactive ingredients such as colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The tablet may, in some embodiments, be coated with a film that includes polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide. One of skill in the art will be familiar with a variety of excipients and formulations that may be used to prepare desirable dosage forms with desired release characteristics and pharmacokinetic properties without undue experimentation.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the disclosure in any manner. Reasonable variations of the described procedures are intended to be within the scope of the present application. While particular aspects of the present application have been illustrated and described, it would be apparent to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the disclosure. It is therefore intended to encompass all such changes and modifications that are within the scope of this disclosure.

EXAMPLES

Example 1: Preparation of solid dispersion of sofosbuvir with PLASDONE™ S-630

Sofosbuvir (0.5 g) and PLASDONE™ S-630 (0.25 g) were dissolved in acetonitrile (22.5 mL) and water (2.5 mL) at 25-30 °C. The resulting clear solution was then distilled out completely under vacuum at 50-60 °C. The obtained solid was identified as amorphous solid dispersion of sofosbuvir (0.6 g).

Example 2: Preparation of solid dispersion of sofosbuvir with PLASDONE™ S-630

Sofosbuvir (0.5 g) and PLASDONE™ S-630 (0.5 g) were dissolved in acetonitrile (22.5 mL) and water (2.5 mL) at 25-30 °C. The resulting clear solution was then distilled out completely under vacuum at 50-60 °C. The obtained solid was identified as amorphous solid dispersion of sofosbuvir (0.8 g).

Example 3: Preparation of amorphous sofosbuvir

Sofosbuvir (5 g) was suspended in distilled water (400 mL) and methanol (16 mL) at 25-30 °C. The suspension was heated at 60-65 °C for 0.5 hours to get a clear solution. The solution was filtered through Hyflo to remove any undissolved particulate and the filtrate was subjected to freeze drying. The resulting solid was identified as amorphous sofosbuvir (4.8 g).

Example 4: Preparation of amorphous sofosbuvir

Sofosbuvir (1 g) was dissolved in acetonitrile (45 mL) and water (5 mL) at 25-30 °C. The clear solution was distilled out completely under vacuum at 60-70 °C to obtain foamy solid. To the resulting solid, n-heptane (10 mL) was added and stirred for 15 hours at 25-30 °C. The resulting solid was filtered, washed with n-heptane and dried under vacuum. The obtained product was identified as amorphous sofosbuvir (0.1 g).

Example 5: Preparation of amorphous sofosbuvir

Sofosbuvir (10 g) was dissolved in acetonitrile (450 mL) and water (50 mL) at 25-30 °C. The clear solution was subjected to downward distillation under vacuum at 60-70 °C. To the resulting solid, n-heptane (100 mL) was added and stirred for 2 hours at 25-30 °C. The resulting solid was filtered, washed with n-heptane and dried under vacuum at 40 °C for 5 hours. The obtained product was identified as amorphous sofosbuvir (5.8 g).

Example 6: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in acetonitrile (5 mL) and water (5 mL) at 24-30 °C. The clear solution was concentrated under reduced pressure at 45-50 °C to yield a white solid. Thereafter acetonitrile (5 mL) was added and distilled to yield a white solid, which was identified as amorphous sofosbuvir (0.3 g).

Example 7: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in methanol (0.6 mL), acetonitrile (5 mL), and water (5 mL) at 24-30 °C. The clear solution was concentrated under reduced pressure at 45-50 °C to yield a white solid, thereafter acetonitrile (5 mL) was added and distilled to yield a white solid, which was identified as amorphous sofosbuvir (0.3 g).

Example 8: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in acetonitrile (5 mL), and water (5 mL) at 24-30 °C. The clear solution was subjected to freeze drying. The resulting solid was identified as amorphous sofosbuvir (0.3 g).

Example 9: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in methanol (0.6 mL), acetonitrile (5 mL), and water (5 mL) at 24-30 °C. The clear solution was subjected to freeze drying. The resulting solid was identified as amorphous sofosbuvir (0.3 g).

