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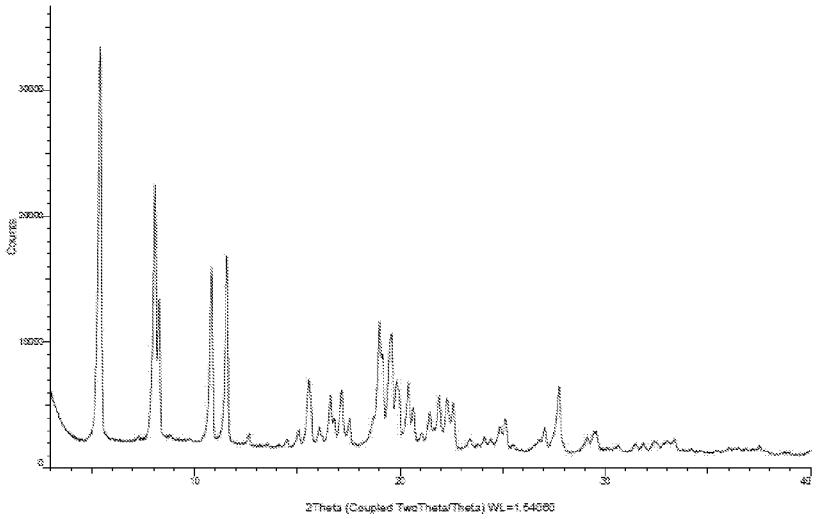
[Continued on next page]

(54) **Title**: SOLID FORMS OF NUCLEOSIDE PHOSPHORAMIDATE

Figure- 1



(57) **Abstract**: The present invention provides new crystalline compounds containing nucleoside phosphoramidate and a cocrystal former. Particularly, the present invention relates to Sofosbuvir Piperazine cocrystals.

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SOLID FORMS OF NUCLEOSIDE PHOSPHORAMIDATE

FIELD OF THE INVENTION

The present invention relates to new crystalline compounds containing nucleoside phosphoramidate and a cocrystal former.

The present invention relates to novel cocrystals of nucleoside phosphoramidates. Particularly, the present invention relates to novel Sofosbuvir cocrystals, therapeutic uses thereof and pharmaceutical compositions containing them.

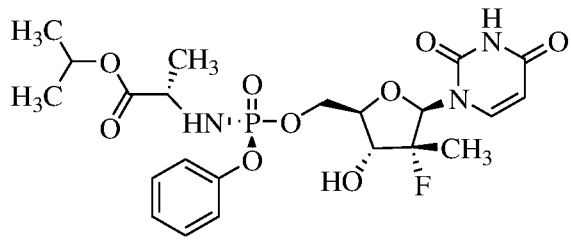
More particularly, the present invention relates to Sofosbuvir Piperazine cocrystals.

The present invention also relates to a process for the preparation of novel cocrystals of nucleoside phosphoramidates.

The present invention also relates to an improved process for the preparation of Sofosbuvir crystalline Form V1.

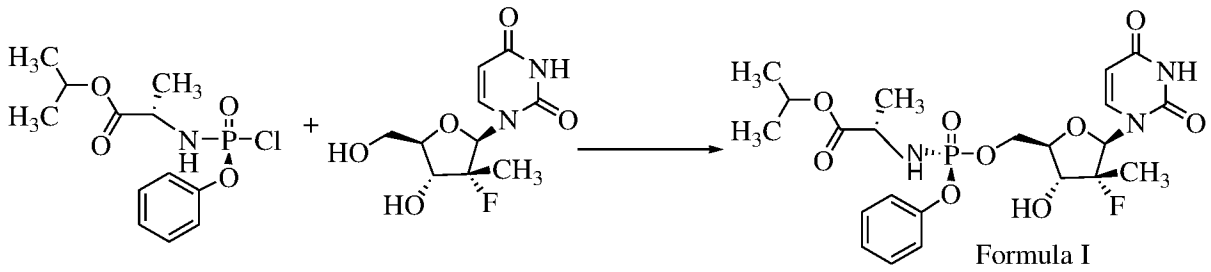
BACKGROUND OF THE INVENTION

Sofosbuvir is sold under the brand name SOVALDI® and is a Hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. The chemical name of Sofosbuvir is (*S*)-isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)-(phenoxy)phosphorylamino)propanoate and the molecular formula is $C_{22}H_{29}FN_3O_9P$ with a molecular weight of 529.4. The structural formula of Sofosbuvir is:



Formula I

Sofosbuvir is disclosed for the first time in US 7,964,580 B2. This patent also discloses process for preparing Sofosbuvir by reacting phosphorochloridate compound with nucleoside analog to give Sofosbuvir. The process is shown in the scheme given below:



Scheme I

US Pat No. 8,618,076 B2 discloses polymorphic Forms 1, 2, 3, 4, 5 and 6 of Sofosbuvir characterized by XRPD.

Due to the development of the drug discovery strategy over the last 20 years, physicochemical properties of drug development candidates have changed significantly. The term "drug" as used herein is meant to include active pharmaceutical ingredient. The development candidates are generally more lipophilic and less water soluble, which creates huge problems for the industry. Research has shown that some drug candidates fail in the clinical phase due to poor human bioavailability and/or problems with their formulation. Traditional methods to address these problems, without completely redesigning the molecule, include salt selection, producing amorphous material, particle size reduction, prodrugs, and different formulation approaches.

Although therapeutic or clinical efficacy is the primary concern for a drug (or an active pharmaceutical ingredient), the salt and solid-state form (i.e., the crystalline or amorphous form) of a drug candidate can be critical to its pharmacological properties and to its development as a viable drug. Crystalline forms of drugs have been used to alter the physicochemical properties of a particular drug. Each crystalline form of a drug candidate can have different solid-state (physical and chemical) properties which may be relevant for drug delivery. Crystalline forms often have better chemical and physical properties than corresponding non-crystalline forms such as the amorphous form. The differences in physical properties exhibited by a novel solid form of a drug (such as a cocrystal or polymorph of the original drug) affect pharmaceutical parameters such as storage stability, compressibility and density (relevant for formulation and product manufacturing), and dissolution rates and solubility (relevant factors in achieving suitable bioavailability).

Dissolution rates of an active ingredient invivo (e.g., gastric or intestinal fluid) may have therapeutic consequences since it affects the rate at which an orally administered active ingredient may reach the patient's bloodstream. In addition, solubility, a thermodynamic

quantity, is a relevant property in evaluating drug delivery because a poorly soluble crystalline form of a drug will deliver less drug than a more soluble one in the same formulation.

Because these practical physical properties are influenced by the solid-state properties of the crystalline form of the drug, they can significantly impact the selection of a compound as a drug, the ultimate pharmaceutical dosage form, the optimization of manufacturing processes, and absorption in the body. Moreover, finding the most adequate solid state form for further drug development can reduce the time and the cost of that development.

Cocrystals have generated tremendous interest in pharmaceutical research and development because of the potential to customize physicochemical properties of the solid while maintaining the chemical integrity of the drug. Cocrystals are part of a broader class of multicomponent crystals, where two or more molecules (commonly referred to as drug and coformer) populate a homogeneous crystalline lattice in a well defined stoichiometry. What distinguishes cocrystals from other types of multicomponent crystals such as salts and solvates is that drug and coformer are solids at ambient temperature and that the intermolecular interactions are nonionic in nature.

