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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 September 2016 (15.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/145269 A1

(51) International Patent Classification:
*C07D 403/14* (2006.01) *A61P 31/12* (2006.01)
*A61K 31/4184* (2006.01)

(21) International Application Number:
PCT/US2016/021905

(22) International Filing Date:
11 March 2016 (11.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 673/DEL/2015 | 12 March 2015 (12.03.2015) | IN |
| 962/DEL/2015 | 6 April 2015 (06.04.2015) | IN |
| 1058/DEL/2015 | 16 April 2015 (16.04.2015) | IN |
| 1625/DEL/2015 | 4 June 2015 (04.06.2015) | IN |
| 2011/DEL/2015 | 3 July 2015 (03.07.2015) | IN |
| 2171/DEL/2015 | 17 July 2015 (17.07.2015) | IN |
| 2356/DEL/2015 | 31 July 2015 (31.07.2015) | IN |
| 3612/DEL/2015 | 5 November 2015 (05.11.2015) | IN |
| 4327/DEL/2015 | 30 December 2015 (30.12.2015) | IN |
| 201611004860 | 11 February 2016 (11.02.2016) | IN |


(71) Applicant *(for all designated States except BB)*: **TEVA PHARMACEUTICALS INTERNATIONAL GMBH** [CH/CH]; Schusselstrasse 12, 8645 Jona (CH).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors: **ALAM, Mohammad, Mahboob**; Village: Kharua, Post: Kharua, Via-Muria, District: Darbhanga, Bihar, Pincode 847115 (IN). **ARONHIME, Judith**; Maor Yosef St. 5A, 7621745 Rehovot (IL). **KANSAL, Vinod, Kumar**; D5/501, The Pranayam, Puri Construction, Sector-82-85, Greater Faridabad, Haryana 1021002 (IN). **MUPPALLA, Siva Rama, Krishna**; K 505 AVJ Heights: Zeta Sector-1, Greater Noida: Uttar Pradesh 201306 (IN). **MUTHUSAMY, Anantha, Rajmohan**; 104, Amman Kovil Patti South Street, Sivakasi, Tamilnadu 626123 (IN). **NIGHOT, Dnyaneshwar, Kondibhau**; AT-Nighotwadi, Post-Manchar, Taluka-Ambegaon, Dist-Pune 410503 (IN). **PANDEY, Ghanshyam**; Village: Bada Kathar, Post: Janghai Bazar, (Maharchha) District: Allahadad, Pincode, Uttar Pradesh 212401 (IN). **SHINDE, Pramod, Kadappa**; 4A, Narsinha Naga, Modi, Solapur, Maharashtra 413001 (IN). **TANEJA, Amit, Kumar**; House No. 1088/1, Chorlian Street, Railway Road, Jagadhri: Dist: Yamuna Nagar, Haryana (IN). **VADIVELAN, Rengasamy**; Angarayanallur and Post, Udayarpalayam Taluk, Ariyalur District, Tamilnadu 621802 (IN). **VASOYA, Sanjay, Lakhabhai**; Veraval (shaper), MAA, Khodiyar Nagar Main Road, Via-Bhaktinagar-2, Ta-Kotada Sangani, Dist.-Rajkot, Gujrat 360002 (IN).

(74) Agents: **VALLA, Maurice, S.** et al.; Baker & Hostetler LLP, Cira Centre, 12th Floor, 2929 Arch Street, Philadelphia, PA 19104-2891 (US).

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

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

**Published**:

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

WO 2016/145269 A1

(54) Title: SOLID STATE FORMS LEDIPASVIR AND PROCESSES FOR PREPARATION OF LEDIPASVIR

(57) Abstract: The present disclosure encompasses solid state forms of Ledipasvir, pharmaceutical compositions thereof and processes for preparation of Ledipasvir.

# Solid State Forms of Ledipasvir and Processes for Preparation of Ledipasvir

## Cross Reference to Related Applications

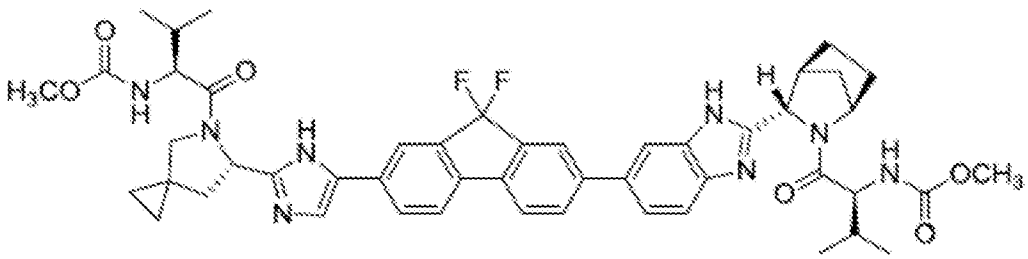
**[0001]** The present application claims the benefit of Indian Application No. 673/DEL/2015, filed March 12, 2015; Indian Application No. 962/DEL/2015, filed April 6, 2015; Indian Application No. 1058/DEL/2015, filed April 16, 2015; Indian Application No. 1625/DEL/2015, filed June 4, 2015; Indian Application No. 2011/DEL/2015, filed July 3, 2015; Indian Application No. 2171/DEL/2015, filed July 17, 2015; Indian Application No. 2356/DEL/2015, filed July 31, 2015; Indian Application No. 3612/DEL/2015, filed November 5, 2015; Indian Application No. 4327/DEL/2015, filed December 30, 2015; and Indian Application No. 201611004860, filed February 11, 2016, the entireties of which are incorporated by reference herein

## Field of the Disclosure

**[0002]** The present disclosure encompasses solid state forms of Ledipasvir, pharmaceutical compositions thereof and processes for preparation of Ledipasvir.

## Background of the Disclosure

**[0003]** Ledipasvir, methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate, has the following chemical structure:



Compound 1

**[0004]** Ledipasvir is a hepatitis C virus (HCV) NS5A inhibitor. It is a component of the fixed-dose combination HARVONI® and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

**[0005]** Ledipasvir is described in US 8,088,368. Solid state forms of Ledipasvir are described in WO 2013/184698, CN 104961733 and CN 105237517. Solid dispersions comprising Ledipasvir are described in WO 2014/120982. WO 2014/120981 describes pharmaceutical compositions that comprise an effective amount of Ledipasvir, wherein the Ledipasvir is substantially amorphous, and an effective amount of sofosbuvir, wherein the sofosbuvir is substantially crystalline. WO 2013/101550 describes a solid composition comprising an HCV inhibitor. Processes for preparation of Ledipasvir were described in US 8088368, WO 2013/184702 and in J. Med Chem. **2014**, *57* (5), pp 2033–2046.

**[0006]** Polymorphism, the occurrence of different crystalline forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g. measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), X-ray diffraction pattern, infrared absorption fingerprint, and solid state ($^{13}C$) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

**[0007]** Different salts and solid state forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, changing the dissolution profile in a favorable direction, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also offer improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to assess variations in the properties and characteristics of a solid active pharmaceutical ingredient.

**[0008]** Discovering new solid state forms and solvates of a pharmaceutical product may yield materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New solid state forms of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher

crystallinity, or polymorphic stability, which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life (chemical/physical stability). For at least these reasons, there is a need for additional solid state forms (including solvated forms) of Ledipasvir.

**[0009]** WO 2013/184698 reports that the acetone solvate offers significant impurity purging capability in that the reaction mixture with 96-97.5% AN before crystallization was upgraded to -99.6% AN when Form I was isolated. WO 2014/120982 describes preparation of solid dispersions from the acetone solvate. Use of solvates as starting material for preparation of the final dosage form requires monitoring the residual solvent content in the final dosage form. Further, the known synthetic processes have several drawbacks such as lower overall yield, use of column chromatography and use of toxic and costly solvents. For at least these reasons, there is a need to develop robust, high yield and plant friendly processes for preparation and purification of ledipasvir, that afford non solvated stable forms or solvated stable forms that can be easily converted to other crystalline forms that do not contain residual solvents, amorphous or premix that can be used directly for formulation.

## Summary of the Disclosure

**[0010]** The present disclosure provides solid state forms of Ledipasvir, processes for preparation thereof, and pharmaceutical compositions thereof. These solid state forms can be used to prepare other solid state forms of Ledipasvir, Ledipasvir salts and their solid state forms.

**[0011]** The present disclosure provides solid state forms of Ledipasvir for use in the preparation of pharmaceutical compositions of Ledipasvir.

**[0012]** The present disclosure also encompasses the use of the Ledipasvir solid state forms of the present disclosure for the preparation of pharmaceutical compositions of Ledipasvir.

**[0013]** The present disclosure comprises processes for preparing the above mentioned pharmaceutical compositions. The processes comprise combining the Ledipasvir solid state forms with at least one pharmaceutically acceptable excipient.

**[0014]** The solid state forms and the pharmaceutical compositions of Ledipasvir of the present disclosure can be used as medicaments, particularly for the treatment of Hepatitis C.

**[0015]** The present disclosure also provides methods of treating Hepatitis C, comprising administering a therapeutically effective amount of a Ledipasvir solid state form

of the present disclosure, or at least one of the above pharmaceutical compositions, to a subject suffering from Hepatitis C, or otherwise in need of the treatment.

**[0016]** The present disclosure also provides processes for preparation of Ledipasvir.

## Brief Description of the Drawings

**[0017]** Figure 1 shows an X-ray powder diffractogram of Form A of Ledipasvir.

**[0018]** Figure 2 shows an X-ray powder diffractogram of Form B of Ledipasvir.

**[0019]** Figure 3 shows an X-ray powder diffractogram of Form C of Ledipasvir.

**[0020]** Figure 4 shows an X-ray powder diffractogram of Form D of Ledipasvir.

**[0021]** Figure 5 shows an X-ray powder diffractogram of Form E of Ledipasvir.

**[0022]** Figure 6 shows an X-ray powder diffractogram of Form F of Ledipasvir.

**[0023]** Figure 7 shows an X-ray powder diffractogram of Form III of Ledipasvir.

**[0024]** Figure 8 shows an X-ray powder diffractogram of Form G of Ledipasvir.

**[0025]** Figure 9 shows an X-ray powder diffractogram of Form H of Ledipasvir obtained by example 8.

**[0026]** Figure 10 shows an X-ray powder diffractogram of Form C of Ledipasvir

**[0027]** Figure 11 shows an X-ray powder diffractogram of Form J of Ledipasvir.

**[0028]** Figure 12 shows an X-ray powder diffractogram of Form K of Ledipasvir.

**[0029]** Figure 13 shows an X-ray powder diffractogram of Form L of Ledipasvir.

**[0030]** Figure 14 shows an X-ray powder diffractogram of Form M of Ledipasvir, obtained by procedure 1 of example 14.

**[0031]** Figure 15 shows an X-ray powder diffractogram of Form M of Ledipasvir, obtained by procedure 2 of example 14.

**[0032]** Figure 16 shows an X-ray powder diffractogram of Form N of Ledipasvir, obtained by procedure 1 of example 15.

**[0033]** Figure 17 shows an X-ray powder diffractogram of Form N of Ledipasvir, obtained by procedure 2 of example 15.

**[0034]** Figure 18 shows an X-ray powder diffractogram of Form O of Ledipasvir.

**[0035]** Figure 19 shows an X-ray powder diffraction of form H of Ledipasvir obtained by example 17.

**[0036]** Figure 20 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 1 of example 18.

**[0037]** Figure 21 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 2 of example 18.

**[0038]** Figure 22 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 3 of example 18.

**[0039]** Figure 23 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 4 of example 18.

**[0040]** Figure 24 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 5 of example 18.

**[0041]** Figure 25 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 6 of example 18.

**[0042]** Figure 26 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 7 of example 18.

**[0043]** Figure 27 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 8 of example 18.

**[0044]** Figure 28 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 9 of example 18.

**[0045]** Figure 29 shows an X-ray powder diffraction of form P of Ledipasvir obtained by example 19.

**[0046]** Figure 30 shows an X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 1 of example 21.

**[0047]** Figure 31 shows an X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 2 of example 21.

**[0048]** Figure 32 shows an X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 3 of example 21.

**[0049]** Figure 33 shows an X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 4 of example 21.

**[0050]** Figure 34 shows an X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 10 of example 18.

**[0051]** Figure 35 shows the Solid-state 13C NMR spectrum of form G

## Detailed Description of the Disclosure

**[0052]** The present disclosure encompasses solid state forms of Ledipasvir. Solid state properties of Ledipasvir can be influenced by controlling the conditions under which the Ledipasvir is obtained in solid form.

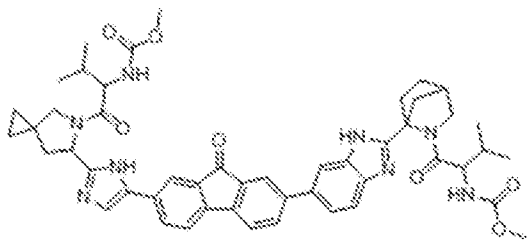
**[0053]** The present disclosure further encompasses novel processes for preparation of Ledipasvir.

**[0054]** The processes described in the literature have significant disadvantages. WO2010/132601 discloses a process having a very low overall yield (< 10%), and requiring the use of column chromatography for purification in several steps. The process uses toxic and costly solvents such as 1,4-dioxane, DME (dimethoxy ethane ) and xylene, as well as hazardous chemicals like NBS and tributyl (1-ethoxyvinyl) stannane and HATU [1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate], HBr in acetic acid and catalysts like As(PPh)3.

**[0055]** The alternative approach, disclosed in WO2013/184702 also involves the use of toxic and/or non-economical solvents such as 2-methoxy ethanol, t-amyl alcohol as well as non-economical reagents such as Bis(neopentyl glycolato)diboron, potassium propionate and PdCl2[(Pt-Bu)2Ph]2 and MePhos(2-dicyclohexylphosphino-2''methylbiphenyl)

**[0056]** In contrast to the prior art processes, the processes of the present disclosure avoids use of hazardous or non-economical reagents and solvents, several intermediates are not required to be isolated and others can be directly isolated with high yield and/or with high purity. Therefore, the processes of the present disclosure can be adapted to production in an industrial scale, i.e., greater than 1 kilogram scale.

**[0057]** Further, the process of the present disclosure provides Ledipasvir in overall high yield, of about 40%, and high quality, i.e. high chemical purity. Specifically, the process of the present disclosure provide Ledipasvir which contains about 0.1 % or less, preferably about 0.08% or less, more preferably 0.05% or less of methyl (1-(6-(5-(7-(2-(2-((methoxycarbonyl)valyl)-2-azabicyclo[2.2.1]heptan-1-yl)-1H-benzo[d]imidazol-6-yl)-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl)carbamate (herein designated as "keto impurity") as an impurity and is represented by the following structural formula:



**[0058]** Prior art ledipasvir/ledipasvir pharmaceutical compositions typically may contain quantities of the keto impurity.

**[0059]** In some embodiments, the crystalline forms of Ledipasvir of the disclosure are substantially free of any other forms of Ledipasvir, or of specified polymorphic forms of Ledipasvir, respectively.

**[0060]** As used herein, "substantially free" is meant that the solid state forms of the present disclosure contain about 20% (w/w) or less of polymorphs, or of a specified polymorph of Ledipasvir. According to some embodiments, the solid state forms of the present disclosure contain about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, about 0.5% (w/w) or less, or about 0.2% (w/w) or less of polymorphs, or of a specified polymorph of Ledipasvir. In other embodiments, solid state forms of Ledipasvir of the present disclosure contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of any solid state forms or of a specified polymorph of Ledipasvir.

**[0061]** Depending on which other solid state forms comparison is made, the crystalline forms of Ledipasvir of the present disclosure have advantageous properties selected from at least one of the following: chemical purity, flowability, solubility, dissolution rate, morphology or crystal habit, stability- such as chemical stability, thermal and/or mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

**[0062]** A solid state form, such as a crystal form or amorphous form, may be referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which cannot necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to certain factors such as, but not limited to, variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of

Ledipasvir referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure will thus be understood to include any crystal forms of Ledipasvir characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the Figure.

**[0063]** The modifier "about" should be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression "from about 2 to about 4" also discloses the range "from 2 to 4." When used to modify a single number, the term "about" may refer to plus or minus 10% of the indicated number and includes the indicated number. For example, "about 10%" may indicate a range of 9% to 11%, and "about 1" means from 0.9-1.1.

**[0064]** As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline forms of Ledipasvir, relates to a crystalline form of Ledipasvir which does not include any crystalline water (or other solvents) in a defined, stoichiometric amount within the crystal. Moreover, an "anhydrous" form would typically not contain more than about 1% (w/w), of either water or organic solvents as measured for example by TGA.

**[0065]** The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

**[0066]** As used herein, the term "isolated" in reference to solid state forms of Ledipasvir of the present disclosure corresponds to a solid state form of Ledipasvir that is physically separated from the reaction mixture in which it is formed.

**[0067]** As used herein, unless stated otherwise, the XRPD measurements are taken using copper Kα radiation wavelength of about 1.5418 Å.

**[0068]** As used herein, unless stated otherwise, chemical purity (area percent) may be measured by HPLC analysis. Preferably, the HPLC analysis is carried out using a reversed phase silica gel column (e.g. C18 column) using UV detection at 215 nm. Any suitable eluent can be used to carry out the separation (preferably a mixture of acetonitrile/isopropanol is used). Chemical purity may also be measured by wt%.

**[0069]** A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature" or "ambient temperature", often abbreviated as "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*,

the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C, or about 22°C to about 27°C, or about 25°C.

**[0070]** The amount of solvent employed in a chemical process, e.g., a reaction or crystallization, may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending a 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding solvent X (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of solvent X was added.

**[0071]** A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, *e.g.*, for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10-18 hours, typically about 16 hours.

**[0072]** As used herein, the term "reduced pressure" refers to a pressure that is less than atmospheric pressure. For example, reduced pressure is about 10 mbar to about 50 mbar.

**[0073]** As used herein, The term "Halo" means a halogeno group. Specifically, fluoro, chloro, bromo, or iodo. In preferred embodiments, "Halo" refers to chloro or bromo, and preferably bromo.

**[0074]** As used herein, and unless indicated otherwise, the term "one pot process" refers to a continuous process for preparing a desired product, in which penultimate product is converted to the desired product in the same vessel.

**[0075]** As used herein, and unless indicated otherwise, the term "Protecting group" refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group. Examples of protecting groups can be found in Green et al., "Protective Groups in Organic Chemistry", (Wiley,2$^{nd}$ ed. 1991) and Harrison et al., "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996).

**[0076]** Representative amine protecting groups include, but are not limited to, those where the amine group is converted to carbamate and amide such as Fmoc, cbz, benzyl, trityl, Boc, trifluoroacetyl derivative, phthalic anhydride, succinic anhydride derivative.

**[0077]** As used herein, Specific Surface area is defined in units of square meters per gram ($m^2/g$). Preferably, Specific Surface area as referred to herein, is measured by nitrogen absorption analysis (more preferably by Micromeritics TriStar II Plus surface area and porosity analyzer).

**[0078]** Specific Surface area (SSA) of an active pharmaceutical ingredient may be affected by various factors. There is a general connection between Specific Surface Area and Particle Size Distribution (PSD); the smaller the Particle Size, the higher the Specific Surface Area. Additional factors affecting SSA are the particle shape, the particle porosity, and inter-particle binding forces known to create aggregation. Generally high SSA is correlated to greater dissolution and bioavailability.

**[0079]** As used herein, unless otherwise indicated, the term "bulk density" designates the ratio between mass (weight) and bulk volume for the powder blend. Testing for bulk density is typically performed by determining the bulk volume and the weight of a dry powder in a graduated cylinder. The bulk volume in this case takes into consideration the volume of the powder as well as any void spaces that may exist. High bulk density is desirable for reducing shipping and packaging costs.

**[0080]** As used herein, the term "tapped density" refers to a density measurement of a substance that has been tapped or vibrated, thus minimizing the volume of the substance by eliminating or minimizing the air trapped between particles.

**[0081]** The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped and volume or mass readings are taken until little further volume or mass change is observed.

**[0082]** Preferably, as used herein, unless otherwise indicated, tapped density is measured by Jolting Volumeter STAV-II (Lengelsmann, AG, more preferably with dropping height 3 mm ± 0.1 mm) and tap speed: 250/min ± 15/min and measurement of volume after 1250 taps).

**[0083]** Carr's compressibility index (CI) and Hausner ratio (HR) are calculated according to the following equations – and provide a measure of the flow properties and compressability.

$$CI = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \times 100$$

$$HR = \frac{\rho tap}{\rho bulk}$$

where ρtap is the tapped density and ρbulk is the bulk density.

**[0084]** As used herein, and unless indicated otherwise, the term ledipasvir Premix refers to a co-precipitate of Ledipasvir with a pharmaceutically acceptable carrier, and optionally other pharmaceutically acceptable excipients. Such a co-precipitate may be prepared by mixing Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a mixture, and removing the solvent(s) from the mixture. The mixture may be a solution (e.g. wherein the components are dissolved), or a suspension or dispersion (e.g. wherein none of the components are dissolved but form a suspension or dispersion, or wherein some but not all of the components are dissolved). In a preferred embodiment according to any aspect of the present disclosure, the term ledipasvir Premix refers to a coprecipitate of Ledipasvir with copovidone, and optionally other pharmaceutically acceptable excipients.

**[0085]** In a preferred embodiment, a co-precipitate of Ledipasvir can be prepared by mixing Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a solution, and removing the solvent(s) from the solution.

**[0086]** In another preferred embodiment, a co-precipitate of Ledipasvir can be prepared by mixing Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a mixture wherein the pharmaceutically acceptable carrier is dissolved and the Ledipasvir is substantially undissolved, and removing the solvent(s) from the mixture.

**[0087]** In another preferred embodiment, a co-precipitate of Ledipasvir can be prepared by mixing Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a mixture wherein both the Ledipasvir and the pharmaceutically acceptable carrier form a suspension, and removing the solvent(s) from the mixture.

**[0088]** As used herein, and unless indicated otherwise, the term amorphous premix refers to a premix comprising substantially amorphous Ledipasvir. In a preferred embodiment, an amorphous premix may be prepared dissolving Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a solution, and removing the solvent(s) from the solution.