Example 10: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in ethyl acetate (5 mL) and water (5 mL) at 24-30 °C. The clear solution was concentrated under reduced pressure at 45-50 °C to yield a white solid, which was identified as amorphous sofosbuvir (0.3 g).

Example 11: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in ethyl acetate (10 mL), methylene chloride (15 mL), and water (5 mL) at 24-30 °C. The clear solution was concentrated under reduced

pressure at 45-50 °C to yield a white solid, which was identified as amorphous sofosbuvir (0.3 g).

Example 12: Preparation of amorphous sofosbuvir

Sofosbuvir (0.3 g) was dissolved in ethyl acetate (5 mL) at 24-30 °C. The clear solution was concentrated under reduced pressure at 45-50 °C to yield a white solid, which was identified as amorphous sofosbuvir (0.3 g).

Example 13: Preparation of crystalline sofosbuvir form-M1.

Sofosbuvir (1 g) was suspended in benzyl amine (2 mL) at 25-30 °C and stirred for 10 minutes to get a clear solution. To the clear solution, diisopropyl ether (30 mL) was added at 25-30 °C and stirred for 3-5 hours. The resulting solid was filtered, washed with diisopropyl ether (10 mL), and dried under vacuum at 40 °C for 15 hours to yield crystalline sofosbuvir form-M1 (0.8 g).

Example 14: Preparation of crystalline sofosbuvir form-M1.

Sofosbuvir (5 g) was suspended in benzyl amine (10 mL) at 25-30 °C. The suspension was stirred for 10 minutes to get a clear solution. To the clear solution, diisopropyl ether (150 mL) was added at 25-30 °C and then stirred for 3-5 hours. The resulting solid was filtered, washed with diisopropyl ether (10 mL), and dried under vacuum at 40 °C for 15 hours to yield crystalline sofosbuvir form-M1 (5.3 g).

Example 15: Preparation of crystalline sofosbuvir form-M2.

Sofosbuvir (1.2 g) was suspended in isobutyl acetate (7.2 mL) at 25-30 °C and heated to 70 °C to get a clear solution. To the clear solution, n-heptane (12 mL) was added at 70 °C and the temperature was slowly raised to 115 °C. The reaction mass was stirred at 115°C for 5 hours. The reaction mass was then cooled to 80 °C, filtered, washed with n-heptane (4 mL), and dried at 50 °C for 15 hours. The solid obtained was identified as crystalline sofosbuvir form-M2.

Example 16: Preparation of crystalline sofosbuvir form-M2.

Sofosbuvir (0.1 g) was suspended in anisole (2 mL) and IPA (6 mL) mixture at 25-30 °C and heated to 40 °C. To the clear solution, n-Heptane (6 mL) was added at 40 °C and the temperature was slowly raised to 80 °C. The reaction mass was stirred at 80 °C for 16 hours. The reaction mass was then cooled to room temperature (RT) and diisopropyl ether (10 mL) was added. The mixture was allowed to stand at RT without agitation for 24 hours. The product crystallized was filtered, dried at 50 °C for 1 hour, and identified as crystalline sofosbuvir form-M2.

Example 17: Preparation of crystalline sofosbuvir form-M2.

Sofosbuvir (0.2 g) was suspended in n-butyl acetate (2 mL) at 25-30 °C and stirred to obtain a clear solution. In another flask, heptane (5 mL) was taken, seeds of form-M2 (1 mg) were added, and the mixture was maintained under stirring. To the reaction mass, the above solution of sofosbuvir in n-butyl acetate was added slowly at 25-30 °C over 10 minutes. The reaction mass was then maintained for 15 hours at 25-30 °C. The solid obtained was filtered, washed with heptane, and suck-dried at 25-30 °C. The product obtained was identified as crystalline sofosbuvir form-M2.

Example 18: Preparation of crystalline sofosbuvir form-M2.