The diversity of solid forms that can be generated from a drug greatly increases through cocrystallization; the physicochemical properties of the cocrystals can vary depending on the characteristics of its constituent molecules. Pharmaceutically relevant properties that can change via cocrystallization include but are not limited to solubility, dissolution, moisture uptake, chemical stability, mechanical properties, and bioavailability. Of these properties, solubility is the most widely appreciated in the literature. Cocrystals have the potential to address the solubility limitations of poorly soluble pharmaceutical compounds, a problem which can pose a serious challenge to successful formulation.

Obtaining suitable crystalline forms of a drug is a necessary stage for many orally available drugs. Suitable crystalline forms possess the desired properties of a particular drug. Such suitable crystalline forms may be obtained by forming a cocrystal between the drug and a coformer. Cocrystals often possess more favorable pharmaceutical and pharmacological properties or may be easier to process than known forms of the drug itself. For example, a cocrystal may have different dissolution and solubility properties than the drug. Further, cocrystals may be used as a convenient vehicle for drug delivery, and new drug formulations comprising cocrystals of a given drug may have superior properties, such as solubility, dissolution, hygroscopicity, and storage stability over existing formulations of the drug.

A cocrystal of a drug (an active pharmaceutical ingredient) is a distinct chemical composition between the drug and coformer, and generally possesses distinct crystallographic and spectroscopic properties when compared to those of the drug and coformer individually. Unlike salts, which possess a neutral net charge, but which are comprised of charge-balanced components, cocrystals are comprised of neutral species. Thus, unlike a salt, one cannot determine the stoichiometry of a cocrystal based on charge balance. Indeed, one can often obtain cocrystals having stoichiometric ratios of drug to coformer of greater than or less than 1:1. The stoichiometric ratio of an API to coformer is a generally unpredictable feature of a cocrystal.

Without limiting the present invention to any particular definitional construct because others may define the term differently, the term "cocrystals" may be thought of as multi-component crystals composed of neutral molecules. These multi-component assemblies are continuing to excite and find usefulness, particularly within the pharmaceutical arena, for their ability to alter physicochemical properties. More specifically, cocrystals have been reported to alter aqueous solubility and/or dissolution rates, increase stability with respect to relative humidity, and improve bioavailability of active pharmaceutical ingredients.

A necessary consideration when designing cocrystals, if the end goal is a potential marketed drug-product, is incorporating a suitable cocrystal former (coformer) with an acceptable toxicity profile. Within the pharmaceutical industry, coformers are typically selected from the same list of pharmaceutically accepted salt formers, generally regarded as safe (GRAS) and/or everything added to food in the United States (EAFUS) lists, due to previous occurrence of these molecules in FDA approved drug or food products. An additional group of molecules to be considered as possible coformers are the naturally occurring compounds, nutraceuticals.

In a cocrystal, the drug and the coformers each possess unique lattice positions within the unit cell of the crystal lattice. Crystallographic and spectroscopic properties of cocrystals can be analyzed as with other crystalline forms such as with X-ray powder diffraction (XRPD), single crystal X-ray crystallography, and solid state NMR, among other techniques. Co-crystals often also exhibit distinct thermal behavior compared with other forms of the corresponding drug. Thermal behavior may be analyzed by such techniques as capillary melting point, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) to name a few. These techniques can be used to identify and characterize the cocrystals.

OBJECTIVE OF THE INVENTION

The main object of the present invention is to provide novel Sofosbuvir cocrystals.

Another objective of the present invention is to provide different polymorphic forms of novel Sofosbuvir cocrystals.

Another objective of the present invention is to provide process for the preparation of novel Sofosbuvir cocrystals.

Another objective of the present invention is to provide compositions of novel Sofosbuvir cocrystals.

Still another objective of the present invention is to provide pharmaceutical dosage forms of novel Sofosbuvir cocrystals.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides new crystalline compounds containing nucleoside phosphoramidate and a cocrystal former.

In a preferred aspect, the present invention provides novel Sofosbuvir cocrystals, comprising Sofosbuvir and a cocrystal former, wherein the cocrystal former is Piperazine.

In a more preferred aspect, the present invention provides novel Sofosbuvir-Piperazine cocrystals.

In a still more preferred aspect, the present invention provides novel Sofosbuvir-Piperazine cocrystals in the ratio of 1:1.

In yet another aspect, the present invention provides Sofosbuvir-Piperazine cocrystal characterized by X-ray powder diffraction pattern having peaks at 5.41, 8.08, 8.28, 10.86, 11.60, 15.61, 19.01, 19.09, 19.54, 19.86, 20.40 and 27.74± 0.2° 2θ values, depicted in Figure 1.

In yet another aspect, the present invention provides novel Sofosbuvir-Piperazine cocrystals further characterized by X-ray powder diffraction pattern having peaks at 5.416, 8.085, 8.286, 10.861, 11.603, 12.667, 14.521, 15.081, 15.619, 16.127, 16.658, 17.207, 17.580, 19.014, 19.549, 19.864, 20.403, 20.643, 21.455, 21.877, 22.270, 22.572, 23.393, 24.869, 25.121, 27.026, 27.743, 29.138, 29.527, 32.401 ± 0.2° 2θ values, depicted in Figure 1.

In yet another aspect, the present invention provides novel Sofosbuvir-Piperazine cocrystals further characterized by ^{1}H NMR as shown in Figure 2.

In yet another aspect the present invention provides novel Sofosbuvir-Piperazine cocrystals, further characterized by a TGA curve corresponding to a weight loss of less than about 6.2 % as depicted in Figure 3.

In yet another aspect, the present invention provides Sofosbuvir-Piperazine cocrystal characterized by DSC having endothermic peak at 144.65ºC, depicted in Figure 4.

In yet another aspect, the present invention provides a process for the preparation of Sofosbuvir-Piperazine cocrystal which comprises the steps of:

a) providing a solution of Sofosbuvir and Piperazine in a solvent, and

b) isolating crystalline Sofosbuvir-Piperazine cocrystal.

In yet another aspect, the present invention provides different crystalline forms of novel Sofosbuvir-Piperazine cocrystals.

In yet another aspect, the present invention provides processes for the preparation of novel Sofosbuvir-Piperazine cocrystals, comprising providing a solution of a mixture of Sofosbuvir and Piperazine in an organic solvent or water optionally seeding with co-crystals of Sofosbuvir and Piperazine cocrystals.

In yet another aspect, the present invention provides processes for the preparation of novel Sofosbuvir- Piperazine cocrystals, which comprises providing a solution of Sofosbuvir and Piperazine former in a solvent, and combining an anti-solvent with the solution.

In yet another aspect, the present invention provides a novel process for the preparation of crystalline Form V1 of Sofosbuvir of Formula I which comprises the steps:

a) providing a solution of Sofosbuvir in a ketone solvent,

b) adding the solution obtained in step (a) to a hydrocarbon solvent, and

c) isolating crystalline Form V1 of Sofosbuvir of Formula I.