**[0089]** As used herein, and unless indicated otherwise, the term crystalline premix refers to a premix comprising ledipasvir wherein the ledipasvir is in substantially crystalline form. In a preferred embodiment, a crystalline premix can be prepared by mixing Ledipasvir and a pharmaceutically acceptable carrier and optionally other pharmaceutically acceptable excipients in solvent(s) to form a mixture wherein the pharmaceutically acceptable carrier is dissolved and wherein the Ledipasvir is substantially undissolved, and removing the solvent(s) from the mixture.

**[0090]** As used herein, and unless indicated otherwise, the term "substantially amorphous" is intended to mean greater than about 70%; or greater than about 75%; or greater than about 80%; or greater than about 85%; or greater than about 90%; or greater than about 95%, or greater than about 99% of the compound present in a composition is in amorphous form.

**[0091]** As used herein, and unless state indicated otherwise, the term "substantially crystalline" is intended to mean that greater than about 70%; or greater than about 75%; or greater than about 80%; or greater than about 85%; or greater than about 90%; or greater than about 95%, or greater than about 99% of the compound is present in a composition is in crystalline form.

**[0092]** As used herein crystalline form III of Ledipasvir refers to a crystalline form which may be characterized by X-ray powder diffraction pattern as depicted in Figure 7.

**[0093]** In one embodiment, the present disclosure comprises a crystalline form of Ledipasvir, designated form A, having an X-ray powder diffraction pattern substantially as depicted in Figure 1, wherein form A is not an acetone solvate.

**[0094]** Crystalline form A of Ledipasvir may be further characterized by an X-ray powder diffraction pattern having peaks at 6.5, 9.0 and 12.5 degrees two theta ± 0.2 degrees two theta. Alternatively, crystalline form A of Ledipasvir may be characterized by an X-ray powder diffraction pattern having peaks at 6.5, 9.0 and 12.5 degrees two theta ± 0.2 degrees two theta and the absence of peaks at 10.2, 19.8 and 23.8 degrees two theta ± 0.1 degrees two theta. In one embodiment of the present disclosure, form A of Ledipasvir is isolated.

**[0095]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form B, having an X-ray powder diffraction pattern substantially as depicted in Figure 2, wherein form B is not an acetone solvate. Crystalline form B of Ledipasvir may be further characterized by X-ray powder diffraction pattern having peaks at 6.9, 9.6 and 13.5 degrees two theta ± 0.2 degrees two theta.

**[0096]** Alternatively, crystalline form B of Ledipasvir may be characterized by an X-ray powder diffraction pattern having peaks at 6.9, 9.6 and 13.5 degrees two theta ± 0.2 degrees two theta and the absence of a peak at 11.0 degrees two theta ± 0.1 degrees two theta.

**[0097]** Crystalline form B of Ledipasvir may be a hydrate. In certain embodiments form B may contain from about 2% to about 6% of water by weight, preferably about 3 % of water by weight as measured by Karl Fischer titrator and TGA. In certain embodiments, crystalline form B of Ledipasvir may be a mono to trihydrate.

**[0098]** In one embodiment of the present disclosure, form B of Ledipasvir is isolated.

**[0099]** In another aspect the present disclosure relates to solid state form of Ledipasvir, preferably in crystalline form, wherein said form is a hydrate.

**[00100]** In another aspect the present disclosure relates to solid state form of Ledipasvir, preferably in crystalline form, wherein said form contain from about 2% to about 6% of water, preferably about 3% of water by weight.

**[00101]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form C, characterized by X-ray powder diffraction pattern having peaks at 6.8, 8.8, 12.3 and 20.4 degrees two theta ± 0.1 degrees two theta.

**[00102]** Alternatively, crystalline form C of Ledipasvir may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 3 or in Figure 10. Crystalline form C of Ledipasvir may be further characterized by X-ray powder diffraction pattern having peaks at 6.8, 8.8, 12.3 and 20.4 degrees two theta ± 0.1 degrees two theta.

**[00103]** In one embodiment of the present disclosure, form C of Ledipasvir is isolated.

**[00104]** In some embodiments, crystalline form C may be an acetone and cyclohexane solvate. In certain embodiments, form C may contain from about 5 % to about 7 % of acetone and from about 2 % to about 5 % of cyclohexane, specifically, about 6 % of acetone and about 2.5% of cyclohexane by weight.

**[00105]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form D, characterized by X-ray powder diffraction pattern having peaks at 6.7, 12.3, 18.2 and 23.6 degrees two theta ± 0.1 degrees two theta.

**[00106]** Alternatively, crystalline form D may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 4.

**[00107]** In yet another alternative, form D can be characterized by a combination of these data.

**[00108]** In one embodiment of the present disclosure, form D of Ledipasvir is isolated.

**[00109]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form E, characterized by X-ray powder diffraction pattern having peaks at 8.7, 12.3, 18.2 and 22.6 degrees two theta ± 0.1 degrees two theta. In certain embodiments, form E is not a methyl ethyl ketone (MEK) solvate.

**[00110]** Alternatively, crystalline form E may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 5. Crystalline form E of Ledipasvir may be further characterized by X-ray powder diffraction pattern having peaks at 8.7, 12.3, 18.2 and 22.6 degrees two theta ± 0.1 degrees two theta.

**[00111]** In one embodiment of the present disclosure, form E of Ledipasvir is isolated.

**[00112]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form F, characterized by X-ray powder diffraction pattern having peaks at 10.2, 12.3, 17.4 and 21.6 degrees two theta ± 0.1 degrees two theta. In some embodiments, form F is not a methyl tert-butyl ether (MTBE) solvate.

**[00113]** Alternatively, crystalline form F may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 6. Crystalline form F of Ledipasvir may be further characterized by X-ray powder diffraction pattern having peaks at 10.2, 12.3, 17.4 and 21.6 degrees two theta ± 0.1 degrees two theta.

**[00114]** In one embodiment of the present disclosure, form F of Ledipasvir is isolated.

**[00115]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form G, characterized by data selected from: an X-ray powder diffraction pattern substantially as depicted in Figure 8; an X-ray powder diffraction pattern having peaks at 7.3, 14.0, 19.5 and 20.4 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta; or any combination thereof. Crystalline form G of Ledipasvir may be further characterized by an X-ray powder diffraction pattern having an additional peak at 26.6 degrees two theta ± 0.1 degrees two theta.

**[00116]** Alternatively, crystalline form G of Ledipasvir may be characterized by data selected from: an X-ray powder diffraction pattern substantially as depicted in Figure 8; an X-ray powder diffraction pattern having peaks at 7.3, 9.5, 11.3, 12.1, 14.0, 19.5, 20.4 and 26.6 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta; or any combination thereof.

**[00117]** In yet another alternative, crystalline form G may be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 8.7, 13.2, 14.6, 15.5, 17.2, 18.0, 23.1, 24.2, 24.9 and 26.6 degrees two theta ± 0.1 degrees two theta. Crystalline form G of Ledipasvir may be further characterized by an X-ray powder diffraction pattern having no peaks 3.2 and 12.7 degrees two theta ± 0.1 degrees two theta.

**[00118]** Alternatively, crystalline form G may be characterized by data selected from: a solid state 13C NMR spectrum having peaks at 139.5, 137.7, 122.0 and 111.8 ppm ± 0.2 ppm; a solid state 13C NMR spectrum having chemical shift differences between said characteristic peaks at 139.5, 137.7, 122.0 and 111.8 ppm ± 0.2 ppm and a reference peak at 107.4 ppm ± 0.2 ppm of 32.1, 30.3, 14.6 and 4.4 and ppm ± 0.1 ppm , respectively; a solid state 13C NMR spectrum substantially as depicted in Figure 35; or any combination thereof

**[00119]** Crystalline form G of Ledipasvir may be further characterized by data selected from: a solid state 13C NMR spectrum with peaks at 61.5, 40.0, 38.4 and 25.4 ppm ± 0.2 ppm; a solid state 13C NMR spectrum having chemical shift differences between said characteristic peaks at 61.5, 40.0, 38.4 and 25.4 ppm ± 0.2 ppm and a reference peak at 107.4 ppm ± 0.2 ppm of 45.9, 67.4, 69.0 and 82.0 and ppm ± 0.1 ppm , respectively; or combination thereof.

**[00120]** Form G may be characterized by any one of the above embodiments or any combination thereof.

**[00121]** In any of the above embodiments for Form G, the form G may be an acetone solvate or an acetone and MDC solvate.

**[00122]** In certain embodiments, crystalline form G may be an acetone solvate. In certain embodiments, Form G may contain from about 3 % to about 7 % of acetone, preferably about 5 % of acetone by weight.

**[00123]** In other embodiments, Form G may contain from about 3 % to about 7 % of acetone and from about 1% to about 3% of MDC, preferably, about 5 % of acetone and about 2% MDC by weight.

**[00124]** In one embodiment of the present disclosure, form G of Ledipasvir is isolated.

**[00125]** Crystalline Form G of Ledipasvir may be characterized by each of the above characteristics alone and/or by all possible combinations, e.g. by an X-ray powder diffraction pattern having peaks at 7.3, 14.0, 19.5 and 20.4 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta wherein form G is an acetone solvate.

**[00126]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form H, characterized by data selected from: an X-ray powder diffraction pattern substantially as depicted in Figure 9; an X-ray powder diffraction pattern substantially as depicted in Figure 19; X-ray powder diffraction pattern having peaks at 17.0, 19.0, 19.8 and 20.9 degrees two theta ± 0.1 degrees two theta and having no peaks at 12.8 and 16.7 degrees two theta ± 0.1 degrees two theta; or any combination thereof.

**[00127]** Alternatively crystalline form H of Ledipasvir may be characterized by data selected from: an X-ray powder diffraction pattern substantially as depicted in Figure 9; an X-ray powder diffraction pattern substantially as depicted in Figure 19; X-ray powder diffraction pattern having peaks at 7.6, 9.0, 12.1, 17.0 and 19.0 degrees two theta ± 0.1 degrees two theta and having no peaks at 12.8 and 16.7 degrees two theta ± 0.1 degrees two theta; or any combination thereof.

**[00128]** In some embodiments, crystalline form H may be anhydrous.

**[00129]** In one embodiment of the present disclosure, form H of Ledipasvir is isolated. Crystalline Form H of Ledipasvir may be characterized by each of the above characteristics alone and/or by all possible combinations, e.g. by an X-ray powder diffraction pattern having peaks at 17.0, 19.0, 19.8 and 20.9 degrees two theta ± 0.1 degrees two theta and having no peaks at 12.8 and 16.7 degrees two theta ± 0.1 degrees two theta wherein form H is anhydrous.

**[00130]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form J. Form J may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 11. Form J may be further characterized by an X-ray powder diffraction pattern having peaks at 7.2, 8.9, 12.2, 17.2, 18.0, 19.3, 20.8 and 21.3 degrees two theta ± 0.2 degrees two theta.

**[00131]** In some embodiments, crystalline form J may be a cyclohexane solvate. In certain embodiments, Form J may contain from about 2 % to about 7 % of cyclohexane by weight.

**[00132]** In an alternative embodiment, crystalline form J may be characterized by an X-ray powder diffraction pattern having peaks at 7.2, 8.9, 17.2, 18.0 and 19.3 degrees two theta ± 0.1 degrees two theta wherein form J is a cyclohexane solvate.

**[00133]** In one embodiment of the present disclosure, form J of Ledipasvir is isolated.

**[00134]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form K. Form K may be characterized by an X-ray powder diffraction

pattern substantially as depicted in Figure 12. Form K may be further characterized by an X-ray powder diffraction pattern having peaks at 5.4, 7.1, 11.2, 12.1, 13.8, 15.3, 20.1, 21.5 and 22.5 degrees two theta ± 0.2 degrees two theta.

**[00135]** In some embodiments, crystalline form K may be a cyclohexane solvate. In certain embodiments, Form K may contain from about 2 % to about 7 % of cyclohexane by weight.

**[00136]** In an alternative embodiment, crystalline form K may be characterized by X-ray powder diffraction pattern having peaks at 5.4, 7.1, 11.2, 13.8 and 15.3 degrees two theta ± 0.1 degrees two theta, with the absence of peaks at 6.7 and 16.8 degrees two theta ± 0.1 degrees two theta wherein form K is a cyclohexane solvate.

**[00137]** In one embodiment of the present disclosure, form K of Ledipasvir is isolated.

**[00138]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form L. Form L may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 13. Form L may be further characterized by an X-ray powder diffraction pattern having peaks at 3.3, 6.7, 8.7, 10.0, 12.2, 16.0, 16.8, 17.8, 18.8, 21.5, 24.9 and 26.1 degrees two theta ± 0.2 degrees two theta.

**[00139]** In some embodiments, crystalline form L may be a cyclohexane solvate. In certain embodiments, Form L may contain from about 2 % to about 7 % of cyclohexane by weight.

**[00140]** In an alternative embodiment, crystalline form L may be characterized by X-ray powder diffraction pattern having peaks at 3.3, 6.7, 8.7, 10.0, 16.0 and 21.5 degrees two theta ± 0.1 degrees two theta wherein form L is a cyclohexane solvate.

**[00141]** In one embodiment of the present disclosure, form L of Ledipasvir is isolated.

**[00142]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form M. Form M may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 14 or Figure 15. Form M may be further characterized by an X-ray powder diffraction pattern having peaks at 7.0, 11.2, 22.6 and 24.7 degrees two theta ± 0.1 degrees two theta

**[00143]** In some embodiments, crystalline form M may be an acetone/toluene solvate. In certain embodiments, Form M may contain from about, 3% to about 10% of acetone by weight and from about 2% to about 10% of toluene by weight, preferably from

about 3 % to about 8 % of acetone by weight and from about 2 % to about 7 % of toluene by weight.

**[00144]** In an alternative embodiment, crystalline form M may be characterized by an X-ray powder diffraction pattern having peaks at 7.0, 11.2, 22.6 and 24.7 degrees two theta ± 0.1 degrees two theta, wherein form M is an acetone/toluene solvate.

**[00145]** Form M may be further characterized by an X-ray powder diffraction pattern having no peaks at 9.3, 17.8, 23.1 and 23.8 degrees two theta ± 0.1 degrees two theta

**[00146]** Form M may be characterized by any one of the above embodiments or any combination thereof.

**[00147]** In other embodiments of the present disclosure, form M of Ledipasvir is isolated.

**[00148]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form N. Form N may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 16 or Figure 17. Form N may be further characterized by an X-ray powder diffraction pattern having peaks at 11.5, 15.2 and 19.2 degrees two theta ± 0.1 degrees two theta.

**[00149]** In some embodiments, crystalline form N may be anhydrous.

**[00150]** In alternative embodiments, crystalline form N may be characterized by an X-ray powder diffraction pattern having peaks at 11.5, 15.2 and 19.2 degrees two theta ± 0.1 degrees two theta, wherein form N is anhydrous.

**[00151]** Form N may be further characterized by X-ray powder diffraction pattern having peaks at 7.6 and 24.6 degrees two theta ± 0.1 degrees two theta and having no peaks at 9.4, 21.3 and 21.6 degrees two theta ± 0.1 degrees two theta.

**[00152]** Form N may be characterized by any one of the above embodiments or any combination thereof.

**[00153]** In some embodiments of the present disclosure, form N of Ledipasvir is isolated.

**[00154]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form O. Form O may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 18. Form O may be further characterized by an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta, X-ray powder diffraction pattern with no peaks at 7.6 and 21.3 degrees two theta ± 0.1 degrees two theta; or combination thereof.

**[00155]** In some embodiments, crystalline form O may be an acetonitrile/toluene solvate. In certain embodiments, Form O may contain from about 0.5 % to about 2.0 % of acetonitrile by weight and from about 2.5% to about 12% of toluene by weight, preferably from about 0.5% to about 2.0% of acetonitrile by weight and from about 3 % to about 9 % of toluene by weight, and more preferably about 2% of acetonitrile and about 9% of toluene by weight.

**[00156]** In alternative embodiments, crystalline form O may be characterized by an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta, wherein form O is an acetonitrile/toluene solvate.

**[00157]** Form O may be characterized by any one of the above embodiments or any combination thereof.

**[00158]** In some embodiments of the present disclosure, form O of Ledipasvir is isolated.

**[00159]** In another aspect, the present disclosure comprises a crystalline form of Ledipasvir, designated form P. Form P may be characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 29. Form P may be further characterized by an X-ray powder diffraction pattern having peaks at 7.4, 9.0, 11.4, 18.8, 19.6 and 21.7 degrees two theta ± 0.1 degrees two theta, X-ray powder diffraction pattern having peaks at 12.3, 20.6, 14.8, 18.2 and 24.0 degrees two theta ± 0.1 degrees two theta; or combination thereof.

**[00160]** In some embodiments, crystalline form P may be an acetonitrile/MDC (dichloromethane) solvate. In certain embodiments, Form P may contain from about 2 % to about 4% of acetonitrile by weight and from about 2 % to about 4% of MDC by weight, preferably about 2% acetonitrile and about 3% of MDC by weight.

**[00161]** In certain embodiments, Form P may be characterized by an X-ray powder diffraction pattern having peaks at 7.4, 9.0, 11.4, 18.8, 19.6 and 21.7 degrees two theta ± 0.1 degrees two theta wherein form P is a MDC/ acetonitrile solvate.

**[00162]** Form P may be characterized by any one of the above embodiments or any combination thereof.

**[00163]** In some embodiments of the present disclosure, form P of Ledipasvir is isolated.

**[00164]** In another aspect the present disclosure provides a process for preparing crystalline form B comprising crystallizing Ledipasvir from a mixture of water and acetonitrile. In one embodiment the present disclosure provides a process for preparing crystalline form B comprising a) combining ledipasvir with a solvent system comprising an

organic solvent and water; b) optionally heating to a temp of about 0 °C to about 80 °C; c) cooling to about 20 °C to about 25 °C; d) optionally seeding with form B seeds; e) optionally adding water; and f) isolating Crystalline form B.

**[00165]** Preferably, the organic solvent in step a is acetonitrile or acetone and the mixture in step a comprises about 20% to about 50%, more preferably about 30 % of water (by volume) in the organic solvent. Preferably, the heating in step b is to a temperature of about 20 °C to about 70°C and the reaction mass is stirred for 1-2 hours.

**[00166]** Preferably the process of the present disclosure is performed with stirring.

**[00167]** The crystalline form B can be isolated by any method known in the art, For example, crystalline form B of Ledipasvir can be separated by filtering the slurry or decanting the solvent from the slurry. The isolating method can further comprise washing and drying the crystalline form B of Ledipasvir. Preferably crystalline form B of Ledipasvir is dried at a temperature of about 50 °C to about 90 °C, more preferably at a temperature of about 70 °C to about 85 °C under reduced pressure.

**[00168]** In a specific embodiment the present disclosure provides a process for preparing crystalline form B of Ledipasvir comprising a) combining ledipasvir with a solvent system comprising 30% acetonitrile in water, b) heating to a temperature of about 20 °C to about 70 °C and stirring for 1-5 hours, c) cooling to about 20 °C to about 25 °C and optionally stirring, d) seeding with form B seeds e) adding water 3-10 vol and optionally stirring and f) isolating crystalline form B.

**[00169]** In another aspect the disclosure relates to form B produced by the above described process.

**[00170]** In another aspect the present disclosure provides a process for preparing crystalline form G comprising crystallizing Ledipasvir from a mixture of MDC and acetone. In one embodiment the present disclosure provides a process for preparation of form G comprising a) providing a solution of ledipasvir in MDC, b) adding acetone, c) stirring and d) separating the crystalline solid formed and optionally drying.

**[00171]** In another aspect the present disclosure provides a process for preparing crystalline form G comprising recrystallizing a Ledipasvir acetone solvate from water. In one embodiment the present disclosure provides a process for preparation of form G comprising a) providing a Ledipasvir acetone solvate in water, b) heating the reaction mass to a temperature of about 30 °C to about 60 °C, preferably to a temperature of 45 °C to about 50 °C, optionally under stirring, c) cooling to a temperature of 20 °C to about 25 °C and d) separating the crystalline solid formed and optionally drying. Preferably, the reaction

mixture in step a and/or b is heated to about 20°C to about 40 °C., more preferably to about 35 °C. Preferably the Ledipasvir acetone solvate can be Ledipasvir diacetone solvate.

**[00172]** Preferably the process of the present disclosure for preparation of form G is performed with stirring.

**[00173]** The crystalline form G can be isolated by any method known in the art, For example, crystalline form G of Ledipasvir can be separated by filtering the slurry or decanting the solvent from the slurry. The isolating method can further comprise washing and drying the crystalline form G of Ledipasvir. Preferably crystalline form G of Ledipasvir is dried at a temperature of about 0°C to about 40°C under reduced pressure, more preferably at a temperature of about 30°C to about 40°C, under reduced pressure.

**[00174]** In another aspect the disclosure relates to form G produced by the above described process.

**[00175]** In another aspect the present disclosure provides a process for preparing crystalline form P comprising crystallizing Ledipasvir from a mixture of MDC and acetonitrile. In one embodiment the present disclosure provides a process for preparation of form P comprising a) providing a solution of ledipasvir in MDC, b) adding acetonitrile, c) stirring and d) separating the crystalline solid formed.

**[00176]** Preferably, the reaction mixture in step a and b is heated to a temperature of about 20°C to about 40°C, more preferably to a temperature of about 35°C to about 40°C.

**[00177]** Preferably the process of the present disclosure for preparation of form P is performed with stirring.

**[00178]** The crystalline form P can be isolated by any method known in the art, For example, crystalline form P of Ledipasvir can be separated by filtering the slurry or decanting the solvent from the slurry. The isolating method can further comprise washing and drying the crystalline form P of Ledipasvir. Preferably crystalline form P of Ledipasvir is dried at a temperature of about 0°C to about 40°C under reduced pressure, more preferably at a temperature of about 30°C to about 40°C under reduced pressure.

**[00179]** In another aspect the disclosure relates to form P produced by the above described process.

**[00180]** In another aspect the present disclosure provides a process for preparation of form H comprising drying of form G or form P. Preferably crystalline form G of Ledipasvir is dried at a temperature of about 40°C to about 110°C, more preferably at a temperature of about 95°C to about 100°C under reduced pressure.