Sofosbuvir (0.2 g) was suspended in ethyl acetate (2 mL) at 25-30 °C and stirred to obtain a clear solution. In another flask, heptane (6 mL) was taken, seeds of form-M2 (1 mg) were added, and the mixture was maintained under stirring. To the reaction mass above solution of sofosbuvir in ethyl acetate was added slowly at 25-30 °C for 10 minutes. The reaction mass was then maintained for 15 hours at 25-30 °C. The solid obtained was filtered, washed with heptane, and suck-dried at 25-30 °C. The product obtained was identified as crystalline sofosbuvir form-M2.

Example 19: Preparation of crystalline sofosbuvir form-M2.

Sofosbuvir (0.5 g) was suspended in isobutyl acetate (2.5 mL) at 25-30 °C and heated to 40-45 °C to obtain a clear solution. In another flask, heptane (15 mL) was taken, seeds of form-M2 (5 mg) were added, the mixture was heated to 60-70 °C, and the mixture

was maintained under stirring. To the reaction mass, the above solution of sofosbuvir in isobutyl acetate was added slowly at 60-70 °C over 10-15 minutes. The reaction mass then maintained for 20 hours at 60-70 °C. The solid obtained was filtered in hot condition, washed with heptane, and suck-dried at 25-30 °C. The product obtained was identified as crystalline sofosbuvir form-M2.

We claim:

1. Amorphous solid dispersion of sofosbuvir with a pharmaceutically acceptable carrier.
2. The solid dispersion of claim 1, wherein the pharmaceutically acceptable carrier is selected from the group consisting of PLASDONE™ S-630 or polyvinylpyrrolidine K-30.
3. A process for the preparation of amorphous solid dispersion of sofosbuvir and a pharmaceutically acceptable carrier, comprising the steps of:
   a) dissolving sofosbuvir and a pharmaceutically acceptable carrier in a mixture of water and an organic solvent; and
   b) removing the mixture of water and organic solvent to obtain a solid dispersion of amorphous sofosbuvir and a pharmaceutically acceptable carrier.
4. The process according to claim 3, wherein the organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, dimethylformamide, and mixtures thereof.
5. A process for the preparation of amorphous sofosbuvir comprising the steps of:
   a) dissolving sofosbuvir in a mixture of water and organic solvent; and
   b) removing the mixture of water and organic solvent to obtain amorphous sofosbuvir.
6. The process according to claims 5, wherein the organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, acetonitrile, dichloromethane, ethyl acetate, and mixtures thereof.
7. A process for the preparation of amorphous sofosbuvir, comprising the steps of:
   a) dissolving sofosbuvir in a mixture of water and organic solvent;
   b) removing the mixture of water and organic solvent;

c) adding a hydrocarbon solvent; and

d) isolating amorphous sofosbuvir.

8. The process according to claim 7, wherein the organic solvent is selected from methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, tetrahydrofuran, and mixtures thereof and the hydrocarbon solvent is selected from the group consisting of hexane, cyclohexane, methylcyclohexane, heptane, pentane, and mixtures thereof.

9. Crystalline sofosbuvir form-M1.

10. The crystalline sofosbuvir form-M1 of claim 9, which has a powder X-ray diffraction pattern with significant peaks about 2Θ values of about 5.44, 13.77, 14.45 and 19.06 (±) 0.2° 2-theta.

11. The crystalline sofosbuvir form-M1 of claim 9, which has a powder X-ray diffraction pattern as shown in FIGURE 2.

12. A process for the preparation of crystalline sofosbuvir form-M1 comprising the steps of:

a) dissolving sofosbuvir in an organic solvent;

b) adding an anti-solvent; and

c) isolating crystalline sofosbuvir form-M1.

13. The process according to claim 12, wherein the organic solvent is benzyl amine and anti-solvent is selected from the group consisting of diethyl ether, diisopropyl ether, methyl tert-butyl ether, and mixtures thereof.