BRIEF DESCRIPTION OF DRAWINGS

Fig.1: Represents X-ray Powder Diffraction Pattern of Sofosbuvir-Piperazine cocrystal.

Fig.2: Represents ^{1}H NMR of Sofosbuvir-Piperazine cocrystal.

Fig.3: Represents TGA of Sofosbuvir-Piperazine cocrystal.

Fig.4: Represents Differential Scanning Calorimetry (DSC) thermogram of Sofosbuvir-Piperazine cocrystal.

Fig.5: Represents Overlay of X-ray Powder Diffraction Pattern of Sofosbuvir-Piperazine Cocrystal at 60 °C.

Fig.6: Represents Overlay of X-ray Powder Diffraction Pattern of Sofosbuvir-Piperazine Cocrystal at normal packed condition for 6 months 15 days.

Fig.7: Represents Overlay of X-ray Powder Diffraction Pattern of Sofosbuvir-Piperazine Cocrystal at 90 % RH for 24 hrs, open condition.

Fig.8: Represents X-ray Powder Diffraction Pattern of novel crystalline Form V1 of Sofosbuvir.

Fig.9: Represents Differential Scanning Calorimetry (DSC) thermogram of novel crystalline Form V1 of Sofosbuvir.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel co-crystals of (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 (Sofosbuvir) with a Piperazine cocrystal former.

In a preferred embodiment, the present invention provides novel Sofosbuvir-Piperazine cocrystal characterized by X-ray powder diffraction pattern having peaks at 5.41, 8.08, 8.28, 10.86, 11.60, 15.61, 19.01, 19.09, 19.54, 19.86, 20.40 and 27.74 ± 0.2° 2θ values as depicted in Figure 1.

In another preferred embodiment, the present invention provides novel Sofosbuvir-Piperazine cocrystals, characterized by proton NMR as depicted in Figure 2.

In another preferred embodiment, the present invention provides novel Sofosbuvir-Piperazine cocrystals, further characterized by a TGA curve corresponding to a weight loss of less than about 6.2 %, depicted in Figure 3.

In still another preferred embodiment, the present invention provides novel Sofosbuvir-Piperazine cocrystal further characterized by DSC having endothermic peak at 144.65ºC, depicted in Figure 4.

In still another preferred embodiment, the present invention provides stable Sofosbuvir-Piperazine cocrystal, wherein the XRD pattern of Sofosbuvir-Piperazine cocrystal after stability study is depicted in Figures 5, 6 and 7.

Sofosbuvir Piperazine cocrystal is stable at 60°C drying (ATD) for 3 hrs. Sofosbuvir-Piperazine cocrystal appears to be very promising and exhibits good physical stability at normal packed condition for 6 months 15 days and it further appears to be physically stable at 90 % RH for 24 hrs, open condition.

In yet another embodiment, the present invention provides a pharmaceutical composition comprising Sofosbuvir cocrystals and a pharmaceutically acceptable excipient.

The pharmaceutical composition may contain one or more additional excipients such as binder, filler, lubricant, emulsifier, suspending agent, sweetener, flavoring, preservative, buffer, wetting agent, disintegrant, effervescent agent, additive, and mixtures thereof.

The pharmaceutical compositions comprising novel Sofosbuvir cocrystals may be further formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using procedures such as direct blending, dry granulation, wet granulation, or extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present application may further comprise one or more pharmaceutically acceptable excipients.

In yet another embodiment, the starting material Sofosbuvir used in the present invention is prepared by any procedures disclosed in the prior-art or any of the known Forms of Sofosbuvir can also be used as starting material.

In yet another embodiment, solvents used in the present invention are selected from"alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran and dimethoxyethane and/or mixtures thereof.

According to the present invention isolation of solid from the reaction mixture is carried out by conventional methods such as evaporation, partial removal of the solvent from the solution, sonication, solvent/antisolvent method, slurry, cooling, seeding, filtration, distillation, decanting, vacuum drying, spray drying, freeze drying or any other methods known in the art.

In yet another embodiment, the present invention provides a process for the preparation of Sofosbuvir-Piperazine cocrystal which comprises the steps:

a) providing a solution of Sofosbuvir and Piperazine in an alcoholic, ester or nitrile solvent, and

b) isolating crystalline Sofosbuvir-Piperazine cocrystal.

In yet another most preferred embodiment, the present invention provides a process for the preparation of Sofosbuvir-Piperazine cocrystal which comprises the steps:

a) providing a sonic slurry of Sofosbuvir and Piperazine in an alcoholic or nitrile solvent, and

b) isolating crystalline Sofosbuvir-Piperazine cocrystal.

In another embodiment, the present invention provides a process for the preparation of crystalline Form V1 of Sofosbuvir of Formula I which comprises the steps:

a) providing a solution of Sofosbuvir in acetone,

b) adding the solution obtained in step (a) to heptane, and

c) isolating crystalline Form V1 of Sofosbuvir of Formula I.

In yet another embodiment, the present invention provides a process for the preparation of crystalline Form V1 of Sofosbuvir of Formula I which comprises the steps:

a) providing a solution of Sofosbuvir in acetone,

b) adding the solution obtained in step (a) to hexane and

c) isolating crystalline Form V1 of Sofosbuvir of Formula I.

In yet another embodiment, crystalline Form V1 of Sofosbuvir is characterized by X-ray powder diffraction pattern having peaks at 8.07, 10.36, 12.40, 16.88, 17.17, 18.73, 19.38, 20.02, 20.81, 23.27, 24.94, 27.10 and 27.97 ± 0.2° 2θ values, depicted in Figure 8.

In yet another embodiment, crystalline Form V1 of Sofosbuvir is further characterized by DSC having endothermic peak at 123.17° C, depicted in Figure 9.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The invention is illustrated below with reference to inventive and comparative examples and should not be construed to limit the scope of the invention.

EXAMPLES

Example 1: Process for the preparation of Sofosbuvir-Piperazine cocrystal:

163 mg of Piperizine was dissolved in 1ml of ethanol at room temperature. To this clear solution, 1 gm of Sofosbuvir was added and sonicated for 20 min. Added 0.5 ml of ethanol and continued sonication for 20 min. Filtered the material and identified as Sofosbuvir-Piperazine cocrystal.

Example 2: Process for the preparation of Sofosbuvir-Piperazine cocrystal:

30 mg of Sofosbuvir and 5.6 mg piperazine were dissolved in 0.3 ml of propyl acetate at 60ºC and kept aside for slow solvent evaporation. After one day crystalline powder observed and decanted the solution.

Example 3: Process for the preparation of Sofosbuvir-Piperazine cocrystal:

1.14 gms of Piperazine was dissolved in 14ml of ethanol at room temperature. To this clear solution, 7 gm of Sofosbuvir was added. After 15min slurry, precipitation observed and added 35ml of cyclohexane and continued the slurry for 3 hrs. Filtered the material and PXRD analyzed.

Example 4: Process for the preparation of crystalline Form V1:

100 mg of Sofosbuvir was dissolved in 0.5 ml of acetone at room temperature. The clear solution was added to 10 ml of hexane and observed precipitate immediately. Slurry continued for 24 hrs and sonicated for 5 min. Filtered the material and identified as Form V1.