**[00181]** In another aspect the disclosure relates to form H produced by the above described process.

**[00182]** In another aspect the present disclosure provides a process for preparing crystalline form M comprising crystallizing Ledipasvir from a mixture of toluene and acetone.

**[00183]** In one embodiment the present disclosure provides a process for preparation of form M comprising a) providing a solution comprising ledipasvir, toluene and acetone, b) stirring c) isolating crystalline form M.

**[00184]** Preferably, the solution in step a comprises about 40% to about 45% of toluene (by volume) in acetone. Preferably the stirring in step b is performed for about 7 to about 24 hours. Preferably, the reaction mixture in steps a and b is heated to a temperature of about 10°C to about 70°C , more preferably to a temperature of about 20°C to about 30°C.

**[00185]** Preferably the process of the present disclosure for preparation of form M is performed with stirring.

**[00186]** The crystalline form M can be isolated by any method known in the art, For example, crystalline form M of Ledipasvir can be separated by filtering the slurry or decanting the solvent from the slurry. The isolating method can further comprise washing and drying the crystalline form M of Ledipasvir. Preferably crystalline form M of Ledipasvir is dried at a temperature of about 0°C to about 40°C under reduced pressure, more preferably at a temperature of about 30°C to about 40°C under reduced pressure.

**[00187]** In another aspect the disclosure relates to form M produced by the above described process

**[00188]** In another aspect the present disclosure provides a process for preparing crystalline form O comprising crystallizing Ledipasvir from a mixture of toluene and acetonitrile.

**[00189]** In one embodiment the present disclosure provides a process for preparation of form O comprising a) providing a solution of ledipasvir in toluene c) optionally cooling to about 25 °C to about 30 °C, d) adding acetonitrile e) optionally cooling to about 0 °C to about 5 °C, f) optionally seeding with form M seeds or form O seeds and stirring and g) isolating crystalline form O

**[00190]** In one embodiment the present disclosure provides a process for preparation of form O comprising a) providing a solution comprising ledipasvir, toluene and acetonitrile, optionally at elevated temperature, b) optionally adding charcoal and passing the reaction mass through diatomaceous earth (e.g. Celite®), c) cooling to about 25 °C to about 30 °C d) adding acetonitrile e) cooling to about 0 °C to about 10 °C, f) seeding with form M

seeds or form O seeds and stirring and g) separating the crystalline solid formed. Alternatively, step f can be performed prior to step e. Preferably, the solution in step a comprises about 50% to about 60% of toluene (by volume) in acetonitrile, the stirring in step f is for about 2 to about 30 hours and the drying in step g is carried for about 0.5 to about 1.0 hours at a temperature of from about 10°C to about 40°C.

**[00191]** Preferably, the reaction mixture in step a is heated to a temperature of about 40°C to about 80°C, more preferably to a temperature of about 50°C to about 55°C. The solution obtained in step a can be filtered, if desired, to dispose of foreign particles while maintaining the filtered solution and filtrate at almost the same temperature.

**[00192]** Preferably the process of the present disclosure for preparation of form O is performed with stirring.

**[00193]** The crystalline form O can be isolated by any method known in the art, For example, crystalline form O of Ledipasvir can be separated by filtering the slurry or decanting the solvent from the slurry. The isolating method can further comprise washing and drying the crystalline form O of Ledipasvir. Preferably crystalline form O of Ledipasvir is dried at a temperature of about 0°C to about 40°C, more preferably at a temperature of about 20°C to about 30°C under reduced pressure.

**[00194]** In another aspect the disclosure relates to form O produced by the above described process.

**[00195]** In another aspect the present disclosure provides a process for preparation of form N comprising drying of form M. Preferably crystalline form M of Ledipasvir is dried at a temperature of about 50°C to about 110°C , more preferably at a temperature of about 80°C to about 105°C under reduced pressure.

**[00196]** In another aspect the disclosure relates to form N produced by the above described process.

**[00197]** The solid forms of the present disclosure may exhibit favourable specific surface area properties. In a preferred embodiment, crystalline form B exhibits preferred specific surface area properties. Form B exhibits a specific surface are of above $100m^2/g$, preferably of about $110m^2/g$. Preferably, crystalline form B exhibits a specific surface area (SSA) of from: 10-500 $m^2/g$, 20-400 $m^2/g$, 50-300 $m^2/g$, 70-200 $m^2/g$, 80-150 $m^2/g$ or 90-120 $m^2/g$. Preferably, crystalline form B exhibits a specific surface area (SSA) of from: 10-500 $m^2/g$, 20-400 $m^2/g$, 50-300 $m^2/g$, 70-200 $m^2/g$, 80-150 $m^2/g$ or 90-120 $m^2/g$.

**[00198]** In another aspect the present disclosure relates to a solid form of Ledipasvir, preferably in crystalline form having a specific surface area (SSA) of not less than 10 $m^2/g$,

preferably not less than 50 $m^2/g$, more preferably not less than 90 $m^2/g$. In preferred embodiments, the solid form of Ledipasvir, preferably in crystalline form has a specific surface area (SSA) of from: 10-500 $m^2/g$, 20-400 $m^2/g$, 50-300 $m^2/g$, 70-200 $m^2/g$, 80-150 $m^2/g$ or 90-120 $m^2/g$. The solid form may be any crystalline or amorphous form of Ledipasvir, preferably, the crystalline form may be any one of the forms disclosed in the present application. In one embodiment, the crystalline form is form B.

**[00199]** Gravimetric moisture sorption/ desorption experiments were conducted with crystalline forms H and N of the present disclosure. These forms exhibit advantageous hygroscopic properties. Crystalline forms N and H are non-hygroscopic and show less interaction with water vapor at 10%, 20%, 30%, 40%, 50%, 60%, 70% and even at 80% RH (relative humidity, temperature 25°C ± 0.1 °C). The novel crystalline form H and N show a water adsorption of only about 0.5 weight % at 80 % RH. Both forms H and N preserve their initial powder characteristics.

**[00200]** Thus, in a further embodiment of the present disclosure, there is provided a solid state form of Ledipasvir as described in any embodiment described herein (preferably wherein the solid state form is any one of forms B, H, N or O as defined in any embodiment described herein, or particularly one of forms H, N or O as defined in any embodiment described herein, and most preferably, forms H and N) which is non-hygroscropic. Thus, by "non-hygroscopic" it is meant that the solid state form of Ledipasvir shows a water adsorption of: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.6 wt%, ≤ 0.5 wt%, ≤ 0.3 wt%, ≤ 0.1 wt%, or ≤ 0.05 wt%, following storage at for 1 month 25°C and at 40% RH. Preferably, the solid state form of Ledipasvir shows a water adsorption of: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.6 wt%, ≤ 0.5 wt%, ≤ 0.3 wt%, ≤ 0.1 wt%, or ≤ 0.05 wt%, following storage at for 1 month 25°C and at 50% RH. More preferably, the solid state form of Ledipasvir shows a water adsorption of: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.6 wt%, ≤ 0.5 wt%, ≤ 0.3 wt% or ≤ 0.1 wt%, following storage at for 1 month 25°C and at 60% RH. Even more preferably, the solid state form of Ledipasvir shows a water adsorption of: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.6 wt%, ≤ 0.5 wt%, ≤ 0.3 wt%, following storage at for 1 month 25°C and at 70% RH. Most preferably, the solid state form of Ledipasvir shows a water adsorption of: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.6 wt% or ≤ 0.5 wt% following storage at for 1 month 25°C and at 80% RH.

**[00201]** Thus, in a further embodiment of the present disclosure, there is provided a pharmaceutical composition comprising a solid form of Ledipasvir as described in any embodiment, wherein the ledipasvir retains its initial solid state form. Particularly, the solid state form does not become sticky or viscous. Preferably, the term "retains its initial solid

state form" means that: ≤ 10%, ≤ 8%, ≤ 6%, ≤ 5%, ≤ 3%, ≤ 2%, ≤ 1%, ≤ 0.5% or ≤ 0.2% (more preferably ≤ 5%, ≤ 3%, ≤ 2%, ≤ 1% or ≤ 0.5%) of the ledipasvir converts to a different solid state form, as measured by XRPD. For example, the ledipasvir may retain its initial solid state form following storage at 25°C for 1 month at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH, more preferably following storage at 25°C for 3 months at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH, and most preferably following storage at 25°C for 12 months at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH.

**[00202]** Crystalline forms M, O and P exhibit advantageous flow properties. The novel crystalline form M, O, and P exhibit higher bulk density 0.274 (mg/mL), 0.253(mg/mL), and 0.241(mg/mL) respectively. High bulk density is desirable for reducing shipping and packaging costs.

**[00203]** The Carr's compressibility index (CI, %) and Hausner ratio (HR) were also calculated based on the equations. The CI and HR were found to be relatively low for the novel crystalline form M, O and P. This is in accordance with density measurements. CI is a measure of powder bridge strength and stability, and the Hausner ratio (HR) is a measure of the interparticulate friction. Flow character is rated based on compressibility index and Hausner ratio. Lower CI or lower Hausner ratios of a material indicate better flow properties than higher ones. The table below shows the CI and HR values, as well as bulk densities and tap densities for forms P, O and M, according to the disclosure.

| Form | Bulk Density (mg/ml) | Tapped Density (mg/ml) | Hausner Ratio HR | Compressibility index CI (%) |
|---|---|---|---|---|
| P | 0.241 | 0.402 | 1.67 | 40 |
| O | 0.253 | 0.380 | 1.50 | 33 |
| M | 0.274 | 0.466 | 1.70 | 41 |

**[00204]** Crystalline forms B, G, H, M, N, O and P of the present disclosure exhibit a high level of purity, i.e. >99%.

**[00205]** It was surprisingly found that the following solvent systems – acetonitrile/toluene, acetonitrile/MDC, THF/toluene, acetone/toluene/ and acetone/MDC have excellent purification power and that Ledipasvir of a purity of about 91-95% before crystallization may be purified to a level of >99% by crystallization using the above solvent systems. Specifically, Ledipasvir having a purity of about 91-95% before crystallization was improved to >99% when any one of forms G, M, O and P were isolated.

**[00206]** In another aspect the disclosure relates to processes for purification of ledipasvir comprising crystallization from any one of the following solvent systems: acetonitrile/toluene, acetonitrile/MDC, THF/toluene, acetone/toluene and acetone/MDC and isolating the crystalline material.

**[00207]** In certain embodiments the crystalline forms isolated by the above processes may be forms any one of forms G, M, O or P, preferably form O or form P

**[00208]** Further, it was surprisingly found that Ledipasvir produced by the processes of the present disclosure contains about 0.1 % or less, preferably 0.08% or less, more preferably 0.05% or less of the keto impurity discussed above. The content of keto-impurity ledipasvir is measured by HPLC. Ledipasvir produced by the process according to any aspect or embodiment of the present disclosure may alternatively contain: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or ≤ 0.05 wt%) of the keto impurity discussed above.

**[00209]** Moreover, it has been surprisingly found that Ledipasvir produced by the processes of the present disclosure may have a total impurity content of: not more than 0.3% area percent, preferably not more than 0.2% area percent, more preferably not more than 0.1% area percent, particularly not more than 0.08% area percent, and most preferably not more than 0.05% area percent, as measured by HPLC. Ledipasvir produced by the process according to any aspect or embodiment of the present disclosure may alternatively contain: ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or ≤ 0.05 wt%) of total impurities.

**[00210]** In another aspect the disclosure relates to a solid form of Ledipasvir, wherein the content of the keto impurity is 0.1 % or less, preferably 0.08% or less, more preferably 0.05% or less of the keto impurity discussed above. According to a further aspect of the present disclosure, there is provided a solid form of Ledipasvir wherein the content of the keto impurity is: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or

≤ 0.05 wt%). The solid form may be any crystalline form, amorphous form, crystalline premix and any amorphous premix comprising ledipasvir, preferably an amorphous premix. In the case of a premix, the % of the keto impurity is calculated with respect to the amount of ledipasvir in the premix.

**[00211]** In another aspect the disclosure relates to a solid form of Ledipasvir, wherein the total impurity content is not more than 0.3% area percent, preferably not more than 0.2% area percent, more preferably not more than 0.1% area percent, particularly not more than 0.08% area percent, and most preferably not more than 0.05% area percent, as measured by HPLC. According to a further aspect of the present disclosure, there is provided a solid form of Ledipasvir wherein the total impurity content is: ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or ≤ 0.05 wt%). The solid form may be any crystalline form, amorphous form, crystalline premix and any amorphous premix comprising ledipasvir, preferably an amorphous premix. In the case of a premix, the % of the keto impurity is calculated with respect to the amount of ledipasvir in the premix.

**[00212]** In one embodiment the crystalline form may be selected from the group consisting of forms B, G, H, M, N, O and P.

**[00213]** In another embodiment the amorphous premix may be prepared by the processes of the present disclosure.

**[00214]** In another aspect the disclosure relate to Forms G, M, O, P, B, H and N wherein the level of the keto impurity is 0.1 % or less, preferably 0.08% or less, more preferably 0.05% or less of the keto impurity discussed above. Alternatively the present disclosure provides Forms G, M, O, P, B, H and N of Ledipasvir wherein the level of the keto impurity is: ≤ 1 wt%, ≤ 0.8 wt%, ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or ≤ 0.05 wt%).

**[00215]** In another aspect the disclosure relate to Forms G, M, O, P, B, H and N wherein the total impurity content is: not more than 0.3% area percent, preferably not more than 0.2% area percent, more preferably not more than 0.1% area percent, particularly not more than 0.08% area percent, and most preferably not more than 0.05% area percent, as measured by HPLC. Alternatively the present disclosure provides Forms G, M, O, P, B, H and N of Ledipasvir wherein the total impurity content is: ≤ 0.5 wt%, ≤ 0.25 wt%, ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt% (preferably ≤ 0.2 wt%, ≤ 0.1 wt% or ≤ 0.05 wt%, and more preferably ≤ 0.1 wt% or ≤ 0.05 wt%).

**[00216]** All of the solid state forms disclosed above can be used to prepare other solid state forms of Ledipasvir, Ledipasvir salts and their solid state forms. Any of the above solid state forms of ledipasvir can be used to prepare amorphous ledipasvir or ledipasvir salts. Preferably forms G, M, O and P may be converted to other crystalline forms of Ledipasvir. More preferably, forms G and P may be used for preparation of form H, form M and O may be used for preparation of form N and form O, M may be used for the preparation of form B.

**[00217]** All of the solid state forms of ledipasvir disclosed above or amorphous ledipasvir can be used for preparation of Ledipasvir pre-mix. Preferably, the disclosure provides the use of any one of Forms G, M, O and P as well as B, H and N for the preparation of ledipasvir Premix. The disclosure also provides for forms G, M, O and P as well as B, H and N for use for the preparation of ledipasvir premix

**[00218]** The Ledipasvir pre-mix can be a co-precipitate of Ledipasvir with a pharmaceutically acceptable carrier, and optionally other pharmaceutically acceptable excipients. Preferably the pharmaceutically acceptable carrier is copovidone.

**[00219]** The Ledipasvir premix can be a crystalline premix or an amorphous premix.

**[00220]** Preferably, the pre-mix of Ledipasvir and the carrier, preferably copovidone, contains a weight ratio of carrier:Ledipasvir of: about 7:3 to about 3:7, about 6:4 to about 4:6**,** about 45:55 to about 55:45, about 50:50.

**[00221]** Preferably, the pre-mix comprises the carrier, preferably copovidone, in an amount of about 70 to about 30 wt%, about 40 to about 60 wt%, about 50 wt%. Preferably, the pre-mix comprises Ledipasvir in an amount of about 70 to about 30 wt%, about 60 to about 40 wt%, about 50 wt%.

**[00222]** In some embodiments the present disclosure relates to processes for preparation of a premix of Ledipasvir comprising combining any one of the above solid state forms of Ledipasvir with a pharmaceutically acceptable carrier, preferably copovidone, and optionally other pharmaceutically acceptable excipients.

**[00223]** In some embodiments, Ledipasvir amorphous pre-mix can be prepared by mixing Ledipasvir with at least one carrier, preferably copovidone, and optionally other pharmaceutically acceptable excipients or mixture of excipients, providing a mixture that is then combined with an alcohol such as ethanol, isopropanol, or the like, to yield a second mixture**.** Preferably, both ledipasvir and the carrier are dissolved in the second mixture. The solvent is then removed from the second mixture by evaporation techniques such as spray drying, EKATO or rotavapor. The resulting mixture may be in the form of a powder, which may be subjected to a particle size reduction step (e.g., by milling).

**[00224]** Preferably, Ledipasvir amorphous pre-mix can be prepared by mixing any one of the above solid state forms of Ledipasvir with copovidone and optionally other pharmaceutically acceptable excipients, providing a mixture that is then combined with ethanol to yield a second mixture. The solvent is then removed from the second mixture by evaporation techniques such as spray drying, an agitated dryer (e.g. EKATO). The resulting mixture may be in the form of a powder, which may be subjected to a particle size reduction step (e.g., by milling).

**[00225]** In some embodiments, Ledipasvir crystalline pre-mix can be prepared by dissolving the carrier, such as copovidone, in a solvent such as water, adding ledipasvir and removing the solvent by methods such as lyophilization or vacuum distillation. Preferably, the ledipasvir is not dissolved in the solution of the carrier and the solvent. The resulting mixture may be in the form of a powder, which may be subjected to a particle size reduction step (e.g., by milling).

**[00226]** In some embodiments, Ledipasvir crystalline pre-mix can be prepared by adding the carrier, such as copovidone, to a solvent such as water, heating the reaction mass to a temp in the range of about 30 deg. C to about 65 deg. C to afford a clear solution, adding ledipasvir with stirring to provide a mixture that is then lyophilized. The resulting mixture may be in the form of a powder, which may be subjected to a particle size reduction step (e.g., by milling).

**[00227]** In some embodiments the present disclosure relates to processes for preparation of a premix of Ledipasvir and other active pharmaceutical ingredients, preferably sofosbuvir and/or velpatasvir and/or other API 's which can be used in combination with Ledipasvir, comprising combining any one of the above solid state forms or amorphous form of Ledipasvir with any form of Sofosbuvir and/or any form of Velpatasvir with a pharmaceutically acceptable carrier, preferably preferably copovidone, and optionally other pharmaceutically acceptable excipients.

**[00228]** The above solid state forms may be used to purify Ledipasvir.

**[00229]** The present disclosure also provides solid state forms of Ledipasvir for use in the preparation of pharmaceutical compositions of Ledipasvir optionally with other API 's which can be used in combination with Ledipasvir,. In some embodiments, the present disclosure also encompasses the use of the Ledipasvir solid state forms of the present disclosure for the preparation of pharmaceutical compositions of Ledipasvir.

**[00230]** The present disclosure further comprises processes for preparing the above mentioned pharmaceutical compositions. The processes comprise combining the Ledipasvir solid state forms with at least one pharmaceutically acceptable excipient.

**[00231]** The solid state forms and the pharmaceutical compositions of Ledipasvir of the present disclosure can be used as medicaments, particularly for the treatment of Hepatitis C.

**[00232]** The present disclosure also provides methods of treating Hepatitis C, comprising administering a therapeutically effective amount of a Ledipasvir solid state form of the present disclosure, or at least one of the above pharmaceutical compositions, to a subject suffering from Hepatitis C, or otherwise in need of the treatment. The present disclosure also provides amorphous Ledipasvir or Ledipasvir premix prepared by the processes of the disclosure for use in the preparation of pharmaceutical compositions of Ledipasvir.

**[00233]** In some embodiments, the present disclosure also encompasses the use of amorphous Ledipasvir or Ledipasvir premix prepared by the processes of the disclosure for the preparation of pharmaceutical compositions of Ledipasvir.

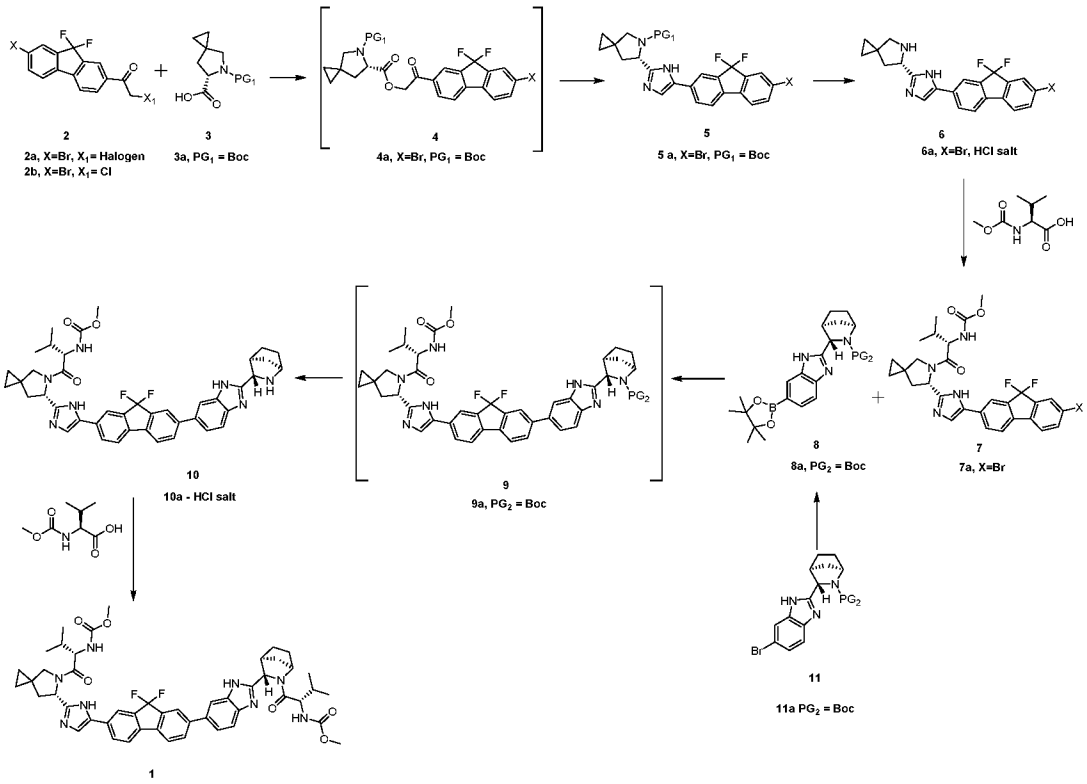
**[00234]** The present disclosure further comprises processes for preparing the above mentioned pharmaceutical compositions. The processes comprise combining amorphous Ledipasvir or Ledipasvir premix prepared by the processes of the disclosure with at least one pharmaceutically acceptable excipient.