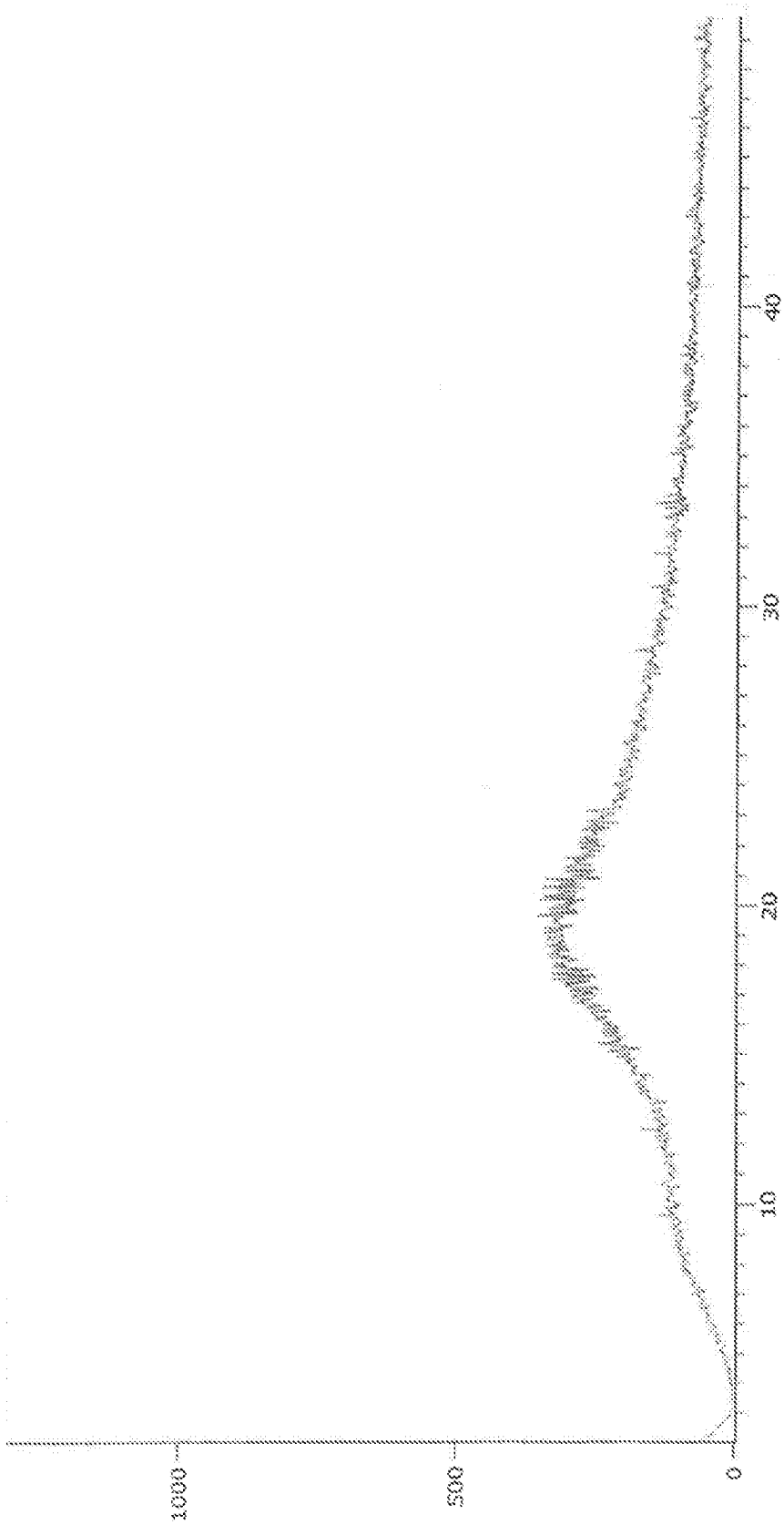


Figure 1-Powder X-ray diffraction pattern of amorphous sofosbuvir