Example 5: Process for the preparation of crystalline Form V1:

100 mg of Sofosbuvir was dissolved in 0.5 ml of acetone at room temperature. The clear solution was added to 10 ml of heptane and observed precipitate immediately. Slurry continued for 24 hrs and sonicated for 5 min. Filtered the material and identified as Form V1.

We Claim:

1. A Sofosbuvir:Piperazine cocrystal.

2. The Sofosbuvir:Piperazine cocrystal as claimed in claim 1, wherein the molar ratio of Sofosbuvir:Piperazine is 1:1.

3. The Sofosbuvir:Piperazine cocrystal as claimed in claim 1, characterized by X-ray powder diffraction pattern having peaks at 5.41, 8.08, 8.28, 10.86, 11.60, 15.61, 19.01, 19.09, 19.54, 19.86, 20.40 and 27.74± 0.2° 2θ.

4. The Sofosbuvir:Piperazine cocrystal as claimed in claim 3, further characterized by X-ray powder diffraction pattern having peaks at 5.416, 8.085, 8.286, 10.861, 11.603, 12.667, 14.521, 15.081, 15.619, 16.127, 16.658, 17.207, 17.580, 19.014, 19.549, 19.864, 20.403, 20.643, 21.455, 21.877, 22.270, 22.572, 23.393, 24.869, 25.121, 27.026, 27.743, 29.138, 29.527, 32.401 ± 0.2° 2θ.

5. The Sofosbuvir:Piperazine cocrystal as claimed in claim 1, characterized by DSC having endothermic peak at 144.65ºC.

6. A composition comprising an amount of Sofosbuvir:Piperazine cocrystal and one or more excipients.

7. The composition as claimed in claim 6, wherein the one or more excipients is one or more of a binder, filler, lubricant, emulsifier, suspending agent, sweetener, flavoring, preservative, buffer, wetting agent, disintegrant, effervescent agent, additive, and mixtures thereof.

8. The composition as claimed in claim 7, wherein the additive is selected from the group consisting of microcrystalline cellulose, lactose, sucrose, fructose, glucose, dextrose, dibasic calcium phosphate, calcium sulfate, cellulose, methylcellulose, cellulose derivatives, kaolin, mannitol, lactitol, maltitol, xylitol, sorbitol, sugar alcohols, dry starch, dextrin, maltodextrin, polysaccharides, and mixtures thereof.

9. The composition as claimed in claim 6, further comprising one or more pharmaceutically acceptable carriers, pharmaceutically acceptable excipients, medicinal agents, pharmaceutical agents, adjuvants, diluents, and mixtures thereof.

10. A process for the preparation of Sofosbuvir:Piperazine cocrystal, which comprises the steps of:
i) providing a solution of Sofosbuvir and Piperazine in a solvent; and
ii) isolating crystalline Sofosbuvir-Piperazine cocrystal.

11. A process for the preparation of Sofosbuvir-Piperazine cocrystal, comprising providing a solution of a mixture of Sofosbuvir and Piperazine in an organic solvent or water, optionally seeding with co-crystal of Sofosbuvir-Piperazine cocrystal.

12. The process as claimed in claims 10 and 11 wherein the solvent is selected from alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like or hydrocarbons such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or ketones such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or nitriles such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or ethers such as di-tert-butylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran and dimethoxyethane and the like and or mixtures thereof.

13. A process for the preparation of Sofosbuvir-Piperazine cocrystals, which comprises the steps of:
i) providing a solution of Sofosbuvir and Piperazine in a solvent,
ii) addition of an anti-solvent to step (i) solution, and
iii) isolating Sofosbuvir-Piperazine cocrystals.

14. The process as claimed in claim 13, wherein the solvent and anti solvent is selected from alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like or hydrocarbons such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or ketones such as acetone, ethyl methyl ketone, diethyl ketone,

methyl tert-butyl ketone, isopropyl ketone and the like or esters such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or nitriles such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or ethers such as di-tert-butylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran and dimethoxyethane and the like and or mixtures thereof.

15. A process for the preparation of crystalline Form V1 of Sofosbuvir, which comprises the steps:
i) providing a solution of Sofosbuvir in a ketone solvent,
ii) adding the solution obtained in step (i) to a hydrocarbon solvent, and
iii) isolating crystalline Form V1 of Sofosbuvir of Formula I.

16. Crystalline Form V1 as prepared according to the process claimed in claim 15, having X-ray powder diffraction pattern peaks at 8.07, 10.36, 12.40, 16.88, 17.17, 18.73, 19.38, 20.02, 20.81, 23.27, 24.94, 27.10 and 27.97 ± 0.2° 2θ.

17. Crystalline Form V1 as prepared according to the process claimed in claim 15, having DSC endothermic peak at 123.17° C.

18. The process as claimed in claim 15, wherein the ketone solvent is selected from acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like and hydrocarbon solvent is selected from benzene, toluene, xylene, heptane, hexane and cyclohexane and the like and or mixtures thereof.