**[00235]** Amorphous Ledipasvir or Ledipasvir premix prepared by the processes of the disclosure and the pharmaceutical compositions of Ledipasvir of the present disclosure can be used as medicaments, particularly for the treatment of Hepatitis C.

**[00236]** The present disclosure also provides methods of treating Hepatitis C, comprising administering a therapeutically effective amount of amorphous Ledipasvir or Ledipasvir premix prepared by the processes of the disclosure, or at least one of the above pharmaceutical compositions, to a subject suffering from Hepatitis C, or otherwise in need of the treatment.

**[00237]** In another aspect the disclosure relates to processes for preparation of Ledipasvir. The processes of the present disclosure can be illustrated by the following Scheme 1:

**Scheme 1**




**[00238]** In another aspect the disclosure provides a process for the preparation of Ledipasvir that comprising:

a) reacting a compound of formula 7, with a compound of formula 8, to provide compound of formula 9;

b) deprotecting the compound of formula 9 to provide compound of formula 10; and

c) reacting the compound of formula 10 with Moc L-Valine to afford Ledipasvir (compound 1)

wherein X is halo, PG2 is an amine protecting group and wherein compound of formula 9 is not isolated.

**[00239]** Preferably, the amine protecting group of the compounds of formula 8 and 9 may be Fmoc, Cbz, benzyl, trityl, Boc, trifluoroacetyl derivative, phthalic anhydride derivative, most preferably, the amine protecting group is Boc.

**[00240]** Preferably, X is chloro or bromo.

**[00241]** Compound 10 may be in free base form, or may be acid salt (e.g. a mono, di or triacid salt of a monovalent acid such as HCl). Preferably compound 10 is a tri-HCl salt.

**[00242]** Step a) is typically carried out in the presence of a suitable solvent, a suitable coupling agent and a suitable base. Suitable solvents may include, for example, pentane, cyclohexane, methyl cyclohexane, toluene, diisopropyl ether, t-butyl methyl ether, ethyl acetate, 2- methoxy ethyl ether (diglyme), tetrahydrofuran (THF), methylene chloride, 2-butanone, acetone, acetonitrile, sulfolane, dimethyl sulfoxide (DMSO), 2-methyl tetrahydrofuran, dimethyl formamide (DMF), xylene, water or mixture thereof. Preferably, the solvent is DMF, DMSO, 2-methyltetrahydrofuran, THF, toluene, acetonitrile, water or combination thereof. Most preferably, the solvent is a combination of DMF, 2-methyltetrahydrofuran and water.

**[00243]** Suitable coupling agents may include, for example metals like Pd, Pt, Rh, and ligand like $PPh_3$, $Cl_2$, $NO_2$, CN, dppa (diphenylphosphoryl azide), dba (dibenzylideneacetone), dppf (1,1'-Ferrocenediyl-bis(diphenylphosphine), Bu (butyl), OAc (acetate), single or mixtures of ligands such as ,$Pd((PPh)_3)_4$, $PdCl_2(PPh)_3$, $As(PPh)_3$, $Pdcl_2[(Pt\text{-}Bu)_2Ph]_2$, Me Phos[(2-dicylohexylphosphino 2-methyl biphenyl],$Pd(OAc)_2$, $Pd(OAc)_2(PPh)_3$, $Pd(dba)_3$,$Pd(dppf)Cl_2$,[ $Pd(dppb)Cl_2$], $Pd(dpa)_2$,(dppf),$Pd(dba)_3$,$Pd(2\text{-}Fur)_3$, $Pd(Pt\text{- }Bu)_3$, [ $Pd(Joshiphos)Cl_2$],$Pd(PhCN)_2Cl_2$.[PdCl2dppp]. Preferably, the coupling agent is a metal complex, preferably $Pd((PPh)_3)_4$ , $PdCl_2(PPh)_3$, $PdCl_2$, $[(Pt\text{-}Bu)_2Ph]_2$, $Pd(OAc)_2$, $Pd(OAc)_2(PPh)_3$, $Pd(dba)_3$, $Pd(dppf)Cl_2$, [ $Pd(dppb)Cl_2$], $Pd(dpa)_2$,(dppf), $Pd(dba)_3$, $Pd(Pt\text{-}Bu)_3$. Most preferably, the coupling agent is $Pd(OAc)_2$,$PPh_3$, $Pd(OAc)_2(PPh)_3$, $Pd((PPh)_3)_4$ , $PdCl_2(PPh)_3$, $PdCl_2[(Pt\text{-}Bu)_2Ph]_2$.

**[00244]** Suitable bases may include organic and inorganic bases, for example, Na2CO3, K2CO3, NaHCO3, DIPEA (N,N-Diisopropylethylamine), TEA (triethylamine) and NMM (N-Methylmorpholine). Preferably, the base may be $Na_2CO_3$, or $K_2CO_3$. Most preferably the base may be $Na_2CO_3$.

**[00245]** Step a may be carried out at a temperature ranging from about 50°C to about 100°C, preferably step a is carried out at a temperature of from about 65°C to about 80°C.

**[00246]** Step b) involves removal of the amine protecting group and is typically carried

**[00247]** out in the presence of a suitable solvent. Suitable solvents may include, for example, Methanol, Ethanol, Isopropanol, acetone, Acetonitrile, THF, 2-methyl tetrahydrofuran (Me-THF), Ethylacetate, water or combination thereof. Preferably, the

solvent is Acetonitrile, acetone, water, Me-THF, THF, methanol, ethanol, isopropanol or combination thereof. Most preferably, the solvent is Acetone, acetonitrile or Me-THF.

**[00248]** Suitable deprotecting reagents for step (b) include, but are not limited to, PTSA (p-toluene sulfonic acid), $H_3PO_4$, Hydrochloric acid, Trifluoroacetic acid, Tetra-n-butylammonium bromide, sulfuric acid, HBr, acetic acid, Methane sulfonic acid, inorganic and organic acid and combination thereof. Preferably, the deprotecting reagent is hydrochloric acid HBr in acetic acid. More preferably, the deprotection is performed in the presence of Hydrochloric acid.

**[00249]** Step c) is typically carried out in the presence of a suitable solvent and a suitable coupling agent. Suitable solvent may include, for example, DMF, DMSO, 2-methyltetrahydrofuran, THF, Toluene and acetonitrile, acetone, MDC, water or combination thereof. Preferably the solvent may be DMF, DME (dimethoxyethane), DMSO, acetonitrile, acetone, toluene, MDC, DMAC ((dimethylacetamide?),Me-THF, THF or combination thereof. More preferably, the solvent may be DMF, Toluene or Me-THF.

**[00250]** A suitable coupling agent for step (c) may be agents that can activate the acid to RCO-L, where in L is better leaving group such as halides, mix anhydrides or other groups described for the activation of acid in the literature. Suitable coupling agents may include, for example HATU [1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate], EDC HCl (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), HOBt (1-Hydroxybenzotriazole

**[00251]** Hydrate), CDI (**1**,**1**'-Carbonyldiimidazole) , Pivaloyl Chloride, Isopropyl chloroformate, ECF (ethyl chloroformate ) and DCC (*N,N'*-Dicyclohexylcarbodiimide). Preferably, the coupling agent is CDI, HATU and EDC/HOBt. Most preferably, the coupling agent is HOBt and EDC HCl.

**[00252]** In another embodiment, the process further comprises the generation of compound of formula 7 by a process that comprises;

i) deprotecting a compound of formula 5 to afford compound of formula 6 and

ii) coupling the compound of formula 6 with Moc L-Valine,

wherein the compound of formula 6 is isolated,

and wherein PG1 is an amine-protecting group, preferably wherein the amine protecting group is Fmoc, Cbz, benzyl, trityl, Boc, trifluoroacetyl derivative, phthalic anhydride derivative, and most preferably, wherein the amine protecting group is Boc, and

X is halo, preferably bromo.

**[00253]** Compound 6 may be in free base form, or may be acid salt (e.g. a mono, di or triacid salt of a monovalent acid such as HCl). Preferably compound 6 is a di HCl salt.

**[00254]** Step i) involves removal of the amine protecting group PG1 and is typically carried out in the presence of a suitable solvent. Suitable solvents may include, for example Methanol, Ethanol, n-propanol, Isopropanol, acetone, Acetonitrile, THF, 2-methyl tetrahydrofuran, Ethylacetate, toluene, xylene and combination thereof. Preferably, the solvent is Acetonitrile, Isopropanol or acetone. Most preferably, the solvent is acetone.

**[00255]** Suitable deprotecting reagents include, but are not limited to, PTSA, $H_3PO_4$,Hydrochloric acid, Trifluoroacetic acid, Tetra-n-butylammonium bromide, Sulfuric acid, MSA (methane sulfonic acid), organic and inorganic acid and mixture of these. Preferably, the deprotecting reagent is selected from PTSA, and hydrochloric acid. Most preferably, the deprotection is performed in the presence of Hydrochloric acid.

**[00256]** Step ii) is typically carried out in the presence of a suitable solvent and suitable coupling agent. Suitable solvents may include, for example Pentane, cyclohexane, methyl cyclohexane, Toluene, Diisopropyl ether, t-Butyl methyl ether, ethyl acetate, 2-methoxy ethyl ether(diglyme), Tetrahydrofuran, Methylene chloride, 2-Butanone, acetone acetonitrile, sulfolane, dimethyl sulfoxide, 2-methyl tetrahydrofuran, dimethyl formamide, NMP, Dimethyl acetamide (DMAc) and xylene or mixture of Xylenes.

**[00257]** Preferably, the solvent is DMF, 2-methyl tetrahydrofuran, THF, DMSO, Toluene, DMAc, acetonitrile, acetone, and may be a single solvent or combination thereof. Most preferably, the solvent is DMF and acetonitrile.

**[00258]** Suitable coupling agents for step ii) are the same as the coupling agents for step c) above.

**[00259]** In some embodiments step ii) is carried out at a temperature ranging from about -30°C to about 60°C. Preferably step ii) is performed at a temperature ranging from about 0°C to about 10°C.

**[00260]** In another embodiment the process further comprises the generation of compound of formula 5 by a process that comprises:

A) reacting a compound of formula 2 wherein X and X1 are independently halo and compound of formula 3, wherein PG1 is an amino protecting group as defined above, to afford a compound of formula 4; and

B) converting the compound of formula 4 to the compound of formula 5;

wherein the compound of formula 4 is not isolated.

**[00261]** In some embodiments step A may be performed in the presence of a suitable organic base. Suitable organic bases may include, for example, DIPEA, DIPA, TEA, NMM, Morpholine, Pyridine and Inorganic bases like $NaHCO_3$, $K_2CO_3$ and $Na_2CO_3$. Preferably the organic base is DIPEA.

**[00262]** In some embodiments step A is carried out at a temperature ranging from about 35°C to about 100°C.

**[00263]** In some embodiments, in step B, compound 4 may be reacted with a source of ammonia. Suitable sources of ammonia may include, for example, ammonium acetate or ammonium hydroxide. Preferably, the source of ammonia is ammonium acetate.

**[00264]** In some embodiments step B is carried out at a temperature ranging from about 60°C to about 120°C.

**[00265]** In some embodiments steps A and B of the above process are performed in a single solvent. Suitable solvents may include, for example, cyclohexane, methyl cyclohexane, Toluene, Diisopropyl ether, t-Butyl methyl ether, ethyl acetate, 2- methoxy ethyl ether(diglyme), isopropyl acetate Tetrahydrofuran, acetone, acetonitrile Methylene chloride, 2-Butanone, acetone acetonitrile, sulfolane, dimethyl sulfoxide, 2-methyl tetrahydrofuran, dimethyl formamide, NMP, Dimethyl acetamide and xylene, mixture of Xylenes. Preferably, the solvent is selected from Toluene, acetonitrile, acetone, ethylacetate, xylene, ethanol, IPA or Tetrahydrofuran. Most preferably, the solvent is selected from Toluene, Acetonitrile, acetone and ethanol.

**[00266]** In a preferred embodiment the disclosure provides a process for the preparation of Ledipasvir that comprises the following steps:

a) Reacting a compound of formula 7a,with compound of formula 8a , in the presence of a coupling agent to provide compound of formula 9a;

b) Deprotecting the compound of formula 9a to provide a compound of formula 10; and

c) Reacting the compound of formula 10 with Moc- L-Valine to afford Ledipasvir

wherein the compound of formula 9 is not isolated, the coupling agent in step a) is selected from a group consisting of a metal complex, preferably $Pd((PPh)_3)_4$ , $PdCl_2(PPh)_3$, $PdCl_2$, $[(Pt\text{-}Bu)_2Ph]_2$, $Pd(OAc)_2$, $Pd(OAc)_2(PPh)_3$, $Pd(dba)_3$, $Pd(dppf)Cl_2$, [ $Pd(dppb)Cl_2$], $Pd(dpa)_2$,(dppf), $Pd(dba)_3$, $Pd(Pt\text{- }Bu)_3$. Most preferably, the coupling agent is $Pd(OAc)_2$,$PPh_3$, $Pd(OAc)_2(PPh)_3$, $Pd((PPh)_3)_4$ , $PdCl_2(PPh)_3$, $PdCl_2[(Pt\text{-}Bu)_2Ph]_2$.

**[00267]** Preferably the coupling agent in step c) is an agent that can activate the acid to RCO-L, where in L is better leaving group such as halides, mix anhydrides or other groups described for the activation of acid in the literature, more preferably, the coupling agent is HOBt and EDC HCl.

**[00268]** In another preferred embodiment, the process further comprises the generation of compound of formula 7a by a process that comprises:

i) deprotecting a compound of formula 5a to afford compound of formula 6a; and

ii) coupling the compound of formula 6a with Moc-L-Valine in the presence of a coupling agent,

wherein the compound of formula 6a is isolated.

**[00269]** Preferably the coupling agent in step c) is an agent that can activate the acid to RCO-L, where in L is better leaving group such as halides, mix anhydrides or other groups described for the activation of acid in the literature.

**[00270]** More preferably, the coupling agent is HOBt and EDC HCl and step ii is carried out at a temperature ranging from about -30°C to about 60°C. Preferably step ii) is performed at a temperature ranging from about 0°C to about 10°C.

**[00271]** In another embodiment the process further comprises the generation of compound of formula 5a by a process that comprises:

A) reacting a compound of formula 2a and compound of formula 3a to afford a compound of formula 4a; and

B) converting the compound of formula 4a to a compound of formula 5a; wherein the compound of formula 4a is not isolated and steps A and B of the above process are performed in a single solvent.

**[00272]** In a most preferred embodiment the disclosure provides a process for the preparation of Ledipasvir that comprises the following steps:

a) reacting a compound of formula 2a and a compound of formula 3a to afford a compound of formula 4a; and

b) converting the compound of formula 4a to a compound of formula 5a; wherein the compound of formula 4a is not isolated and steps A and B of the above process are performed in toluene;

c) deprotecting the compound of formula 5a to afford a compound of formula 6a;

d) coupling the compound of formula 6a with Moc-L-Valine in the presence of HOBt and EDC HCl to afford a compound of formula 7a;

wherein the compound of formula 6a is isolated and step ii) is carried out at a temperature ranging from about -30°C to about 60°C.

Preferably step ii) is performed at a temperature ranging from about 0°C to about 10°C.

e) Reacting a compound of formula 7a, with a compound of formula 8a, in the presence of $Pd(OAc)_2/PPh_3/Na_2CO_3$ o provide a compound of formula 9a;

f) Deprotecting the compound of formula 9a to provide a compound of formula 10; and

g) Reacting the compound of formula 10 with Moc- L-Valine to afford Ledipasvir

wherein the compound of formula 9 is not isolated

**[00273]** Having thus described the disclosure with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the disclosure as described and illustrated that do not depart from the spirit and scope of the disclosure as disclosed in the specification. The Examples are set forth to aid in understanding the disclosure but are not intended to, and should not be construed to limit its scope in any way.

X-Ray Powder Diffraction method

**[00274]** X-ray diffraction analyses were performed on X-Ray powder diffractometer Bruker D8 Advance; CuKα radiation (λ = 1.5418 Å); Lynx eye detector; laboratory temperature 22-25 °C; PMMA specimen holder ring. Prior to analysis, the samples were gently ground by means of mortar and pestle in order to obtain a fine powder. The ground sample was adjusted into a cavity of the sample holder and the surface of the sample was smoothed by means of a cover glass.

Measurement parameters:

Scan range: 2 – 40 ° 2-theta;

Scan mode: continuous;

Step size: 0.05 °;

Time per step: 0.5 s;

Sample spin: 30 rpm;

Sample holder: PMMA specimen holder ring.

Specific Surface Area analysis

**[00275]** SSA is usually measured by nitrogen absorption analysis. In this analysis, nitrogen is absorbed on the surface of the substance. The amount of the absorbed nitrogen (as measured during the absorption or the subsequent desorption process) is related to the surface area via a formula known as the B.E.T. formula. An instrument by Micromeritics TriStar II Plus and Other commercial instrument manufactured by quantachrome (for example model monosorb) are used for this study. The analysis may be performed in a single test (single point measurement) or in a series of tests in various nitrogen pressures (multipoint measurement). Before the Surface area analysis all the samples were degassed at 40 deg C for 3 hours.

DVS analysis

**[00276]** The moisture sorption desorption isotherms were acquired using a DVS Advantage moisture sorption analyzer (Surface measurement system, Ltd). The samples were weighed into Glass sample holders. The measurement cycles for the novel crystalline form according to the present disclosure were started at 0 % RH, increased in % steps to 10 % RH, further increased in 10 % steps to 80 % RH and subsequently increased to 95 % RH, decreased again to 90 % RH, decreased in 10 % steps to 10 % RH, further decreased in 10 % steps to 0 % RH,

**[00277]** The measurement cycles for form III were started at 0 % RH, increased in % steps to 10 % RH, further increased in 10 % steps to 90 % RH and subsequently increased to 95 % RH, decreased again to 90 % RH, decreased in 10 % steps to 10 % RH, further decreased in 10 % steps to 0 % RH,

**[00278]** The equilibrium condition for each step was set to a mass constancy of + 0.002 % over 10 min. The temperature was (25 + 0.1) °C.

Bulk Density

**[00279]** About 500mg of the Ledipasvir which sieved through 425 micron mesh was poured freely into a special glass sample holder (kruss Part no. SH-0810). Record the volume (mL) of material filled.

Calculation:

**[00280]** Bulk density = Weight of the material/volume occupied by the material.

Tapped Density

**[00281]** Tapped density was measured by Jolting Volumeter STAV-II (I.ENGELSMANN. AG) instrument with the dropping height: 3mm ± 0.1mm and the tap speed: 250/min ± 15/min. Volume of the sample was measured on the graduated cylinder after 1250 taps.

Solid-state $^{13}C$ NMR

**[00282]** Solid-state 13C NMR spectra were recorded with variable amplitude cross polarization, magic angle spinning and high power proton decoupling using a BRUKER Avance II+ spectrometer operating at 125MHz at room temperature. A probe using 3.2mm o.d. zirconia rotors was employed. The operation conditions were: contact time:1ms; recycle delay: 4s; 20480scans and spin rate of 20kHz. Chemical shifts were referenced via a replacement sample of glycine (carboxyl carbon chemical shift assigned as 176.03 ppm relative to the signal of tetramethylsilane).

HPLC method Chromatographic Conditions

Column & packing: L-1, 150mm*4.6mm*2.7µm

Buffer: 0.3% v/v Solution of Perchloric acid and 0.15%v/v solution of ortho phosphoric acid in water adjust pH 2.0 with 5% Sodium hydroxide solution.

Eluent A: Buffer, Eluent B: ACN: IPA (40:60)

Flow: 0.7 mL/min, Detector: 215nm

Gradient; Time: % Eluent B, (0-23, 24-32, 49.9-70)

Retention time peak of Ledipasvir: about 18 min

## Examples

**Preparation of Crude Ledipasvir**

**[00283]** Charged 23.95 gm of Moc-L-valine, 18.50 gm of HOBt (anhydrous) and 26.20 gm EDC.HCl then added 500 ml of DMF at 15-20 °C and maintained for next 1h under nitrogen. Reaction mass was cool to 0 – 5° C and added 100 gm on dry basis of methyl ((R)-1-((S)-6-(4-(7-(2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl)carbamate hydrochloride salt then added 72.10 gm N- methyl morpholine at 0

- 5°C slowly over the period of 15 – 30 min and reaction mass was stirred for 3 h. Reaction temperature was raised to 10-20 °C and added 10 gm of EDC.HCl at the same temperature and stirred for 6 hrs. Total reaction volume was 860 ml. Out of 860 ml of the reaction mass 43 mL was taken out for other experiment. Now to the remaining reaction mass 500 mL of water was added and stirred for 2 h. Precipitated material was separated through filtration and washed with 500 ml of water to give **Part A** . 43 ml of 860 ml of the reaction mass was added drop-wise to a 2% acetic acid solution 80 mL and precipitated material was separated through filtration and washed with 50 ml of water to give Part-B. Now Part A and Part B was combined and added 2% acetic acid 500 mL and reaction was stirred for 2 hrs. Suspended material was separated through filtration and washed with 200 ml of water and dried at 70 °C for 15hrs. to give Ledipasvir crude having HPLC purity 91.39 %.