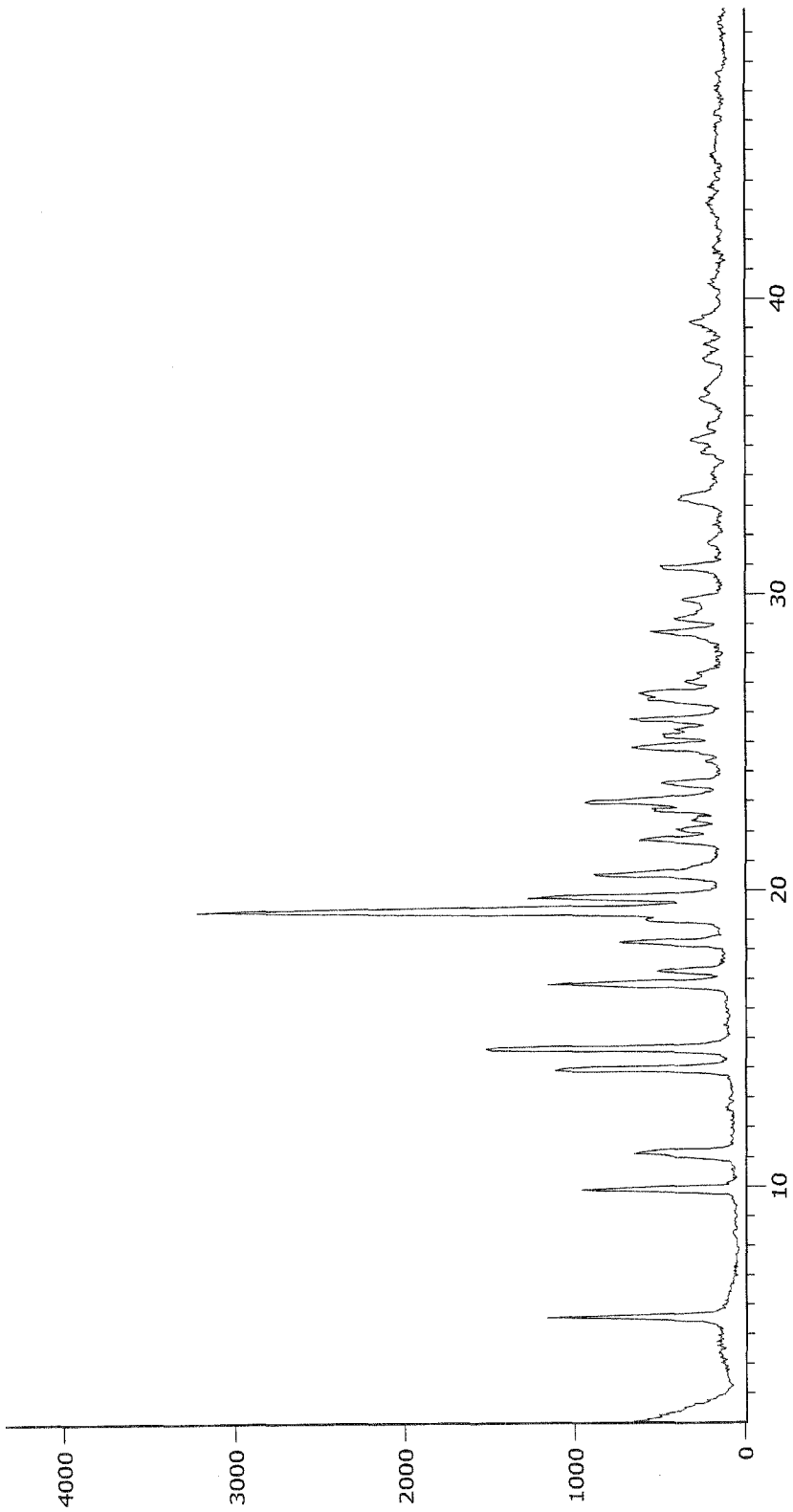


Figure 2-Powder X-ray diffraction pattern of crystalline sofosbuvir Form-M1