Figure- 1

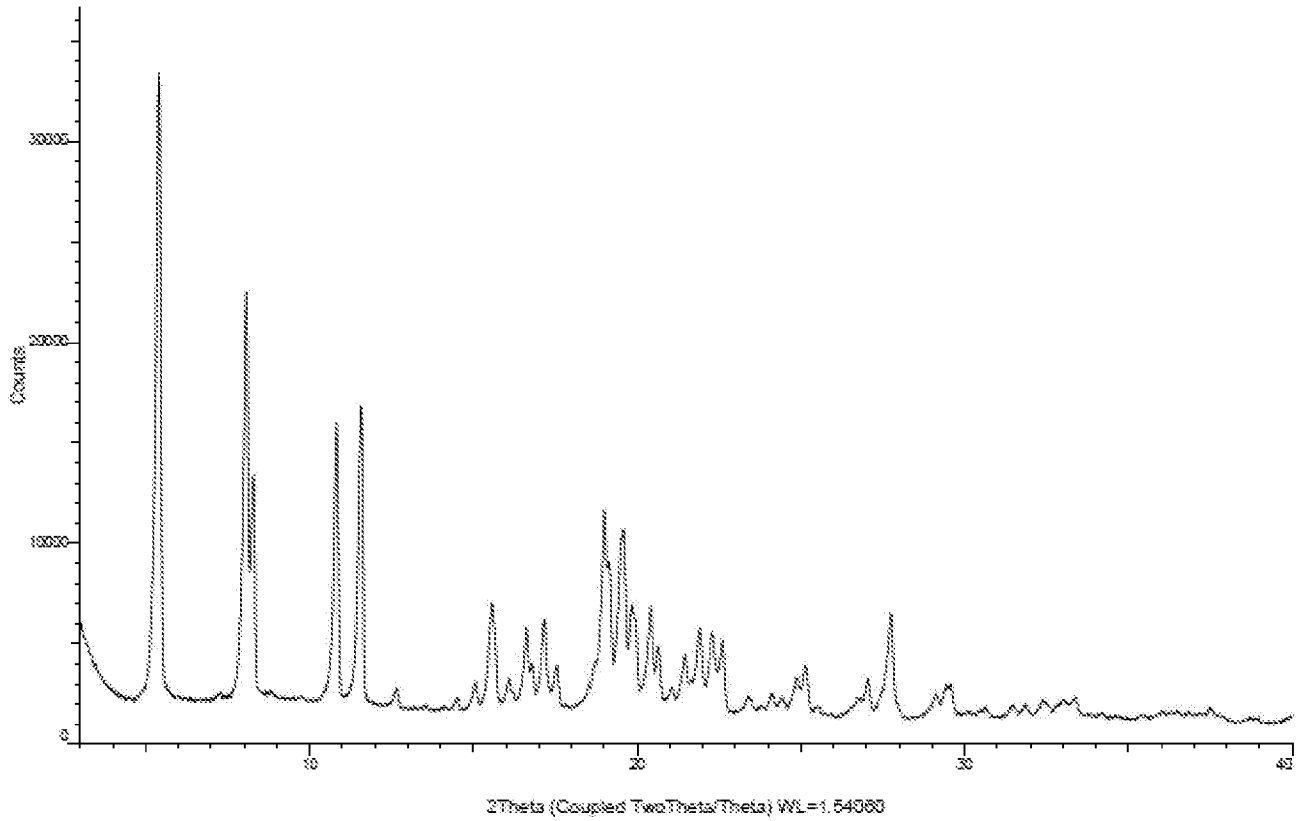


Figure- 2

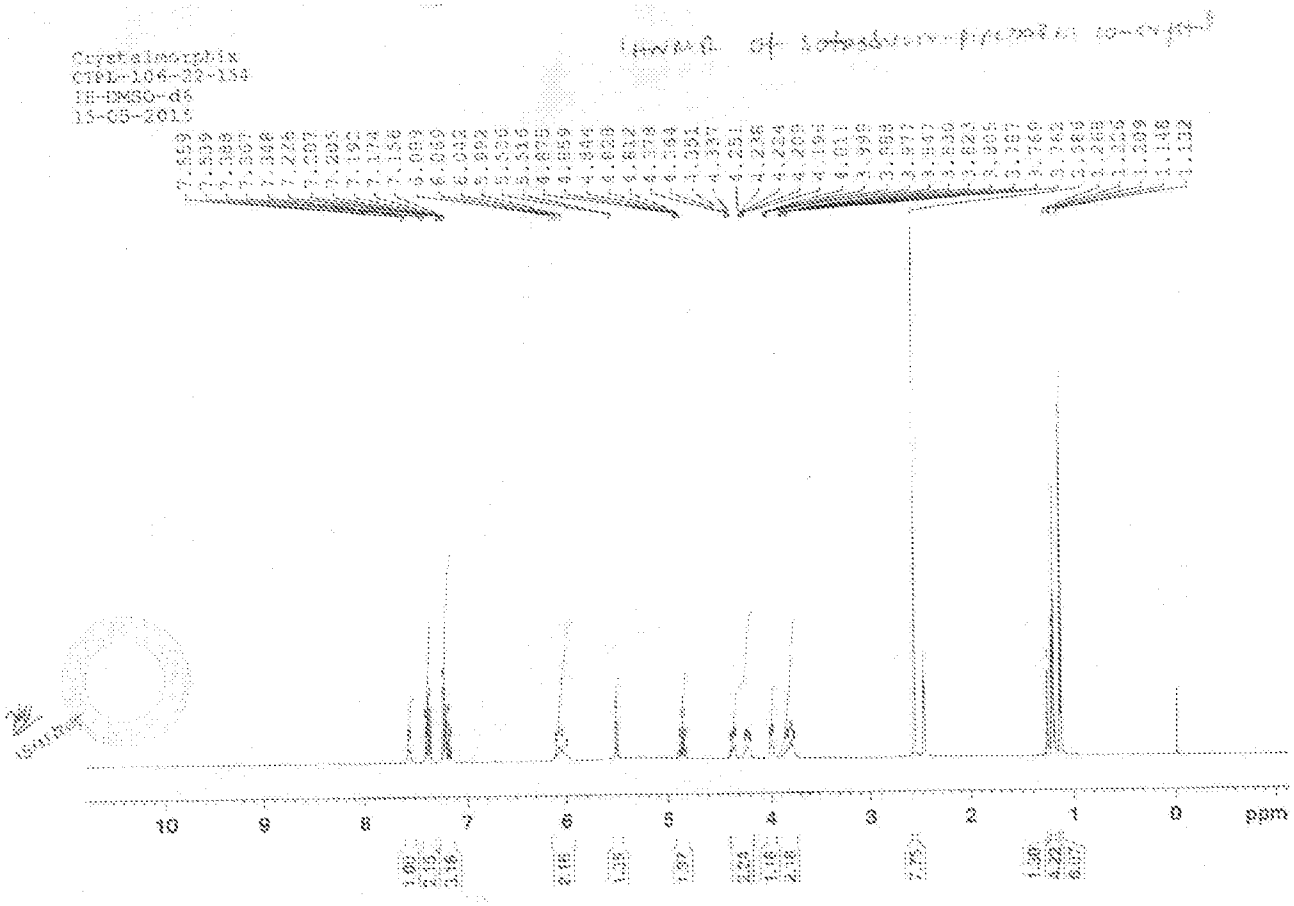

Crystalmorphix
CTRL-106-22-150
1H-DMSO-d6
15-05-2015
10
9
8
7
6
5
4
3
2
1
0
ppm

Figure- 3

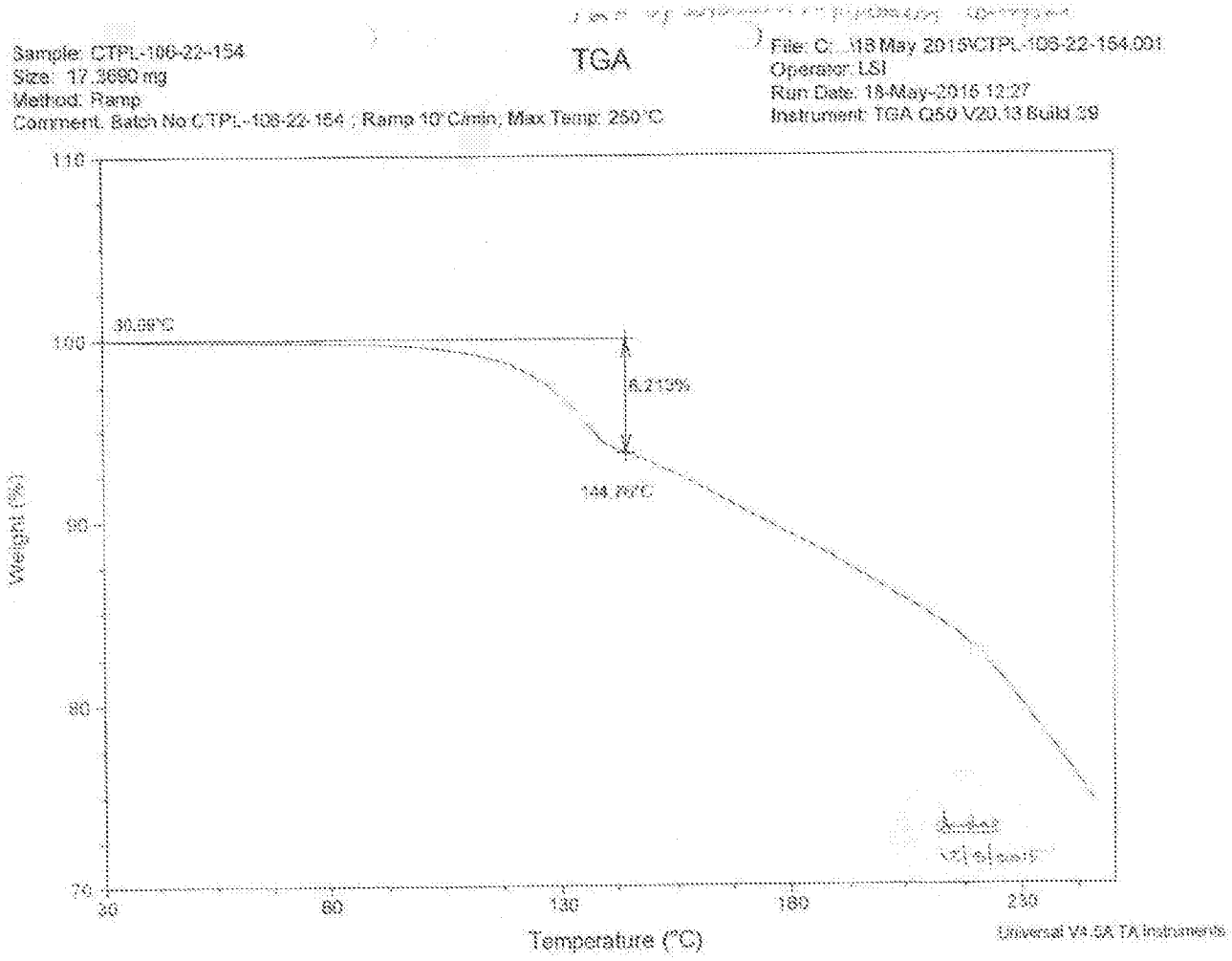

TGA
Sample: CTPL-106-22-154
Size: 17.3690 mg
Method: Ramp
Comment: Batch No CTPL-106-22-154 ; Ramp 10°C/min, Max Temp: 250°C
File: C:\...\18 May 2016\CTPL-106-22-154.001
Operator: LSI
Run Date: 18-May-2016 12:27
Instrument: TGA Q50 V20.13 Build 39
110
100
90
80
70
30.08°C
6.213%
144.79°C
Weight (%)
20
80
130
180
230
Temperature (°C)
Universal V4.5A TA Instruments