**Ledipasvir diacetonate** may be prepared according to example 1 of WO 2013/184698.

**Preparation of Ledipasvir Acetone Solvate Form II**

**[00284]** L-valine carbamate (5.78 g, 0.0323moles) was added in DMF (220 ml) at 20-30°C, followed by EDC.HCl (6.32 g, 0.0328 moles). HOBt (4.45 g, 0.0323 moles) was added at 20-30°C, the reaction was stirred 30-40 min at 20-30°C, and the reaction was cooled to 0-5°C. Methyl ((S)-1-((S)-6-(5-(7-(2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl)carbamate hydrochloride (22 g, 0.0286 moles) was then added, followed by N-methyl morpholine (14.50 g, 0.1433 moles) at 0-5°C, the reaction was stirred 3-4 h at 0-5°C, the reaction was quenched with water (220 ml) and ethyl acetate (330 ml). The organic layer was washed with water twice, the solvent removed by distillation until the residue volume reached 22-44 ml. Acetone (330 ml) was then added, and the mass was stirred for 16 h at 20-30°C. The solution was filtered, washed with acetone, and dried under vacuum at <35°C for 4-6 h. Yield: 12.50g, Purity: 98.42%.

**Preparation of Amorphous Ledipasvir**

**[00285]** Ledipasvir (Acetone solvate form II, 4.20 g, 0.0044 moles) was dissolved in DMF (50.4 ml) at 20-30°C, water (150 ml) was added, and the mass was stirred 3 h at 20-30°C. The product was isolated by filtration, washed with water, and then dried <40°C under vacuum for 15-20 h.

**Preparation of Ledipasvir Form III**

**[00286]** Ledipasvir acetone solvate (form II, 1.0 g) was dried at 115°C for 4-6 h without vacuum and the sample was analyzed by XRD. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 7.

**Example 1: Preparation of Crystalline form A of Ledipasvir**

**A. Procedure 1**

**[00287]** Amorphous Ledipasvir (250 mg) was suspended in cyclohexane (5 ml) at 25°C, heated to 60-65°C, and the suspension was heated for 2h and 30 min. MDC (1.0 ml) was then added drop wise to obtain a clear solution. The reaction mixture was allowed to cool at 20-25°C gradually and was then stirred for 6 h at 20-22°C. The formed solid material was separated by filtration and dried under vacuum at 20-25°C for 30 min. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 1.

**B. Procedure 2**

**[00288]** To amorphous Ledipasvir (300 mg) was added MDC (1.2 ml) slowly drop wise to provide a clear solution at 37 to 45°C. Methyl cyclohexane (2.0 ml) was then added slowly drop wise at the same temperature and the mixture was stirred for 24 h at 20-30°C. The crystallized product was diluted with methyl cyclohexane (4.5 ml), separated through filtration at 20-30°C, and dried under vacuum for 10-15 min. XRD analysis of the a sample of the product showed Form A. Another sample of the wet product was dried under vacuum at 40°C for 15 to provide Form A (as confirmed by XRPD).

**C. Procedure 3**

**[00289]** Amorphous Ledipasvir (2 g) was suspended in cyclohexane (40 ml) at 20-25°C, heated to 60-65°C and MDC (20 ml) was added slowly drop wise to obtain a clear solution. Stirring was continued for 2 h. The solution was allowed to cool to 20-25°C gradually and the mixture was stirred for 6 h at 20-25°C. The solid material was separated by filtration and dried under vacuum at 20-25°C for 30 min to give 2.0 gm Ledipasvir Form-A (as confirmed by XRPD).

**Example 2: Preparation of Crystalline form B of Ledipasvir**

**A. Procedure 1**

**[00290]** Amorphous Ledipasvir (250 mg) was suspended in 30% water in acetonitrile (1.5 ml) and heated to 60-65°C. The solution was stirred for 1 h. The reaction mixture was allowed to cool to 25°C gradually and stirred for 16 h at 20-25°C. The formed solid material was separated by filtration at 20-25°C and dried under vacuum at 20-22°C for 30 min. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 2.

**B. Procedure 2**

**[00291]** Amorphous Ledipasvir (500 mg) was suspended in 30% water in acetonitrile (3.0 ml) at 20-25°C and heated to 60-65°C to obtain a clear solution. The solution was stirred for 1 h. The reaction mixture was allowed to cool to 25°C gradually and stirred for 16 h at 20-25°C. The solid material was separated by filtration at 20-25°C and dried under vacuum at 20-25°C for 30 min. Form B was obtained as analyzed by XRD.

**C. Procedure 3**

**[00292]** morphous Ledipasvir (500 mg) was suspended in 30% water in acetonitrile (5.0 ml) at 20-25°C and heated to 60-65°C to obtain a clear solution. The solution was stirred for 1 h. The reaction mixture was allowed to cool to 25°C gradually and stirred for 22 h at 20-25°C. The solid material was separated by filtration at 20-25°C and dried under vacuum at 20-25°C for 30 min. Form B was obtained as analyzed by XRD.

**D. Procedure 4**

**[00293]** To amorphous Ledipasvir (1.0 g) at 20-25°C was added 30% water in acetone (10 ml) slowly drop wise to provide a clear solution. The solution was heated to 60°C for 30 min, gradually cooled to 20-25°C and stirred for 24 h at 20-25°C. The precipitated material was separated through filtration and dried under reduced pressure at 20-30°C. The sample was dried at less than 45°C for 15 h to give 900 mg of Ledipasvir Form-B (as confirmed by XRPD).

**E. Procedure 5**

**[00294]** To amorphous Ledipasvir (300 mg) was added water (3.0 ml). The reaction flask was heated to 60-67°C and DMSO (8.0 ml) was added at the same temperature slowly drop-wise to provide a clear solution. Heating was maintained at the same temperature for 3-4 h. Heating was then stopped, the oil bath was allowed to come to 20-30°C and the mixture was stirred for about 4.5 days. Water (5.0 ml) was added slowly drop wise at 20-30°C and

the mixture stirred for 24 h. The precipitate was separated using filtration at 20-30°C and dried under vacuum for 1 h to give 230 mg of Ledipasvir Form-B (as confirmed by XRPD).

**F. Procedure 6**

**[00295]** To amorphous Ledipasvir (300 mg) was added water (3.0 ml). The reaction flask was heated to 60-67°C using an oil bath and DMF (9.0 ml) was added at the same temperature slowly drop-wise to provide a clear solution. Heating was maintained at the same temperature for 3-4 h. Heating was stopped, the oil bath was allowed to come to 20-30°C and the mixture stirred for about 4.5 days. Water (5.0 ml) was then added slowly drop wise at 20-30°C and the mixture stirred for 24 h. The precipitate was separated using filtration at 20-30°C and dried under vacuum for 1 h to give 240 mg Ledipasvir form B (as confirmed by XRPD).

**G. Procedure 7**

**[00296]** 5 gm of Ledipasvir Form-O was charged in 35ml Acetonitrile and 15 ml water at 15-20°C. Reaction mass was heated to 45-50°C and cooled to 20-25°C. Ledipasvir form-B seed was charged and stirred for 18-20 hrs. at 20-25°C. 25 ml of water was added to reaction mass and stirred for 2hrs at 20-25°C. Solid material was filtered and washed with 15ml water. Dried under vacuum at 80°C for 18 hrs to give Form-B yield 3.8 gm Purity >99.0%

**H. Procedure 8**

**[00297]** 5 gm of Ledipasvir Form-M was charged in 35ml Acetonitrile and 15 ml water at 25°C. Reaction mass was heated to 60°C and cooled to 20-25°C and Stirred for 1-2hrs. Ledipasvir form-B seed was charged and stirred for 14 hrs. at 20-25°C. 25 ml of water was added to reaction mass in 5hrs.and stirred for 2-3hrs at 20-25°C. Solid material was filtered and washed with 10ml water. Dried under vacuum at 70°C for 14 hrs to give Form-B yield 4.2 purity >99.0

**I. Procedure 9**

**[00298]** 5 gm of Ledipasvir Form-N was charged in 35ml Acetonitrile and 15 ml water at 15-20°C. Reaction mass was stirred at to 20-25°C. Ledipasvir form-B seed was charged and stirred for 18-20 hrs. at 20-25°C. 25 ml of water was added to reaction mass and stirred for 2hrs at 20-25°C. Solid material was filtered and washed with 15ml water. Dried under vacuum at 80°C for 18 hrs. to give Form-B (as confirmed by XRPD) .

**Example 3: Preparation of Crystalline form C of Ledipasvir**

**A. procedure 1**

**[00299]** Amorphous Ledipasvir (250 mg) was suspended into 5% water MIBK solution (10 v) at 25°C and the suspension was heated to 60-65°C to obtain a clear solution. The solution was then stirred for 4 h at the same temperature and gradually cooled to 20-25°C. The reaction mixture was stirred for 24 h at 20-25°C. Cyclohexane (4v) was added slowly and the reaction mixture further cooled to 5-10°C for 30 min. The formed solid material was separated using filtration and dried under vacuum for 30 min at 20-25°C. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 3.

**B. procedure 2**

**[00300]** Amorphous Ledipasvir (0.5 gm) was suspended into cyclohexane (5 vol.) at 20-30°C and heated to 50-60°C, then acetone (5.0 vol.) was added at the same temperature and maintained for 30 min. The reaction flask was allowed to come to 20-30°C and stirred for 18 hrs. The crystallized product was isolated through filtration, washed with 2 vol. of cyclohexane and dried under vacuum at 20-30°C for 30 min. to give 0.35 gm Ledipasvir. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 10.

**C. procedure 3**

**[00301]** Amorphous Ledipasvir (0.3 gm) was dissolved into the THF (1.0 ml) at 20-25°C, methylethylketone (1.0 ml) was added and stirred for 24 hrs at 20-25°C. To the solution, acetonitrile (1.5 ml) was added and stirred for 12 hrs. The crystallized product was isolated through filtration, and dried under vacuum at 20-30°C for 30 min. to give 0.15 gm of Ledipasvir form C (as confirmed by XRPD).

**Example 4: Preparation of Crystalline form D of Ledipasvir**

**A. procedure 1**

**[00302]** Form III of Ledipasvir (250 mg) was suspended in MIBK (0.5 ml) at 25°C. The suspension was heated to 60-65°C to provide a clear solution. Cyclohexane (0.5 ml) was then added drop wise at 60-65°C and a thick mass was formed, which was further diluted with MIBK (0.5 ml) and cyclohexane (0.5 ml) at the same temperature. A thick mass was formed which was diluted with 0.5ml MIBK & 1.5ml cyclohexane at the same temperature. The suspension was allowed to cool to 20-25°C. The reaction mixture was stirred for 72h at

25°C. The solid material was separated using filtration and dried under vacuum for 30 min at 20-25°C. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 4.

**B. procedure 2**

**[00303]** Amorphous Ledipasvir (3 g) was mixed with a solution of THF/acetonitrile in a 1:1 ratio at 25°C and the mixture stirred for 18 h. The precipitate was separated through filtration and the filtered material was washed with THF/acetonitrile (2 ml, 1:1 ratio) solution at 25°C and dried under vacuum for 30 min to give 2.25 g of Ledipasvir form D (as confirmed by XRPD).

**Example 5: Preparation of Crystalline form E of Ledipasvir**

**[00304]** Amorphous Ledipasvir (250 mg) was added to a 10 ml round bottom flask followed by addition of 30% water acetone solution (2.5 ml) at 60°C, slowly drop wise. The reaction mixture was allowed to cool at 20-25 °C gradually and stirred for 24 h at 20-25°C. The solid material was separated using filtration and the filter cake was washed with 33% water acetone solution and dried under vacuum for 30 min at 20-25°C. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 5.

**Example 6: Preparation of Crystalline form F of Ledipasvir**

**[00305]** To amorphous Ledipasvir (250 mg) was added dichloromethane (2.0 ml) at 35-40°C to obtain a clear solution. The solution was allowed to cool to 20-25°C and stirring was continued for 3h but material was not crystallized. The solution was again heated to 35-40°C and cyclohexane (2.1 ml) was added at the same temperature. The reaction mixture was then allowed to cool at 20-25°C and stirred for 24h at 20-25°C. The solid material was separated using filtration and the filter cake was washed with 40% dichloromethane/cyclohexane (10mL) and dried under vacuum for 30 minutes at 20-25°C. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 6.

**Example 7: Preparation of Crystalline form G of Ledipasvir**

**[00306]** Form II of Ledipasvir acetonate (1.0 g) was added to water (4 ml) in a round bottom flask at 20-25°C, and the reaction mass was heated to 45-50°C for 1.5 h under stirring. The reaction mass was allowed to cool to 20-25°C gradually and stirred for 2 h at 20-25°C. The solid material was filtered and washed with water (1 ml) at 20-25°C.

**Example 8: Preparation of Crystalline form H of Ledipasvir**

**[00307]** Form G of Ledipasvir acetonate (0.1 g) was added to a TGA (TA instrument Q500) platinum pan and heated to 150°C under nitrogen atmosphere at a rate of

10°C/min. The sample was kept at 150°C for 10 min, then cooled to 40°C. The solid material was removed at 20-25°C. The product was analyzed by XRPD and the XRPD pattern is presented in Figure 9.

**Example 9: Preparation of Crystalline form G of Ledipasvir**

**[00308]** 1.0 g of Ledipasvir diacetonate was added into water (4 mL) in a round bottom flask at 20-25°C, then the reaction mass was heated to 45-50°C for 1.5 hour under stirring. The reaction mass was allowed to cool to 20-25 °C gradually and stirred for 2 hours at 20-25 °C. The solid material was filtered and washed with 1 ml water at 20-25 °C. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 8.

**Example 10: Preparation of Crystalline form J of Ledipasvir**

**[00309]** 5.0 g of amorphous Ledipasvir was suspended in cyclohexane (6 vol.) at 20-30 °C and heated to 50-60 °C for 30 minutes, then acetone (6.0V) was added at the same temperature and maintained for 1 hr. The reaction flask was allowed to come at 20-30 °C and stirred for 20 hrs, crystallized product was isolated through filtration, washed with 2 vol. of cyclohexane and dried under vacuum at 20-30 °C for 1 hr to give 4.8 g Ledipasvir. The product was dried for 12 hrs at 60-70°C to afford 4.2 g Ledipasvir form J. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 11.

**Example 11: Preparation of Crystalline form K of Ledipasvir**

**[00310]** 4.4 g of Ledipasvir (Form-L) was dried for 12 hrs at 60-70 °C under vacuum to afford 4.0 g of Ledipasvir Form K. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 12.

**Example 12: Preparation of Crystalline form L of Ledipasvir**

**[00311]** 5.0 g of amorphous Ledipasvir was suspended in cyclohexane (20 vol.) at 20-30 °C and heated to 50-60 °C for 1 hr. Then dichloromethane (MDC) (10.0V) was added to get a clear solution and maintained for 30 minutes, gradually cooled to 20-30 °C and stirred for 20 hrs. The crystallized product was isolated through filtration, washed with 2 vol. of cyclohexane and dried under vacuum at 20-30 °C for 1 hr to give 4.6 g Ledipasvir form L. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 13.

**Example 13: Preparation of Crystalline form G of Ledipasvir**

**[00312]** 30.0 g of amorphous Ledipasvir was dissolved in dichloromethane (MDC) (5 Vol.) at 25-35 °C to get a clear solution. Acetone (5 Vol.) was added at 25-35 °C and stirred for 1hr to get solid material and stirring was continued for 3-4 hrs. Crystallized

product was isolated by filtration and dried under vacuum at 20-35 °C for 30 minutes to give 26 g of Ledipasvir form G. The isolated form G was further dried under vacuum at 40 °C for 3 hrs to get Ledipasvir form G (as confirmed by XRPD).

**Example 14: Preparation of Crystalline form M of Ledipasvir**

**A. procedure 1**

**[00313]** 10 g of amorphous Ledipasvir was charged into the solution of toluene (50 ml) and acetone (70 ml) at 20-30°C. The reaction mass was stirred at 20-30°C for around 8 hrs. The reaction mass was separated using filtration at 25°C and the wet cake was washed with 20 ml acetone and isolated. Wet sample was dried at 40°C under vacuum for 30 min to give Ledipasvir form M isolated yield 12 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 14.

**B. procedure 2**

**[00314]** 101.25 ml of DMF was charged with 5.38 g of Moc-L-valine then 8.13 g of EDC.HCl, followed by 4.14 g of HOBt at 25-35°C. The reaction mass was stirred for 30-60 min at 25-35°C and cooled to 0-5°C, 22.5 g of Methyl ((S)-1-((S)-6-(5-(7-(2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl)carbamate trihydrochloride was added at 0-5°C, followed by 11.25 ml DMF, then 16.20 g of N-methyl morpholine was added dropwise at 0-5°C. The reaction mass was stirred at 0-5°C for 2-3 hrs, then the temperature was raised to 10-25°C, 1.0 g EDC.HCl was added at 10-20°C and the reaction mass was stirred for another 12 hrs at 10-20°C. The reaction was monitored by HPLC. After completion of the reaction, half of the reaction mass was worked up by adding toluene (125 mL) and water (125 mL) and heated to 55-60°C for 30 min. The organic layer was separated out and washed with 2% acetic acid solution (500 mL). 1.1 g of activated carbon was added to the separated organic layer and the mass was heated to 55-60°C for 30 min and filtered through a hyflo bed. The filtrate was concentrated till 50 mL remain in the reaction mass and cooled to 20-25 °C and 60 ml acetone was added at 20-35°C and stirred for 4-5 hrs. The precipitated material was filtered and washed with 20 ml acetone, dried under vacuum at 40°C for 30 min to give Ledipasvir form M. Yield: 13.5 g chemical purity >99% . The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 15.

**Example 15: Preparation of Crystalline form N of Ledipasvir**

**A. procedure 1**

**[00315]** 11.5 g of Ledipasvir form M obtained by procedure 1 of example 14 was dried at 80-105°C under vacuum for 14 hrs to give Ledipasvir form N at an isolated yield of 8.0 - 9.0 g. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 16.

**B. procedure 2**

**[00316]** 13.5 g Ledipasvir form M obtained by procedure 2 of example 14 was dried at 80-105°C under vacuum for 14 hrs to give Ledipasvir Form N in an isolated yield of 8.2 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 17.

**Example 16: Preparation of Crystalline form O of Ledipasvir**

**A. procedure 1**

**[00317]** 5.0 gm of ledipasvir (Acetonate) was added to 25 ml Toluene. The reaction mass was heated at 50-55°C for 30 min to get a clear solution. 20 ml of acetonitrile was added at same temperature and maintained for 15-20 min. The reaction mass was cooled to 25-30°C and stirred for 1 hour. The reaction mass was cooled to 5-10°C and seeded with Form-M. Stirring was maintained for next 5.0-5.5 hrs. at 5-10°C. Crystallized product was filtered at 5-10°C and wet material was dried at 40°C under vacuum for 30 min. to give 4.2 gm form-O. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 18.

**B. procedure 2**

**[00318]** Charged 5.0 gm Amorphous ledipasvir followed by addition of 25 ml toluene at 20 to 30°C, reaction mass was heated to 60-70°C for 30 min. 0.5 gm charcoal was added and stirring was continued for 15 min. The reaction mass was passed through celite pad and washed with 10 ml of Toluene. Filtrate was concentrated to attain 25 ml residual volume. Reaction mass was cooled to 25°C and then 20 ml of acetonitrile was added at same temperature and cooled to 0-5°C and 150 mg of Form-M seed was added. Then stirring was maintained for next 9.0 hrs at 5-10°C. Crystallized product was separated through filtration at 5-10°C, washed with 5.0 ml acetonitrile and toluene (4:5 ratio). Wet material was dried at 40°C under vacuum for 30 min. to give 3.91 gm form-O (as confirmed by XRPD).

**C. procedure 3**

**[00319]** Charged 5.0 gm Ledipasvir Crude having purity 91.39% followed by addition of 25 mL of toluene at 20 to 30°C, reaction mass was heated to 60-70°C for 30 min. After that 0.5 gm charcoal was added and stirring was maintained for 15 min. The reaction mass was passed through celite pad and washed with 10 mL of Toluene. Filtrate was concentrated to have 25ML residual volume. Reaction mass was cooled to 20-30°C and then 20 ml of acetonitrile was added at same temperature and cooled to 0-5°C and 150 mg of Form-M seed was added. Then stirring was maintained for next 9.0 hrs at 5-10°C. Crystallized product was separated through filtration at 5-10°C, washed with 5.0 mL acetonitrile and toluene (4:5 ratio) solution. Wet material was dried at 40°C under vacuum for 30 min. to give 3.91 gm Form-O, as confirmed by XRD, having Purity >99.0 %

**D. procedure 4**

**[00320]** Charged 5.98 gm of Moc-L-valine, 4.618 gm of HOBt (anhydrous) followed by addition 125 ml of DMF at 15-20 °C and maintained for next 10-15 minutes. Charged 6.55 gm EDC.HCl and cooled to 5-10 °C then added 25 gm on dry basis of methyl ((R)-1-((S)-6-(4-(7-(2-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-benzo[d]imidazol-6-yl)-9,9-difluoro-9H-fluoren-2-yl)-1H-imidazol-2-yl)-5-azaspiro[2.4]heptan-5-yl)-3-methyl-1-oxobutan-2-yl)carbamate hydrochloride salt then added 18.02 gm N- methyl morpholine at 5-10°C and maintained for next 30 min. reaction mass was warmed to 20-25 °C and stirred for 2 h 30 min. Again added 2.5 gm EDC.HCl and stirred for 14 h at 20-25 °C. Charged 125 mL of Toluene and 125 mL of water at 25 to 30 °C, aqueous and organic layer were separated. Again added 125 mL of Toluene to the aqueous layer and organic layer was separated. Finally combined organic layer was washed twice with 125 mL of water at 65 °C. To the Organic layer added Charcoal 2.5 gm at 65°C and stirred for 30 min and passed through celite pad and filtrate was concentrated to have 65 mL residual mass volume and added 50 mL of acetonitrile and seeded with 0.25 gm of Ledipasvir form-O and stirred for 22h at 25°C. Then it was cooled to 5-10°C and stirring was maintained at the same temperature for next 16 hrs, precipitated material was separated through filtration and washed with 25 mL of 50 % acetonitrile and toluene solution and wet material was dried at 40°C for 30 min. Isolated to give 24.21 gm of Ledipasvir Form-O, as confirmed by XRD, having purity >99% yield 85-90%

**E. procedure 5**

**[00321]** Charged 5 gm of crude Ledipasvir followed by addition of 25 mL Toluene and reaction mass was heated to 70°C for 30 min. Reaction mass was passed through celite bed and wash with 5 mL of toluene, filtrate was concentrated in such a way so that total reaction mass should have 3 Vol. and 3Vol THF was added at 25°C. Reaction mass was cooled to 5°C and seeded with Form-M. Reaction mass was stirred for 5h and 30 min at 5°C. Precipitated material was separated through filtration and washed with 5 mL of toluene/Acetonitrile (3:2) solution. Wet material was dried under vacuum for 30 min. to 1.8 gm for Ledipasvir form O (as confirmed by XRD) having HPLC purity >99% yield 35-40 %.