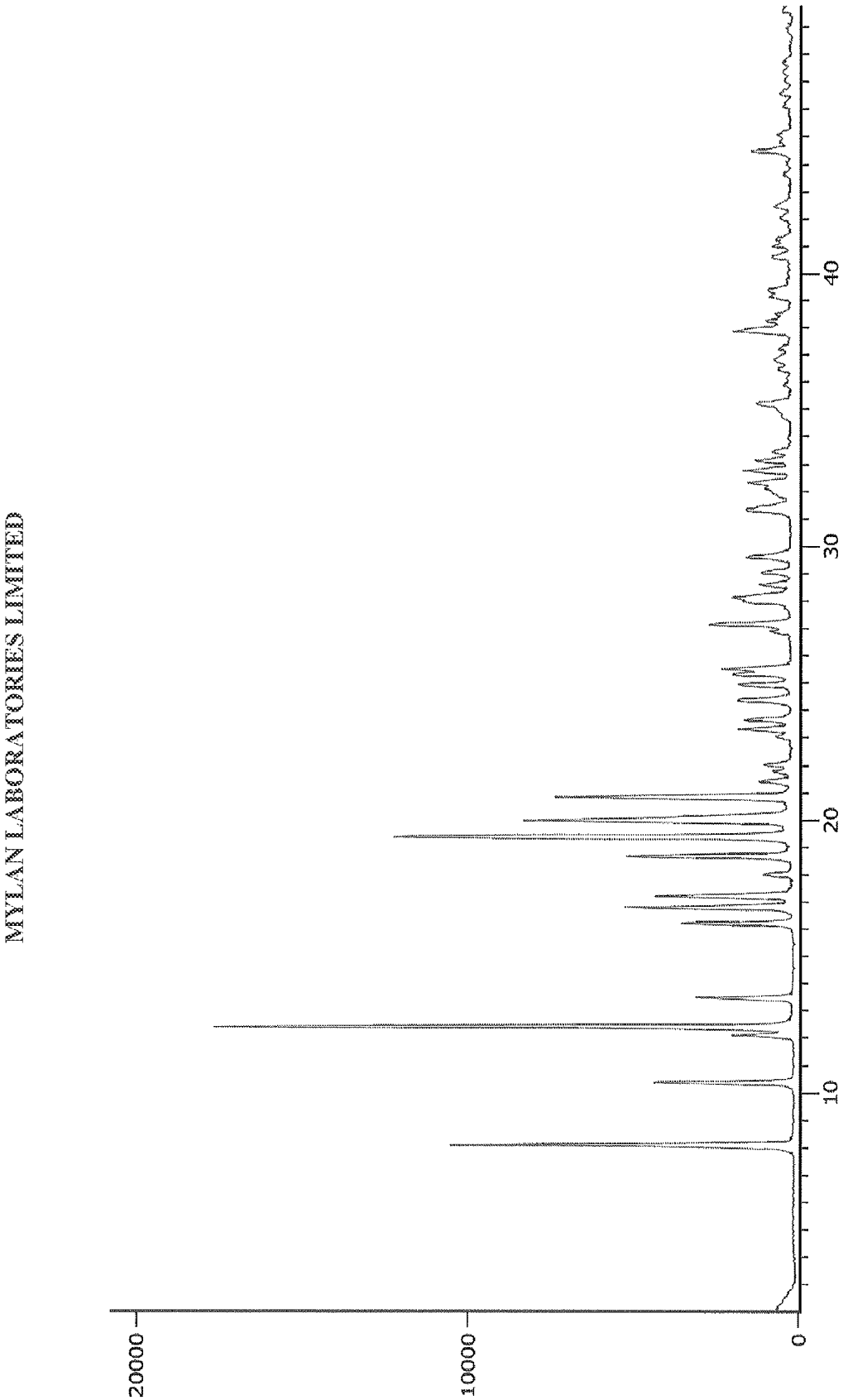


Figure 3-Powder X-ray diffraction pattern of crystalline sofosbuvir Form-M2