Figure- 4

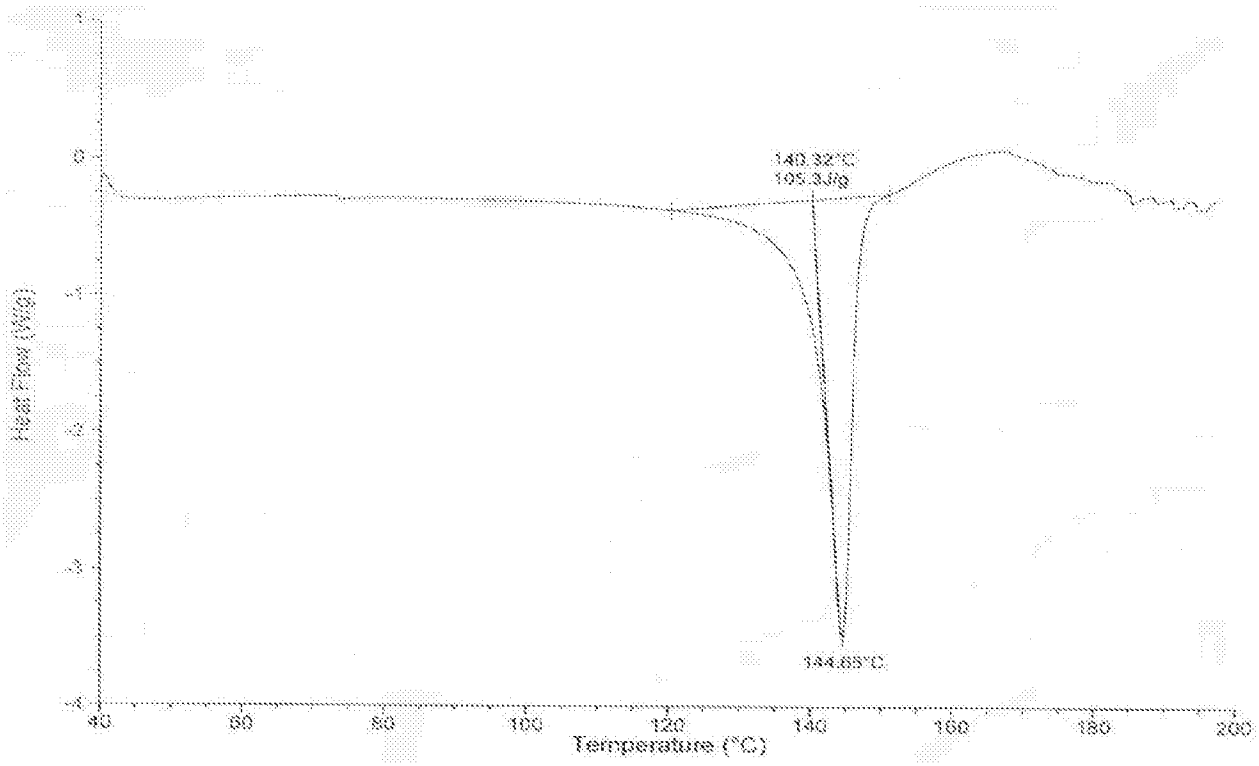

140.32°C
105.3J/g
144.65°C
Temperature (°C)
40
60
80
100
120
140
160
180
200

Figure- 5

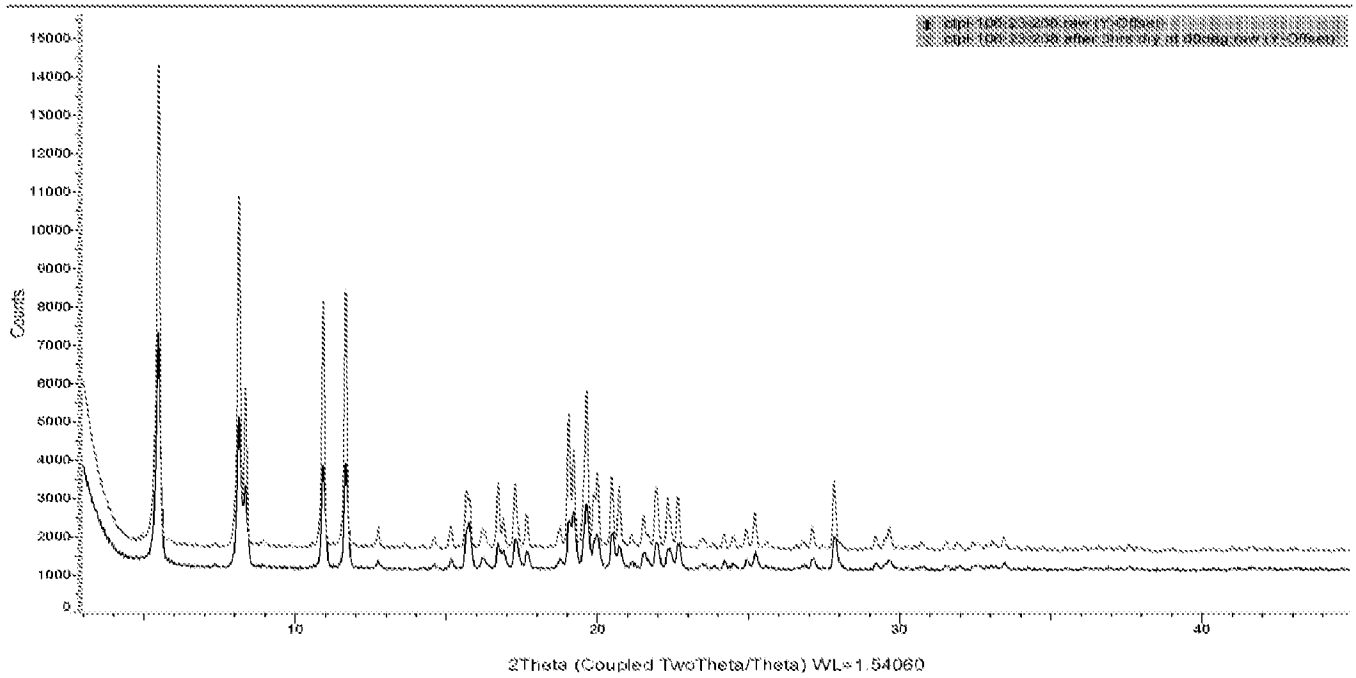

Counts
18000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure- 6