**Example 17: Preparation of Crystalline form H of Ledipasvir**

**[00322]** 100 ML MDC was added to 20 gm of amorphous ledipasvir to get clear solution at 20 to 30 °C followed by addition of 100 ml acetone at same temperature. Stirring was maintained for next 4h and 10 min. Crystallized product was separated by filtration at 20-30°C and dried under vacuum for 30 min. to give form-G (as confirmed by XRD), form-G was further dried at 100° C under vacuum for 40h to give 15.0 gm Form-H. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 19.

**Example 18: Preparation of Ledipasvir Premix (amorphous)**

**A. procedure 1**

**[00323]** Ledipasvir acetonate 10 gm and copovidone 50% (18.74 gm) were dissolved in ethanol (90.63 gm ) at 50-60 °C, and passed through 0.45µm filter paper cool to 20-30 °C, This solution was concentrated to dryness at Rota vapor at 55-60°C & degassed for 3hrs Isolated material was dried at 80°C for 40hrs. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 20.

OVI (Organic Volatile Impurity) is below ICH Limit.

**B. procedure 2**

**[00324]** Ledipasvir Form-L (0.5 gm) and copovidone 50% (o.5 gm) in ethanol (1.0 gm) were dissolved in ethanol (4.5 gm) at 50-60 °C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40°C & degassed for 1hrs Isolated wet material was dried under vacuum at 60-70°C

for 15hrs to give 0.35 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 21.
OVI is below ICH Limit.

**C. procedure 3**

**[00325]** Ledipasvir Form-J (0.5 gm) and 1.0 gm 50% copovidone ethanol soution were dissolved in ethanol (4.5 gm) at 50-60 °C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40°C & degassed for 1hrs Isolated wet material was dried under vacuum at 60-70°C for 15hrs to give 0.35 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 22.
OVI in ppm: Ethanol( 7645), Cyclohexane (17).

**D. procedure 4**

**[00326]** 1.0 gm Ledipasvir Form-B (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-80°C for 40hrs to give 1.75 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 23
OVI is below ICH Limit.

**E. procedure 5**

**[00327]** 1.0gm Ledipasvir Form-M (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-80°C for 40hrs to give 1.72 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 24
OVI is below ICH Limit.

**F. procedure 6**

**[00328]** 1.0 gm Ledipasvir Form-N (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-80°C for 40hrs to give 1.78 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 25
OVI is below ICH Limit.

**G. procedure 7**

**[00329]** 1.0gm Ledipasvir Form-H (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-70°C for 15hrs to give 1.78 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 26
OVI is below ICH Limit.

**H. procedure 8**

**[00330]** 1.0gm Ledipasvir Form-G (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-70°C for 15hrs to give 1.7 gm. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 27
OVI is below ICH Limit.

**I. procedure 9**

**[00331]** 1.0gm Ledipasvir Form-K (on dry Basis) and copovidone (1.0gm) were dissolved in ethanol (10ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-70°C for

15hrs to give 1.74 gm . The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 28
OVI is below ICH Limit.

**J. procedure 10**

**[00332]** 2.0gm Ledipasvir Form-O (on dry Basis) and copovidone (2.0gm) were dissolved in ethanol (20ml) at 25-35 °C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-70°C for 3hrs to give 1.75 gm . The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 34

**J. procedure 11**

**[00333]** 2.0gm Ledipasvir Form-P (on dry Basis) and copovidone (2.0gm) were dissolved in ethanol (40ml) at 25-35 0C, and passed through 0.45µm filter paper. Reaction mass was stirred for 10-15 min This solution was concentrated to dryness at Rota vapor at 40-45°C & degassed for 30min. Isolated wet material was dried under vacuum at 60-70°C for 15hrs to give 3.0 gm. The obtained product was analyzed by XRPD and was identified as amorphous premix.

**Example 19: Preparation of Crystalline form P of Ledipasvir**

**[00334]** Charged Ledipasvir crude 2.0 gm followed by addition MDC 6.0 ml to get clear solution then added acetonitrile 6.0 ml stirring was maintained for 5 hrs. Precipitated material was separated through filtration and filtered material was washed with 5ml of 50 % MDC/acetonitrile solution. Wet material was suck dried for 30 min at 40°C to give 1.3 gm of Ledipasvir. Purity >99.0 %. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 29

**Example 20: Preparation of Crystalline form H of Ledipasvir**

**[00335]** Ledipasvir 0.5 gm form P was kept in vacuum oven and heated at 75°C under -0.1 M pa for 2.5 hrs. The oven temperature was cooled to 40°C and then the vacuum

was released. The sample was taken out from the oven. The obtained product was analyzed by XRPD and was identified as form H.

**Example 21: Preparation of Ledipasvir crystalline Premix**

**A. procedure 1**

**[00336]** Copovidone 5 gm was charged 200 mL of water at 25°C. Reaction mass was heated to 60-65°C to get clear solution and added 5gm of Ledipasvir form-II with gentle stirring and frozen using liquid Nitrogen and then lyophilized in a lyopholizer resulting in Ledipasvir premix crystalline form-II. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 30

**B. procedure 2**

**[00337]** Copovidone 5 gm was charged 200 mL of water at 25°C. Reaction mass was heated to 35-40°C to get clear solution and added 5gm of Ledipasvir form-H with gentle stirring and Freeze it by using liquid Nitrogen. Lyophilize it in lyophilizer giving Ledipasvir premix crystalline From-H. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 31

**C. procedure 3**

**[00338]** Copovidone 5 gm was charged 150 mL of water at 25°C. Reaction mass was heated to 35-40°C to get clear solution and added 5.0gm of Ledipasvir form-N with gentle stirring and Freeze it by using liquid Nitrogen. Lyophilize it in lyophilizer giving Ledipasvir premix crystalline form-N. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 32.

**D. procedure 4**

**[00339]** Copovidone 5 gm was charged 100 mL of water at 25°C. Reaction mass was heated to 60°C to get clear solution and added 5gm of Ledipasvir form-O with gentle stirring and Freeze it by using liquid Nitrogen and then lyophilized in lyophilizer to afford Ledipasvir premix crystalline form-O. The obtained product was analyzed by XRPD and the XRPD pattern is presented in Figure 33.

**Example 22: Preparation of amorphous Ledipasvir**

**A. procedure 1**

**[00340]** 5gm of Ledipasvir form-O was charged in 25 ml Toluene and heated to 50-60°C to get clear solution and cooled to 20-25°C. This solution was added dropwise in to the 50 ml cyclohexane under stirring for 20-30 min at 20-25°C. Reaction mass was stirred for 4-5 hrs. at 20-25°C. Obtained solid was filtered and washed with 15 ml cyclohexane. The solid material was dried under vacuum at 80°C for 18 hrs. Yield 4.0gm and purity >99.0%

**B. procedure 2**

**[00341]** 5 gm of Ledipasvir form-O was charged in 25 ml Toluene and heated to 50-60°C to get clear solution and cooled to 20-25°C. This solution was added dropwise in to the 50 ml n-Heptane under stirring for 20-30 min at 20-25°C. Reaction mass was stirred for 2 hrs. at 20-25°C. Obtained solid was filtered and washed with 15 ml n-Heptane. The solid material was dried under vacuum at 80°C for 18 hrs. Yield 4.1gm Purity >99.0%.

**C. procedure 3**

**[00342]** 5 gm of Ledipasvir Form-O was charged in 5 ml water and 45 ml of Ethanol at 25-30°C and heated to 40-50°C to get clear solution. Concentrated reaction mass completely to remove solvent on rotavapor under vacuum. Dried the solid under vacuum at 70-80°C for 18 hrs. to give amorphous Ledipasvir.

**Example 23: Preparation of Ledipasvir**

**Step-1: Preparation of compound 5a**

**[00343]** A solution of compound 2a (100 gm, 0.2796moles) and compound 3a (67.47gm, 0.2796moles) in toluene (600ml) was heated at 55-65 $^0$C in presence of DIPEA (43.37gm, 0.3355moles) under stirring. After completion of the reaction, ammonium acetate (129.34 gm, 1.678 moles) was added and the reaction mass was heated to 90-100 $^0$C. After completion of the reaction, the reaction mass was cooled to 45-55°C and water (200 ml) was added. The reaction mass was stirred for 30-60 minutes cooled to 10-15 $^0$C under stirring slowly. the product was filtered and washed it with water (200 ml) and pre-cooled toluene (100 ml). and the product was dried under vacuum at 55-60 $^0$C. Yield 100-107gm

**Step-2: Preparation of compound 6a**

**[00344]** A mixture of compound 5a(100gm, 0.184) in acetone (600ml) and 30-35% Conc. HCl (40ml) was stirred after seeding with compound 6a seeds at 40-45 $^0$C for 1 hrs (NB seeding step is optional). Then another 60 ml of 30-35 % Conc. HCl was added and the reaction mass was stirred for 2 hrs. .After completion of reaction, the product was filtered off, washed with acetone (200 ml) and dried under vacuum at 60-65 $^0$C. Yield: 83 to 93 gm

Preparation of compound 6a seeds

**[00345]** A mixture of compound 5a (50gm) in Acetone (250ml) was stirred at 25-30°C Then 30-35% Conc. HCl (50ml) was added slowly after 5-min of stirring and stirred for 1 hr at same temperature. Reaction mass was warmed up to 45°C and maintained for next 2.0 hr. After completion of the reaction it was cooled to 20-25°C and stirred for 3hrs. Precipitated material was separated through filtration and washed with 100 mL of acetone and wet material was dried under vacuum at 60°C for 15hrs to give 45 gm of compound 6a having Purity 98.93%

**Step-3: Preparation of compound 7a**

**[00346]** To the reactor Moc-L-Valine (35.69gm, 0.2037mol) HOBt (28.86gm,0.2134mol) and EDC.HCl (40.92gm,0.2134mol) were charged followed by DMF 250 ml . The reaction mixture was stirred for at least 45 minute at 20-35 $^0$C. The reaction mass was cooled to 0-10°C. Compound 6a was added (100 gm, 0.194 moles) at 0-15°C & DMF (50 ml) was added slowly into it. DIPEA was added to the reaction mass slowly at 0 to 10 $^0$C. The reaction mass was stirred for at least 2 hrs at 0 to 10 $^0$C and the progress of the reaction was monitored by HPLC and the reaction was continued until completion. After completion of reaction, the reaction mass was charged into 500 ml water at 15-30°C followed by washing with 25 ml of DMF & Stirring for 60-90 minutes at 20-35°C. Water 500 ml was added and the reaction mass was stirred for 2-4 hrs at 20-35°C. The precipitated product was filtered & washed with water (200 ml and sucked Dry well. The wet material was given slurry water wash (1000 ml) and stirred for 60-90 minutes. The product was filtered and washed with water (200 ml) and dried under vacuum at 60-65 $^0$C. Yield: 100-110 gm

**Step: 4 Preparation of compound 8a**

**[00347]** To the reactor were charged: a solution of compound 11a (100gm, 0.2549mole) ,Bis Pinacoloto Diboron (77.67gm,0.3058mole), potassium acetate (75.05gm, 0.7647mole) $PdCl_2$(1.36 gm, 0.0076 mole) and triphenyl phosphine (4.011 gm, 0.0153mole) followed by 1000 ml of Me-THF at 25-35 $^0$C under nitrogen atmosphere. The reaction mass was heated to 78-83 $^0$C under stirring. The reaction was monitored by HPLC after 12 hrs. After completion of reaction, the reaction mixture was cooled to 55-60°C & water 300 ml was added under stirring. The organic layer was separated out. To the organic layer 10 gm of activated carbon was added at 55-60°C. the reaction mixture was stirred for 30-45 minutes, filtered over hyflo bed & wash with 100X2 ml of Me-THF. The filtrate was distilled off until 2-3 volume of reaction mass in-side the reactor was reached. Acetonitrile (200 ml) was added and the reaction mass was heated to 75-85°C for at least 30 minute under stirring. Reactions mass was gradually cooled to 25-35 °C and then cooled to 0-10°C. The product was filtered, washed with pre cooled acetonitrile (200 ml) .Yield: 80-90 gm (On LOD Basis)

**Step-5 Preparation of compound 10a**

**[00348]** 550 ml of 2 Methyl THF and 100 ml of DMF were charged in the reactor, argon gas was purged for at least 30 min at 20-35°C and 3.30 gm of triphenyl phosphine was charged at 20-35°C followed by palladium acetate 1.87g. The reaction mass was stirred for 30-45 min at 20-35°C. 100 gm compound 7a and 73.3 gm of compound 8a were charged. The reactor was flushed with 50 ml 2 Methyl THF. 60.10 gm of Na2CO3 were charged followed by 300 ml water. The reaction mass was heated to reflux, and the reflux was continued till reaction complies. The reaction mass was cooled to 35-40°C, organic layer was separated out and washed with 400 ml of water and with 400ml 10% brine solution. The organic layer was separated out and 10 gm activated Carbon were charged and stirred for 30 min at 35-45°C. The mass was filtered through hyflo bed and the bed was washed with 200 ml 2 Methyl THF, 1200 ml Acetonitrile were charged in to it , Argon was purged for 30 min and Conc.HCl (110 ml) was added drop wise at 32-37°C, Seed with compound 10a and stirred till completion of reaction (NB seeding step is optional). reaction mass was cooled to 20-25°C ,stirred for 30 min., further cooled it to 10-15°C and stirred for 30-60 min. The product was filtered, washed with 400 ml acetone and sucked dry for 1-3 hrs. Output (wet weight) 130-225 gm.

Preparation of compound 10a seeds

**[00349]** 825 mL of 2 Methyl THF and 150 mL of DMF in RBF was charged, Nitrogen gas was passed for at least 30 min at 20-30°C. 4.95 gm of triphenyl phosphine was charged at 20-35°C followed by addition of palladium acetate 2.80 gm. The reaction mass was stirred for 30-60 min at 20-35°C under Nitrogen purging, 150 gm Compound 7a and 109.95 gm of Compound 8a was charged and the RBF was flushed with 75 mL of 2 Methyl THF. 90.15 gm of Na2CO3 was charged followed by 450 mL water under nitrogen purging. The reaction mass was heated to reflux, the reflux was continued till reaction complies. The reaction mass was cooled to 30-45°C, the organic layer was separated out washed with 600 mL water, and twice with 600 mL 10% brine solution. The organic layer was separated out and 15 gm of activated Carbon was charged and the reaction mass was stirred for 30 min at 35-45°C, filtered through hyflo bed and washed the bed with 300 mL of 2 Methyl THF, total weight of Organic layer was 1269 gm. The obtained organic layer was divided into 3 equal part i.e 423 gm each Compound 9a. Charged 423 gm of organic layer containing Compound 9a and 600 mL of Acetonitrile into the reactor at 20-30°C and stirred it for 10 min at 30-37°C,Slowly added concentrated hydrochloric acid 55 mL at 30-37°C under stirring and stirring was maintained for 6 hours, but reaction was not complies and reaction was cooled to 20-25°C and hold for 16hrs. Then again reaction mass was warmed to 32-37°C and maintained till reaction complies. Reaction complies after 10.5 hours. Cool it to 10-15°C over 60 minutes and stirred it for 60 minutes at the same temperature. Precipitate material was filtered and washed with 200mL of acetone, wet material was suck dried to give compound 10a. Yield: 71 gm (Wet), and LOD is 26.07% Purity 93.45%.

**Step-6: Preparation of Ledipasvir**

**[00350]** Compound 10a may be converted to ledipasvir according to the procedure described above, or by the following procedure:

**[00351]** 450 ml of DMF followed by 23.95 gm of Moc-L-Valine, 18.50 gm of HOBt, then 26.2 gm of EDC.HCl at 25-35°C were charged in the reactor. The reaction mass was stirred for 30-60 min at 20-30°C and cooled to 0-5°C. 100 gm of compound 10a were charged at 0-5°C followed by 50 ml DMF, then 72.1 gm of N-Methyl Morpholine were added drop wise at 0-5°C. The reaction mass was stirred at 0-5°C for 3 hrs then the temperature was raised to 10-20°C and 10 gm EDC.HCl were charged at 10-20°C. The reaction mixture was stirred for another 15 hrs at 10-20°C, reaction monitored by HPLC.

After completion of reaction, 1000 ml Ethyl acetate was charged followed by 800 ml water. The reaction mass was stirred for 30-40 min at 10-25°C, the organic layer was separated out and washed with 500 ml 2% acetic acid solution. The separated organic layer was again washed 500 ml of water followed by 10% brine solution (2*500 ml). The organic layer was charged into another reactor and 10 gm of activated carbon was added and the reactor was heated to reflux. Reflux was continued for 30 min the reaction mass was filtered through hyflo bed, and washed with 200 ml ethyl acetate. The solvent was distilled out under vacuum at Tj50°C till a residual volume of 75-150 ml was reached. 1000 ml acetone was charged at 50-25°C and heated to 40-45°C and seeded with crystalline Ledipasvir form II 0.5 gm (NB seeding step is optional), stirred for 2 hrs at 40-45°C, further cooled to 20-25°C in 120-180 min, stirred for 60-180 min. at 20-25°C, filtered and washed with 200 ml acetone, Output (wet weight) : 80-160 gm.

Note - Crystalline Ledipasvir form II seeds were prepared according to the above procedure.

**[00352]** The disclosure further provides the following Embodiments (A)-(O):

**[00353]** (A) Ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63 for use in the preparation of other solid state forms of ledipasvir or ledipasvir Premix, wherein the ledipasvir Premix may be a crystalline premix of Ledipasvir or an amorphous premix.

**[00354]** (B) Use of Ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63 for the preparation of other solid state forms of ledipasvir or ledipasvir Premix.

**[00355]** (C) A process for preparation of an amorphous premix comprising:

(a) mixing ledipasvir according to any of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63 with at least one carrier, preferably copovidone, and optionally other pharmaceutically acceptable excipients, to provide a mixture;

(b) combining the mixture with an alcohol, preferably wherein the alcohol is ethanol, isopropanol or a combination thereof, to provide a second mixture; and

(c) removing the solvent from the second mixture to form an amorphous premix.

**[00356]** (D) A process according to Embodiment (C) wherein both the ledipasvir and carrier in the second mixture are dissolved.

**[00357]** (E) The process of any of Embodiments (C)-(D) wherein the amorphous premix is subjected to a particle size reduction step.

**[00358]** (F) An amorphous premix prepared according to any of Embodiments (C)-(E).

**[00359]** (G) Ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix of Ledipasvir according to the following claim 64, or an amorphous premix according to Embodiment (F), for use in the preparation of a pharmaceutical composition.

**[00360]** (H) Use of Ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix of Ledipasvir according to the following claim 64, or an amorphous premix according to Embodiment (F), for the preparation of a pharmaceutical composition.

**[00361]** (I) A pharmaceutical composition comprising a solid form of Ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix of Ledipasvir according to claim 64 or an amorphous premix according to Embodiment (F), or combination thereof.

**[00362]** (J) The pharmaceutical composition according to Embodiment (I), wherein the pharmaceutical composition is a solid composition and the ledipasvir retains its solid state form.

**[00363]** (K) The pharmaceutical composition according to Embodiment (J) wherein the solid form is crystalline form B according to any of the following claims 1-3.

**[00364]** (L) A process for preparation of a pharmaceutical composition according to any of Embodiments (I)-(K), comprising combining the solid form of ledipasvir according to any one of the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix of Ledipasvir according to the following claim 64, or an amorphous premix according to Embodiment (F) with at least one pharmaceutically acceptable excipient.

**[00365]** (M) The crystalline forms of Ledipasvir according to the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix according to the following claim 64, an amorphous premix according to Embodiment (F), or the pharmaceutical compositions according to any of Embodiments (I)-(K), for use in therapy.

**[00366]** (N) The crystalline forms of Ledipasvir according to the following claims 1-25, 31, 38, 43, 46, 52, 60 and 63, a crystalline premix according to the following claim 64, an amorphous premix according to Embodiment (F), or the pharmaceutical compositions according to any of Embodiments (I)-(K), for use in treatment of Hepatitis C.

**[00367]** (O) A method of treating a subject suffering from hepatitis C or otherwise in need of a treatment comprising administering an effective amount of a pharmaceutical composition according to any of Embodiments (I)-(K).