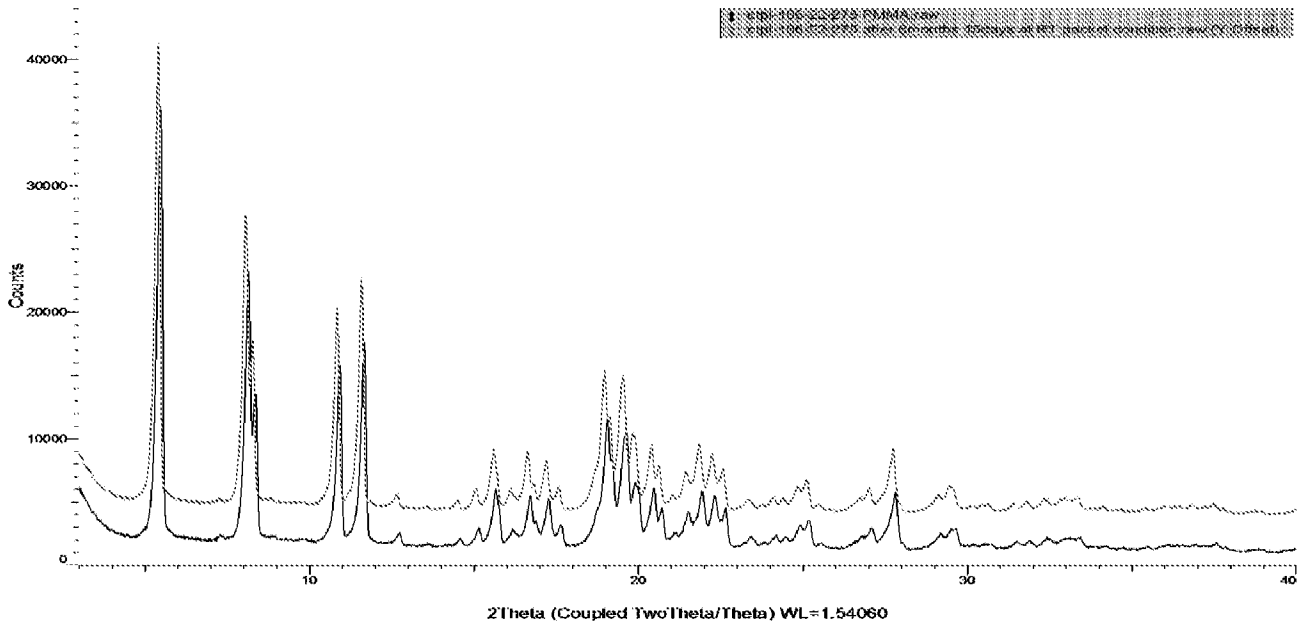

Counts
40000
30000
20000
10000
0
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure- 7

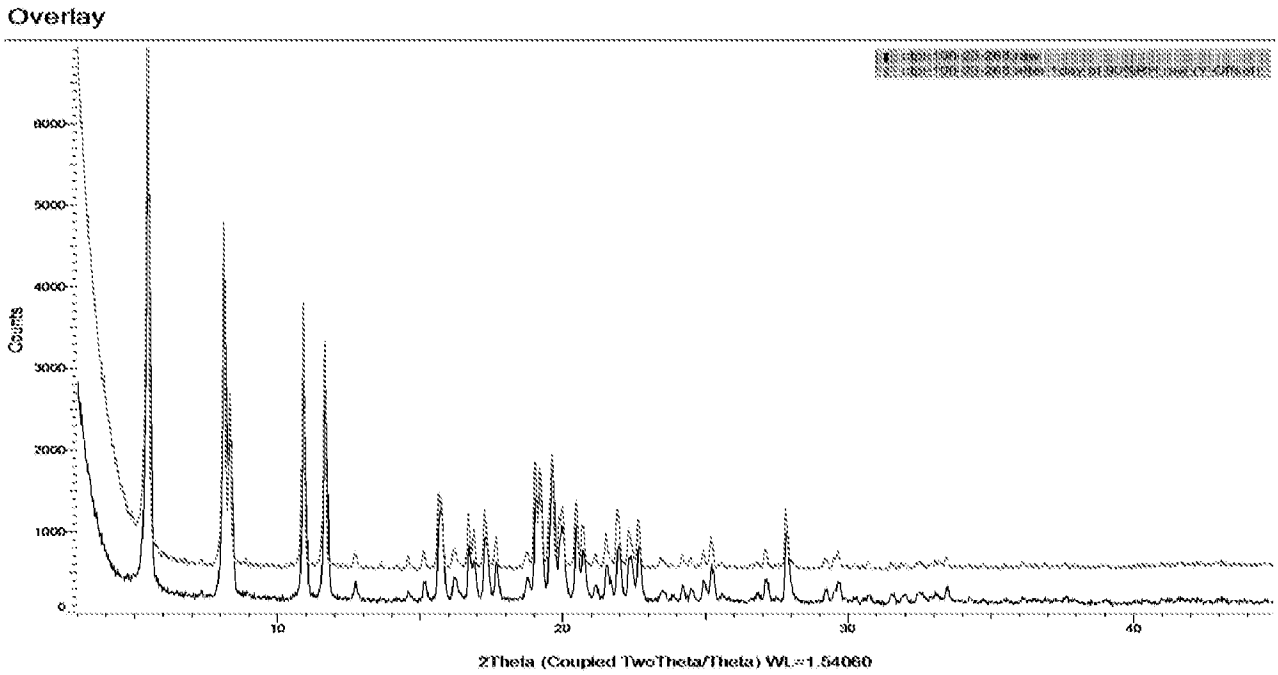

Overlay
Counts
8000
5000
4000
3000
2000
1000
0
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure- 8

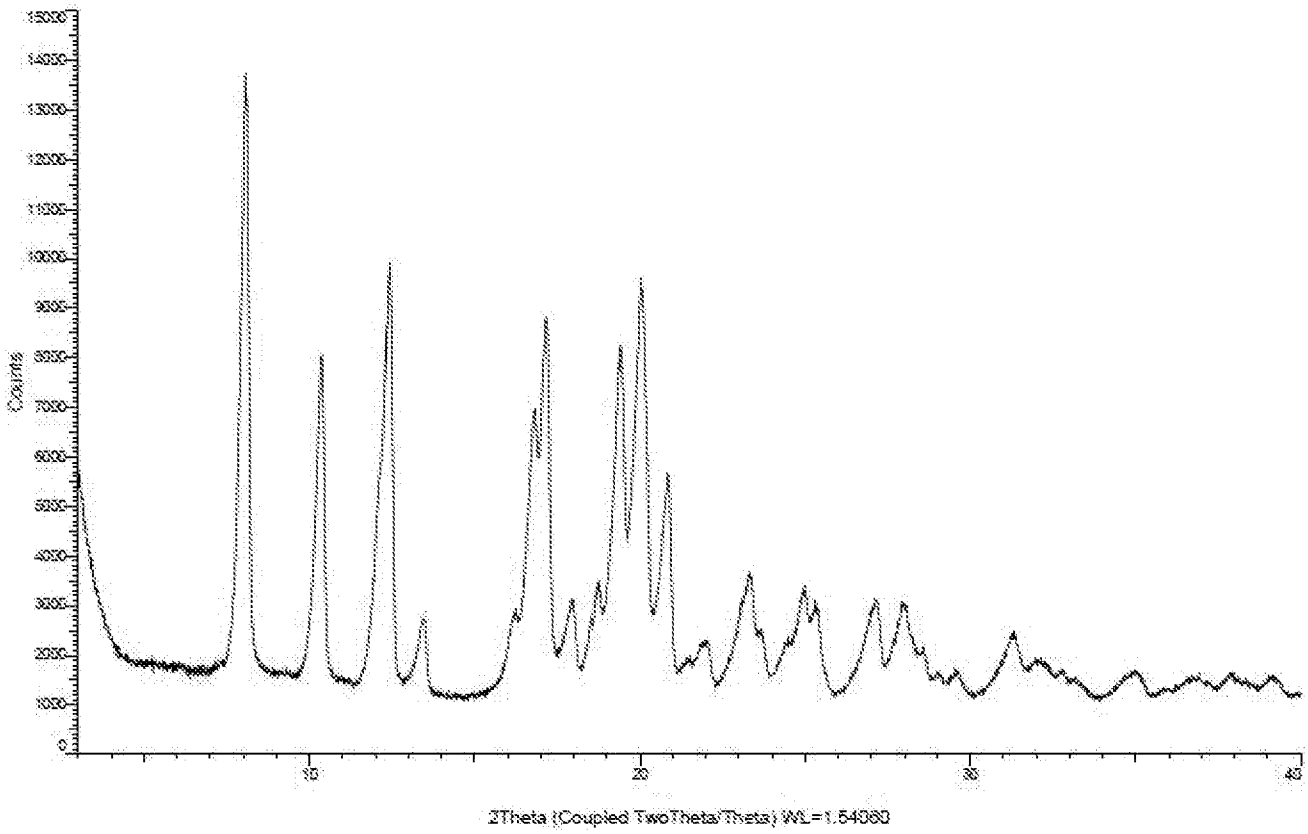
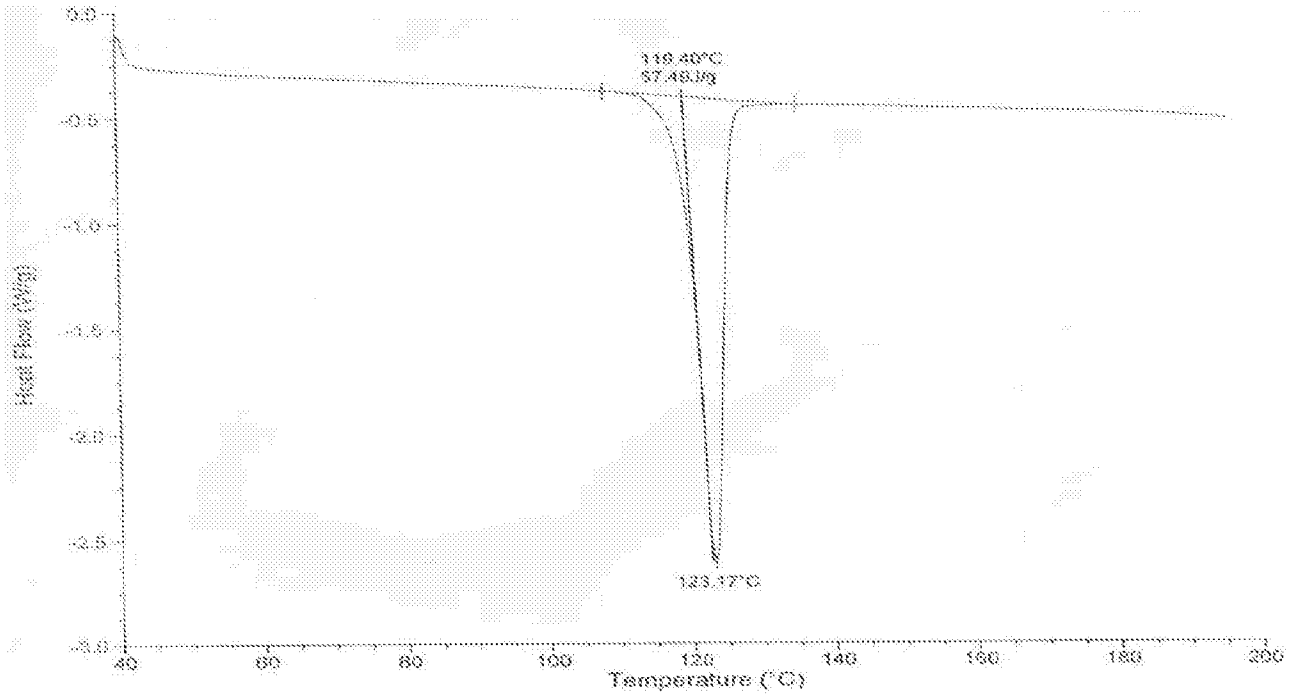


Figure- 9


0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
Heat Flow (W/g)
116.40°C
57.48 J/g
123.17°C
40
60
80
100
120
140
160
180
200
Temperature (°C)