## Claims

1. A crystalline form of Ledipasvir, wherein the crystalline form is:

(A) A crystalline form of Ledipasvir designated form B, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 2, wherein form B is not an acetone solvate;

(ii) an X-ray powder diffraction pattern having peaks at 6.9, 9.6 and 13.5 degrees two theta ± 0.2 degrees two theta and the absence of a peak at 11.0 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern substantially as depicted in Figure 2, wherein form B is not an acetone solvate and further characterized by an X-ray powder diffraction pattern having peaks at 6.9, 9.6 and 13.5 degrees two theta ± 0.2 degrees two theta; or

(iv) Form B according to any one of (i), (ii) or (iii) wherein Form B is a hydrate;

or

(B) A crystalline form of Ledipasvir designated form G, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 8;

(ii) an X-ray powder diffraction pattern having peaks at 7.3, 14.0, 19.5 and 20.4 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern having peaks at 7.3, 14.0, 19.5, 20.4 and 26.6 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta;

(iv) an X-ray powder diffraction pattern having peaks at 7.3, 9.5, 11.3, 12.1, 14.0, 19.5, 20.4 and 26.6 degrees two theta ± 0.1 degrees two theta and having no peaks at 3.9 and 12.7 degrees two theta ± 0.1 degrees two theta;

(v) an X-ray powder diffraction pattern having peaks at 8.7, 13.2, 14.6, 15.5, 17.2, 18.0, 23.1, 24.2, 24.9 and 26.6 degrees two theta ± 0.1 degrees two theta;

(vi) a solid state $^{13}C$ NMR spectrum having peaks at 139.5, 137.7, 122.0 and 111.8 ppm ± 0.2 ppm;

(vii) a solid state 13C NMR spectrum having chemical shift differences between said characteristic peaks at 139.5, 137.7, 122.0 and 111.8 ppm ± 0.2 ppm and a

reference peak at 107.4 ppm ± 0.2 ppm of 32.1, 30.3, 14.6 and 4.4 and ppm ± 0.1 ppm , respectively;

(viii) a solid state 13C NMR spectrum substantially as depicted in Figure 35; or

(ix) Form G according to any one of (i), (ii), (iii), (iv), (v), (vi), (vii) and (viii), wherein the form G is an acetone solvate or wherein the form G is an acetone / dichloromethane (MDC) solvate;

or

(C) A crystalline form of Ledipasvir designated form H, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 9;

(ii) an X-ray powder diffraction pattern substantially as depicted in Figure 19;

(iii) an X-ray powder diffraction pattern having peaks at 17.0, 19.0, 19.8 and 20.9 degrees two theta ± 0.1 degrees two theta and having no peaks at 12.8 and 16.7 degrees two theta ± 0.1 degrees two theta;

(iv) an X-ray powder diffraction pattern having peaks at 7.6, 9.0, 12.1, 17.0 and 19.0 degrees two theta ± 0.1 degrees two theta and having no peaks at 12.8 and 16.7 degrees two theta ± 0.1 degrees two theta; or

(v) Form H according to any one of (i), (ii), (iii) or (iv), which is anhydrous;

or

(D) A crystalline form of Ledipasvir designated form M, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 14 or an X-ray powder diffraction pattern substantially as depicted in Figure 15;

(ii) an X-ray powder diffraction pattern substantially as depicted in Figure 14 or an X-ray powder diffraction pattern substantially as depicted in Figure 15 and further characterized by an X-ray powder diffraction pattern having peaks at 7.0, 11.2, 22.6 and 24.7 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern having peaks at 7.0, 11.2, 22.6 and 24.7 degrees two theta ± 0.1 degrees two theta, wherein form M is an acetone/toluene solvate;

(iv) an X-ray powder diffraction pattern having peaks at 7.0, 11.2, 22.6 and 24.7 degrees two theta ± 0.1 degrees two theta, wherein form M is an acetone/toluene

solvate and further characterised by an X-ray powder diffraction pattern having no peaks at 9.3, 17.8, 23.1 and 23.8 degrees two theta ± 0.1 degrees two theta; or

(v) Form M according to any one of (i) or (ii), wherein form M is an acetone/toluene solvate;

or

(E) A crystalline form of Ledipasvir designated form N, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 16 or an X-ray powder diffraction pattern substantially as depicted in Figure 17;

(ii) an X-ray powder diffraction pattern substantially as depicted in Figure 16 or an X-ray powder diffraction pattern substantially as depicted in Figure 17, which is further characterized by an X-ray powder diffraction pattern having peaks at 11.5, 15.2 and 19.2 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern having peaks at 11.5, 15.2 and 19.2 degrees two theta ± 0.1 degrees two theta, wherein form N is anhydrous;

(iv) an X-ray powder diffraction pattern having peaks at 11.5, 15.2 and 19.2 degrees two theta ± 0.1 degrees two theta and having peaks at 7.6 and 24.6 degrees two theta ± 0.1 degrees two theta, and having no peaks at 9.4, 21.3 and 21.6 degrees two theta ± 0.1 degrees two theta, wherein form N is anhydrous; or

(v) Form N according to any one of (i) or (ii), wherein form N is anhydrous;

or

(F) A crystalline form of Ledipasvir designated form O, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 18;

(ii) an X-ray powder diffraction pattern substantially as depicted in Figure 18 and further characterized by an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern substantially as depicted in Figure 18 with no peaks at 7.6 and 21.3 degrees two theta ± 0.1 degrees two theta;

(iv) an X-ray powder diffraction pattern substantially as depicted in Figure 18 and further characterized by an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta with no peaks at 7.6 and 21.3 degrees two theta ± 0.1 degrees two theta;

(v) an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta, wherein form O is an acetonitrile/toluene solvate;

(vi) an X-ray powder diffraction pattern having peaks at 6.6, 9.9, 11.5, 19.6, 20.9 and 31.5 degrees two theta ± 0.1 degrees two theta with no peaks at 7.6 and 21.3 degrees two theta ± 0.1 degrees two theta, wherein form O is an acetonitrile/toluene solvate; or

(vii) Form O according to any of (i), (ii), (iii) or (iv), wherein form O is an acetonitrile/toluene solvate;

or

(G) A crystalline form of Ledipasvir designated form P, characterized by data selected from one or more of the following:

(i) an X-ray powder diffraction pattern substantially as depicted in Figure 29;

(ii) an X-ray powder diffraction pattern substantially as depicted in Figure 29 and further characterized by an X-ray powder diffraction pattern having peaks at 7.4, 9.0, 11.4, 18.8, 19.6 and 21.7 degrees two theta ± 0.1 degrees two theta;

(iii) an X-ray powder diffraction pattern substantially as depicted in Figure 29 and further characterized by an X-ray powder diffraction pattern having peaks at 12.3, 20.6, 14.8, 18.2 and 24.0 degrees two theta ± 0.1 degrees two theta;

(iv) an X-ray powder diffraction pattern having peaks at 7.4, 9.0, 11.4, 18.8, 19.6 and 21.7 degrees two theta ± 0.1 degrees two theta wherein form P is a dichloromethane (MDC)/acetonitrile solvate; or

(v) Form P according to any of (i), (ii) or (iii), wherein form P is an (dichloromethane) MDC/acetonitrile solvate.

2. The crystalline form B according to claim 1(A), options (i), (ii), (iii) or (iv), having about 2% to about 6% of water by weight, preferably, about 3% of water by weight, measured by Karl Fischer titration and/or thermal gravimetric analysis TGA.

3. The crystalline form B according to any one of claims 1(A), options (i), (ii), (iii) or (iv) or 2 wherein the crystalline form is isolated.

4. The crystalline form G according to claim 1(B), options (i), (ii), (iii), (iv), (v), (vi), (vii), (viii) or (ix), further characterized by an X-ray powder diffraction pattern having no peaks 3.2 and 12.7 degrees two theta ± 0.1 degrees two theta.

5. The crystalline form G according to claim 1(B), options (vi), (vii) and (viii), further characterized by data selected from: a solid state 13C NMR spectrum with peaks at 61.5, 40.0, 38.4 and 25.4 ppm ± 0.2 ppm.

6. The crystalline form G according to claim 5, further characterised by a solid state $^{13}C$ NMR spectrum having chemical shift differences between the peaks at 61.5, 40.0, 38.4 and 25.4 ppm ± 0.2 ppm and a reference peak at 107.4 ppm ± 0.2 ppm, of 45.9, 67.4, 69.0 and 82.0 and ppm ± 0.1 ppm, respectively.

7. The crystalline form G according to claim 1(B), options (i), (ii), (iii), (iv), (v), (vi), (vii), (viii) or (ix), or any of claims 4-6, wherein said form contains from about 3% to about 7% of acetone by weight, preferably about 5% of acetone by weight.

8. The crystalline form G according to claim 1(B), options (i), (ii), (iii), (iv), (v), (vi), (vii), (viii) or (ix), or any of claims 4-6, wherein said form contains from about 3% to about 7% of acetone by weight and from about 1% to about 3% of MDC by weight, preferably about 5% of acetone by weight and about 2% of MDC by weight.

9. The crystalline form G according to claim 1(B), options (i), (ii), (iii), (iv), (v), (vi), (vii), (viii) or (ix), or any of claims 4-8, wherein the crystalline form is isolated.

10. The crystalline form H according to claim 1(C), options (i), (ii), (iii), (iv) or (v), wherein the crystalline form is isolated.

11. The crystalline form M according to claim 1(D), options (i), (ii), (iii), (iv) or (v) wherein said form contains from about 3% to about 10% of acetone by weight and from about 2% to about 10% toluene by weight, preferably from about 3% to about 8% of acetone by weight and from about 2% to about 7% of toluene by weight.

12. The crystalline form M according to any one of claims 1(D), options (i), (ii), (iii), (iv) or (v) and 11, wherein said form is isolated.

13. The crystalline form N according to claim 1(E), options (i), (ii), (iii), (iv) or (v), wherein said form is isolated.

14. The crystalline form O according to claim 1(F), options (i), (ii), (iii), (iv), (v), (vi), or (vii), wherein said form contains from about 0.5 % to about 2 % of acetonitrile by weight and from about 2.5% to about 12% of toluene by weight, preferably, from about 3 % to about 9 % of toluene by weight, more preferably about 2% of acetonitrile and about 9% of toluene by weight.

15. The crystalline form O according to any one of claims 1(F), options (i), (ii), (iii), (iv), (v), (vi) and (vii) and 14, wherein said form is isolated.

16. The crystalline form P according to claim 1(G), options (i), (ii), (iii), (iv) or (v), wherein said form contains from about 2 % to about 4 % of acetonitrile by weight and from about 2 % to about 4 % of MDC by weight, preferably about 2% acetonitrile and about 3% of MDC by weight.

17. The crystalline form P according to any one of claims 1(G), options (i), (ii), (iii), (iv) or (v), and 16, wherein said form is isolated.

18. A solid form of Ledipasvir, preferably in crystalline form wherein said form is a hydrate.

19. The solid form according to claim 18, wherein said form is characterized by a water content of about 3% to about 6% by weight, preferably about 3% of water by weight.

20. A solid form of Ledipasvir, preferably in crystalline form, having a specific surface area (SSA) of not less than 10 $m^2/g$, preferably not less than 50 $m^2/g$, more preferably not less than 90 $m^2/g$.

21. The solid form of Ledipasvir according to claim 20, having a specific surface area (SSA) of from: 10-500 $m^2/g$, 20-400 $m^2/g$, 50-300 $m^2/g$, 70-200 $m^2/g$, 80-150 $m^2/g$ or 90-120 $m^2/g$.

22. The solid form according to claim 21 wherein said solid form is a crystalline form according to any one of claims 1-19.

23. The solid form according to claim 22 wherein said form is crystalline form B according to any one of claims 1-3.

24. A solid form of ledipasvir having::

- a content of the keto impurity of not more than 0.1% area percent preferably not more than 0.08 % area percent more preferably not more than 0.05% area percent, as measured by HPLC; or

- a total impurity content of not more than 0.2% area percent, preferably not more than 0.1% area percent, more preferably not more than 0.08% area percent, particularly not more than 0.06% area percent, and most preferably not more than 0.05% area percent, as measured by HPLC.

25. The solid form according to claim 24 wherein said solid form is a crystalline form, preferably a crystalline form according to any one of claims 1-19; an amorphous form; or a ledipasvir premix, wherein if the solid form is a premix, the % of the keto impurity or the total impurity is calculated with respect to the amount of ledipasvir in the premix.

26. A process for preparing crystalline form B according to any one of claims 1-3 comprising crystallizing ledipasvir from a mixture of water and acetonitrile.

27. A process for preparing crystalline form B according to any one of claims 1-3 comprising a) combining ledipasvir with a solvent system comprising an organic solvent and water; b) optionally heating to a temp of about 0 °C to about 80 °C; c) optionally cooling to about 20 °C to about 25 °C; d) optionally seeding with form B seeds; e) optionally adding water and f) isolating crystalline form B and optionally

drying.

28. The process according to claim 27 wherein the organic solvent in step (a) is acetonitrile or acetone and the mixture in step (a) comprises about 20 % to about 50%, more preferably about 30 % of water (by volume) in the organic solvent.

29. The process according to claims 27-28 wherein in step (b) the solvent system is heated to about 20°C to about 70°C optionally with stirring.

30. The process according to claims 27-29 comprising a) combining ledipasvir with a solvent system comprising 30% acetonitrile in water, b) heating to a temp of about 20 °C to about 70 °C and stirring for 1-2 hours, c) cooling to about 20 °C to about 25 °C and stirring for about 1 hour to about 5 hours, d) seeding with form B seeds e) adding water 3-10 vol and optionally stirring and f) isolating crystalline form B.

31. Crystalline form B produced by the process according to any of claims 26-30.

32. A process for preparing form G according to any one of claims 1 and 4-9 comprising crystallizing ledipasvir from a mixture of dichloromethane (MDC) and acetone.

33. A process for preparing form G according to any one of claims 1 and 4-9 comprising a) providing a solution of ledipasvir in MDC, b) adding acetone, c) stirring and d) separating the crystalline solid formed and optionally drying.

34. The process according to claim 33 wherein the reaction mixture in step a and/or b is heated to about 20°C to about 40°C, preferably to about 35°C , optionally with stirring.

35. The process according to any one of claims 33-34 wherein in step d the drying is performed at a temperature of about 0 °C to about 40 °C, more preferably at a temperature of about 30 °C to about 40 °C under reduced pressure.

36. A process for preparing crystalline form G according to any of claims 1 and 4-9, comprising recrystallizing a Ledipasvir acetone solvate (preferably a diacetone solvate) from water.

37. A process according to claim 36 comprising: a) providing the Ledipasvir acetone solvate in water, b) heating the reaction mass to a temperature of about 30 °C to about 60 °C, preferably to a temperature of 45 °C to about 50 °C, optionally under stirring, c) cooling the mixture to a temperature of 20 °C to about 25 °C, and d) separating the crystalline solid formed and optionally drying.

38. Crystalline form G produced by the process according to any one of claims 32-37.

39. A process for preparing crystalline form P according to any one of claims 1, and 16-17 comprising crystallizing ledipasvir from a mixture of dichloromethane (MDC) and acetonitrile.

40. A process for preparing crystalline form P according to any one of claims 1, and 16-17 comprising a) providing a solution of ledipasvir in MDC, b) adding acetonitrile, c) stirring and d) separating the crystalline solid formed and optionally drying.

41. The process according to claim 40 wherein the reaction mixture in step a and/or b is heated to about 20 °C to about 40 °C, more preferably to about 35 °C, optionally with stirring.

42. The process according to any one of claims 40-41 wherein in step d the drying is performed at a temperature of about 0 °C to about 40 °C, more preferably at a temperature of about30 °C to about 40 °C under reduced pressure.

43. Crystalline form P produced by the process of any of claims 39-42.

44. A process for preparing crystalline form H according to any one of claims 1 and 10, comprising drying of form G according to any one of claims 1, 4-9 or 38, or drying of form P according to any one of claims 1, 16-17 or 43.

45. The process according to claim 44 wherein the drying is performed at a temperature of about 40 °C to about 110 °C, more preferably at a temperature of about 95 °C to about 100 °C under reduced pressure.

46. Crystalline form H produced by the process of any of claims 44-45.

47. A process for preparing crystalline form M according to any one of claims 1 and 11-12 comprising crystallizing ledipasvir from a mixture of toluene and acetone.

48. A process for preparing crystalline form M according to any one of claims 1 and 11-12 comprising a) providing a solution comprising ledipasvir, toluene and acetone, b) stirring c) isolating crystalline form M.

49. The process according to claim 48 wherein the solution in step a comprises 40% to about 45% of toluene (by volume) in acetone.

50. The process according to claims 48-49 wherein the stirring in step b is performed for about 7 to about 24 hours.

51. The process according to claims 48-50 wherein the reaction mixture in step a and b is heated to a temperature of from about 10°C to about 40°C , preferably to a temperature of about 20°C to about 30°C.

52. Crystalline form M produced by the process of any of claims 47-51.

53. A process for preparing crystalline form O according to any one of claims 1 and 14-15 comprising crystallizing ledipasvir from a mixture of toluene and acetonitrile.

54. A process for preparing crystalline form O according to any one of claims 1 and 14-15 comprising: a) providing a solution of ledipasvir in toluene, b) optionally cooling to about 25 °C to about 30 °C, c) adding acetonitrile, d) optionally cooling to about 0 °C to about 5 °C, e) optionally seeding with form M seeds or form O seeds and stirring, and f) isolating crystalline form O.

55. A process for preparing crystalline form O according to any one of claims 1 and 14-15 comprising: a) providing a solution comprising ledipasvir and toluene, optionally at elevated temperature, b) optionally adding charcoal and passing the reaction mass through diatomaceous earth (e.g. Celite®), c) cooling to about 25 °C to about 30 °C, d)

adding acetonitrile, e) cooling to about 0 °C to about 10 °C, f) seeding with form M seeds or form O seeds and stirring and g) separating the crystalline solid formed and optionally drying.

56. The process according to any of claim 54-55 wherein the seeding step is performed prior to the second cooling step.

57. The process according to any one of claims 54-56 wherein the solution in step a comprises about 50% to about 60% of toluene (by volume) in acetonitrile.

58. The process according to any one of claims 54-57 wherein the reaction mixture in step a is heated to a temperature of about 40°C to about 80°C preferably to a temperature of about 50°C to about 55°C.

59. The process according to any one of claims 54-58 wherein the stirring is for about 2 to about 30 hours and the drying in carried out for about0.5 to about 1 hours at a temperature of about 10°C to about 40°C .

60. Crystalline form O produced by the process of any of claims 53-59.

61. A process for preparing crystalline form N according to any one of claims 1 and 13 comprising drying of form M according to any of claims 1, 11, 12 and 52.

62. The process of claim 61 wherein drying is performed at a temperature of about 50°C to about 110°C, more preferably at a temperature of about 80°C to about 105°C under reduced pressure.

63. Crystalline form N produced by the process of any of claims 61-62.

64. A crystalline premix of Ledipasvir comprising Ledipasvir in a crystalline form according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63.

65. Ledipasvir according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63 for use in the preparation of other solid state forms of ledipasvir or crystalline ledipasvir Premix.

66. Use of Ledipasvir according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63 for the preparation of other solid state forms of ledipasvir or crystalline ledipasvir Premix.

67. Ledipasvir according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63, or a crystalline premix of Ledipasvir according to claim 64, for use in the preparation of a pharmaceutical composition.

68. Use of Ledipasvir according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63, or a crystalline premix of Ledipasvir according to claim 64, for the preparation of a pharmaceutical composition.

69. A pharmaceutical composition comprising a solid form of Ledipasvir according to any one of claims 1-25, 31, 38, 43, 46, 52, 60 and 63, or a crystalline premix of Ledipasvir according to claim 64, or combination thereof.

70. The pharmaceutical composition according to claim 69 wherein the pharmaceutical composition is a solid composition and the ledipasvir retains its solid state form, preferably wherein the ledipasvir retains its solid state form following storage at 25°C for 1 month at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH, more preferably following storage at 25°C for 3 months at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH, and most preferably following storage at 25°C for 12 months at: 10%-90% relative humidity (RH), 20%-90% RH, 30%-90% RH, 40%-90% RH, 50%-90% RH, 60%-90% RH, 70%-90% RH or 75%-85% RH.

71. The pharmaceutical composition according to claim 70 wherein the solid form is crystalline form B according to any of claims 1-3.

72. A process for preparation of a pharmaceutical composition according to claims 69-71, comprising combining the solid form of ledipasvir according to any one of claims 1-25,

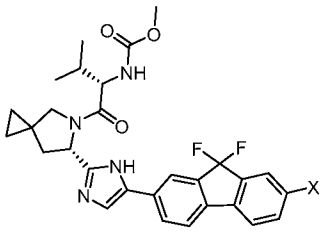
31, 38, 43, 46, 52, 60 and 63, or a crystalline premix of Ledipasvir according to claim 64 with at least one pharmaceutically acceptable excipient.

73. The crystalline forms of Ledipasvir according to claims 1-25, 31, 38, 43, 46, 52, 60 and 63, or a crystalline premix according to claim 64, or the pharmaceutical compositions according to claims 69-71, for use in therapy.

74. The crystalline forms of Ledipasvir according to claims 1-25, 31, 38, 43, 46, 52, 60 and 63, or a crystalline premix according to claim 64, or the pharmaceutical compositions according to claims 69-71, for use in treatment of Hepatitis C.

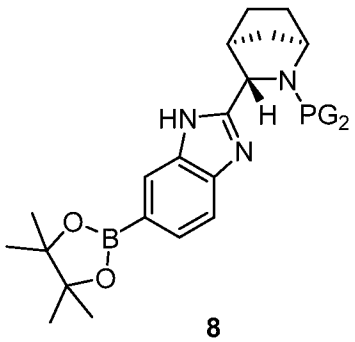
75. A method of treating a subject suffering from hepatitis C or otherwise in need of a treatment comprising administering an effective amount of a pharmaceutical composition according to claims 69-71.

76. A process for preparation of Ledipasvir comprising:
a) reacting a compound of formula 7



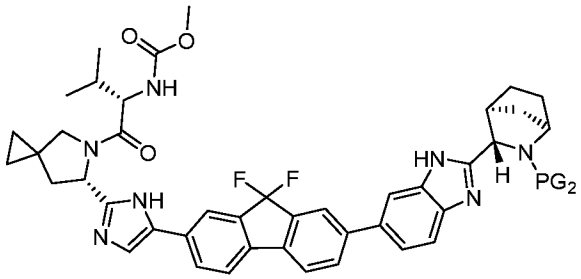

7

with a compound of formula 8



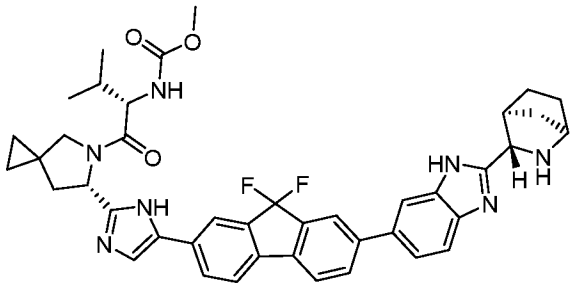

8

to provide a compound of formula 9



9 ;

b) deprotecting the compound of formula 9 to provide compound of formula 10



10

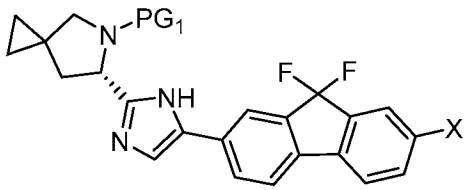
or salt thereof; and

c) reacting the compound of formula 10 or salt thereof with Moc L-Valine to afford Ledipasvir (compound 1),

wherein X is halo, PG2 is an amine protecting group and wherein compound of formula 9 is not isolated.

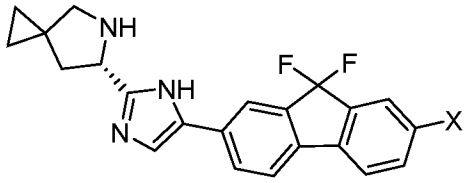
77. The process of claim 76 wherein the compound of formula 7 is prepared by a process comprising:

i) deprotecting a compound of formula 5



5

to afford compound of formula 6 or a salt thereof;

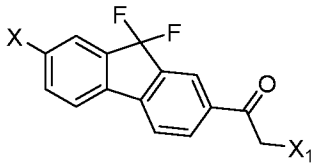


6

and ii) coupling the compound of formula 6 or salt thereof with Moc L-Valine, wherein X is halo, PG1 is an amine protecting group and the compound of formula 6 or the salt thereof is isolated.

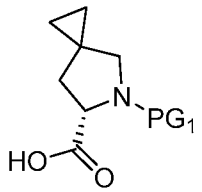
78. The process according to claim 77, wherein the compound of formula 5 is prepared by a process comprising:

A) reacting a compound of formula 2:



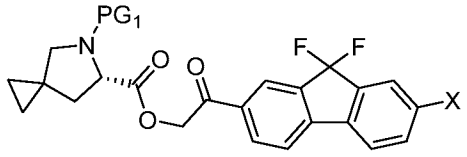
2

and a compound of formula 3



3

to afford a compound of formula 4;



4 ; and

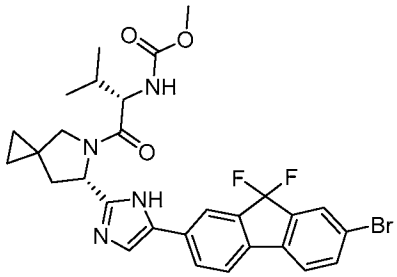
B) converting the compound of formula 4 to the compound of formula 5;

wherein X is halo, X1 is halo, PG1 is an amine protecting group and wherein the compound of formula 4 is not isolated.

79. The process according to any of claims 76-78, wherein PG1 and PG2 are each independently selected from the group consisting of: Fmoc, Cbz, benzyl, trityl, Boc, trifluoroacetyl derivative, or a phthalic anhydride derivative, and X is chloro or bromo, and preferably wherein PG1 is Boc, PG2 is Boc and X is bromo.

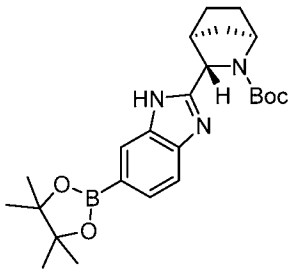
80. A process for preparation of Ledipasvir comprising:

a) reacting a compound of formula 7a



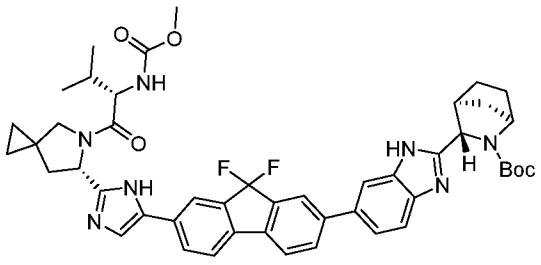
**7a**

with a compound of formula 8a



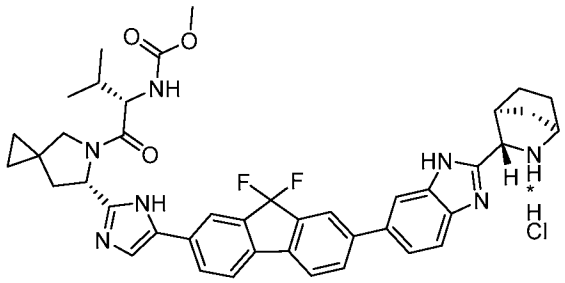
**8a**

to provide a compound of formula 9a



**9a** ;

b) deprotecting the compound of formula 9a to provide compound of formula 10a;



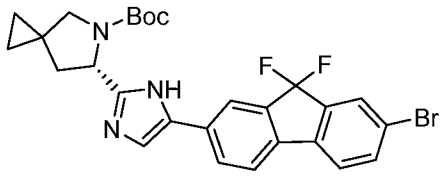
10a ; and

c) reacting the compound of formula 10a with Moc L-Valine to afford Ledipasvir (compound 1)

wherein the compound of formula 9a is not isolated.

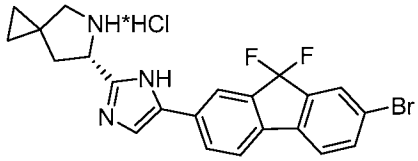
81. The process of claim 80 wherein the compound of formula 7a is prepared by a process comprising:

i) deprotecting compound of formula 5a



5a

to afford compound of formula 6a



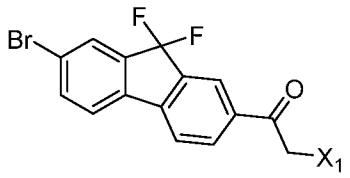
6a ; and

ii) coupling compound of formula 6a with Moc L-Valine,

wherein the compound of formula 6a is isolated, the coupling agent is N-hydroxybenzotriazole (HOBt) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl), and step ii) is carried out at a temperature ranging from about -30°C to about 60°C, preferably step ii) is performed at a temperature of about 0°C to about 10°C.

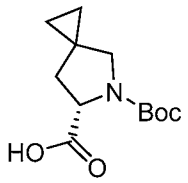
82. The process according to claim 81, wherein the compound of formula 5a is prepared by a process comprising:

A) reacting compound of formula 2a



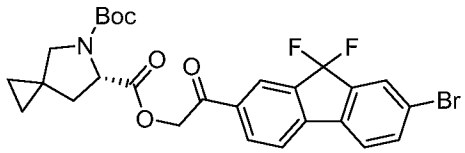
**2a, $X_1$= halogen**

and compound of formula 3a



**3a**

to afford compound of formula 4a;



**4a** ; and

B) converting the compound of formula 4a to the compound of formula 5a;

wherein compound of formula 4a is not isolated, and steps A and B are performed in the same solvent, preferably wherein the solvent is a single solvent, and more preferably wherein the solvent is toluene.

83. A process for purification of Ledipasvir comprising crystallizing ledipasvir from a solvent system selected from the group consisting of: acetonitrile/toluene, acetonitrile/MDC, THF/toluene, acetone/toluene and acetone/MDC.

84. A process according to claim 83, wherein the purified Ledipasvir is a crystalline form selected from any one of forms G, M, O or P, preferably form O or form P.

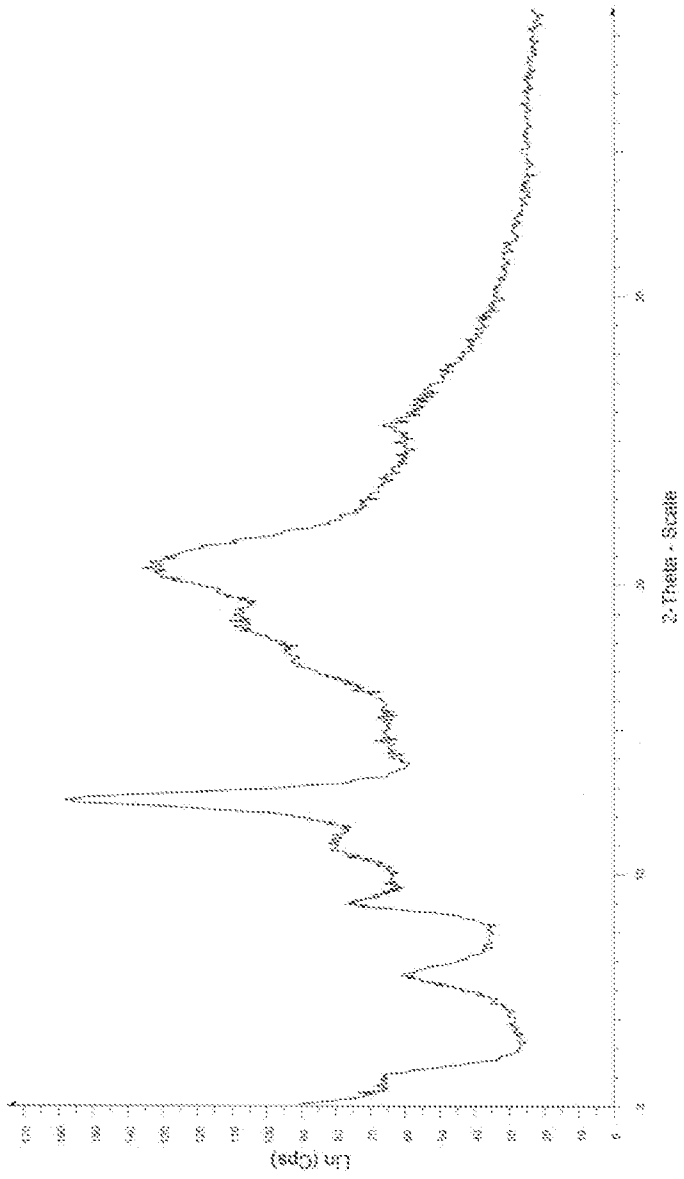



Figure 1.X-ray powder diffractogram of Form A of Ledipasvir.

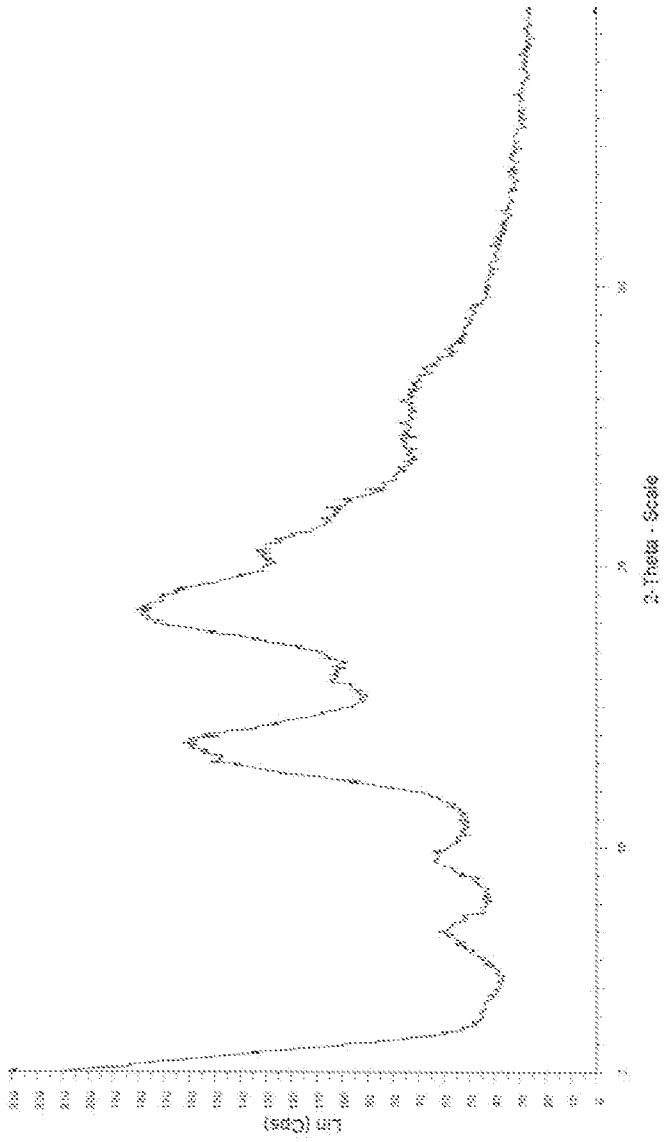



Figure 2.X-ray powder diffractogram of Form B of Ledipasvir.

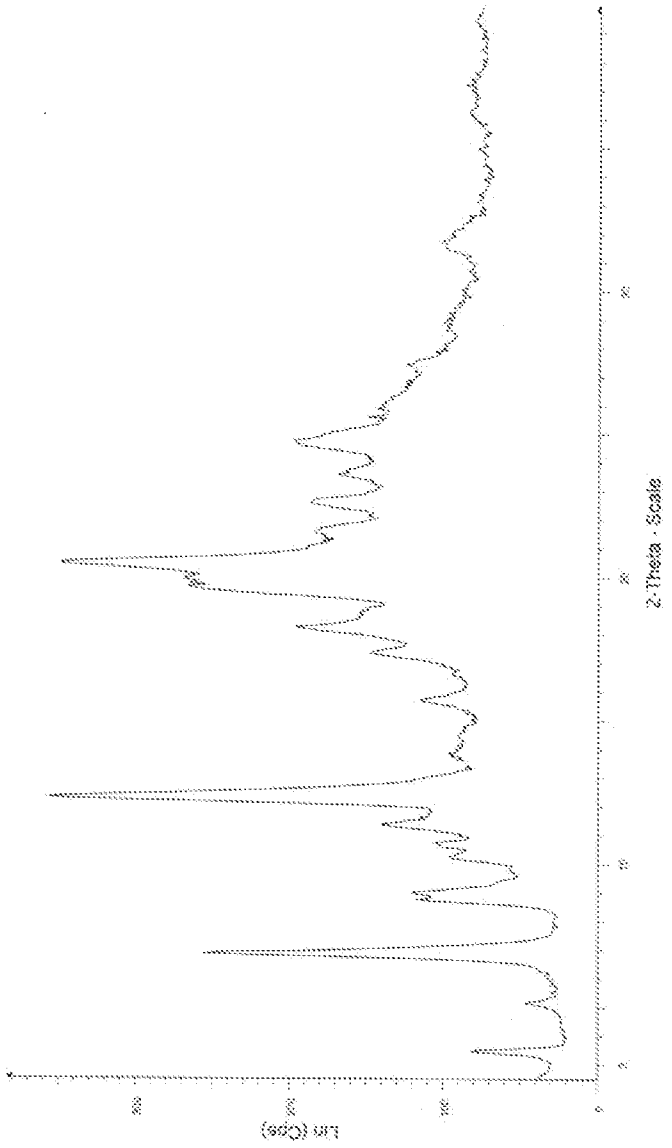



Figure 3.X-ray powder diffractogram of Form C of Ledipasvir.

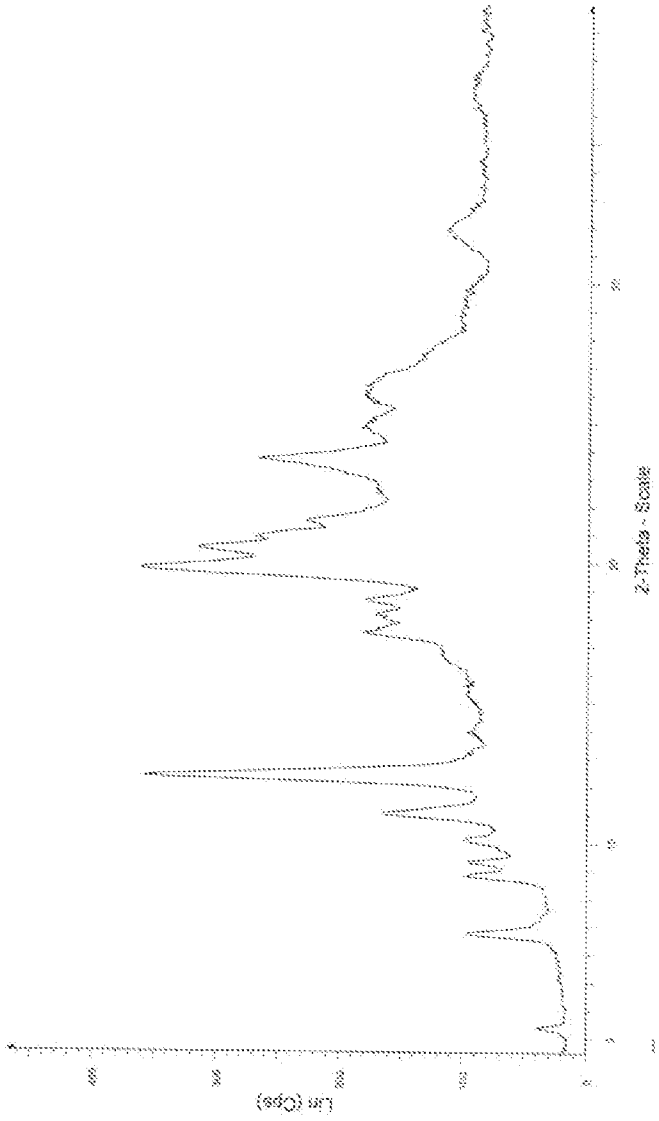



Figure 4.X-ray powder diffractogram of Form D of Ledipasvir.

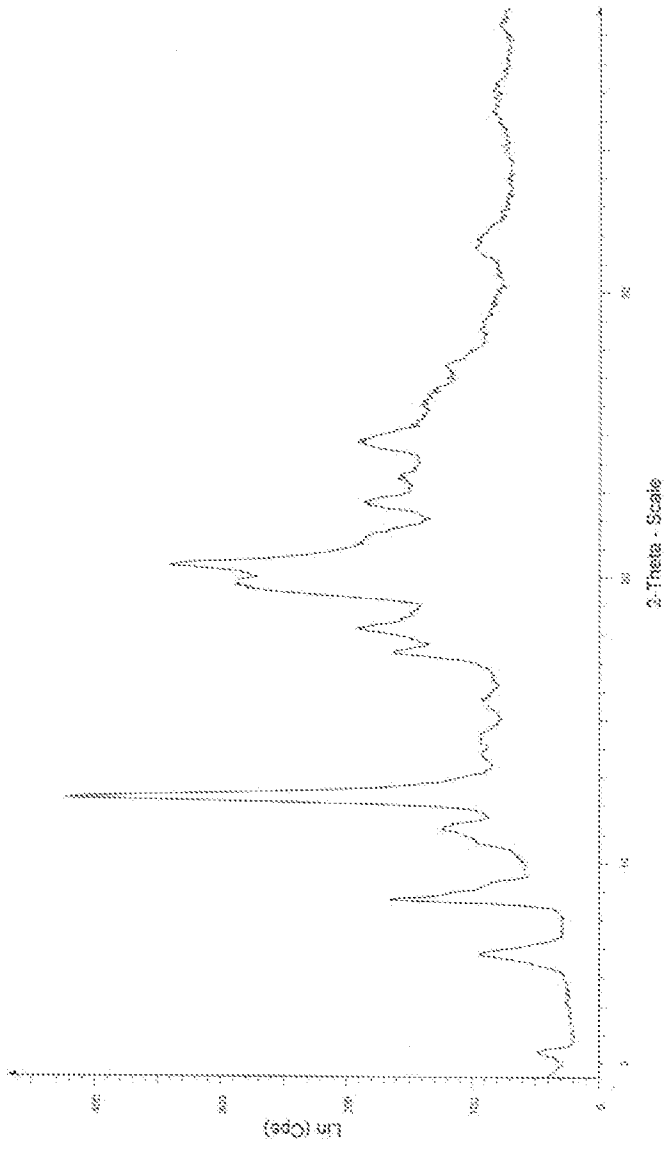



Figure 5.X-ray powder diffractogram of Form E of Ledipasvir.

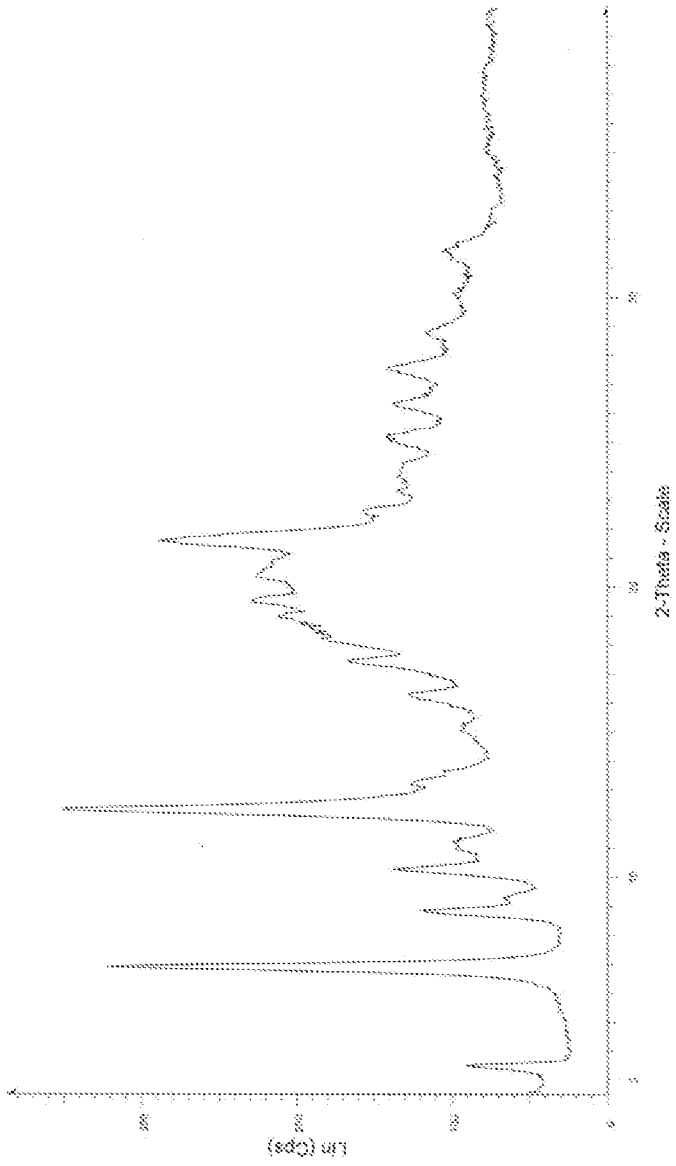



Figure 6.X-ray powder diffractogram of Form F of Ledipasvir.

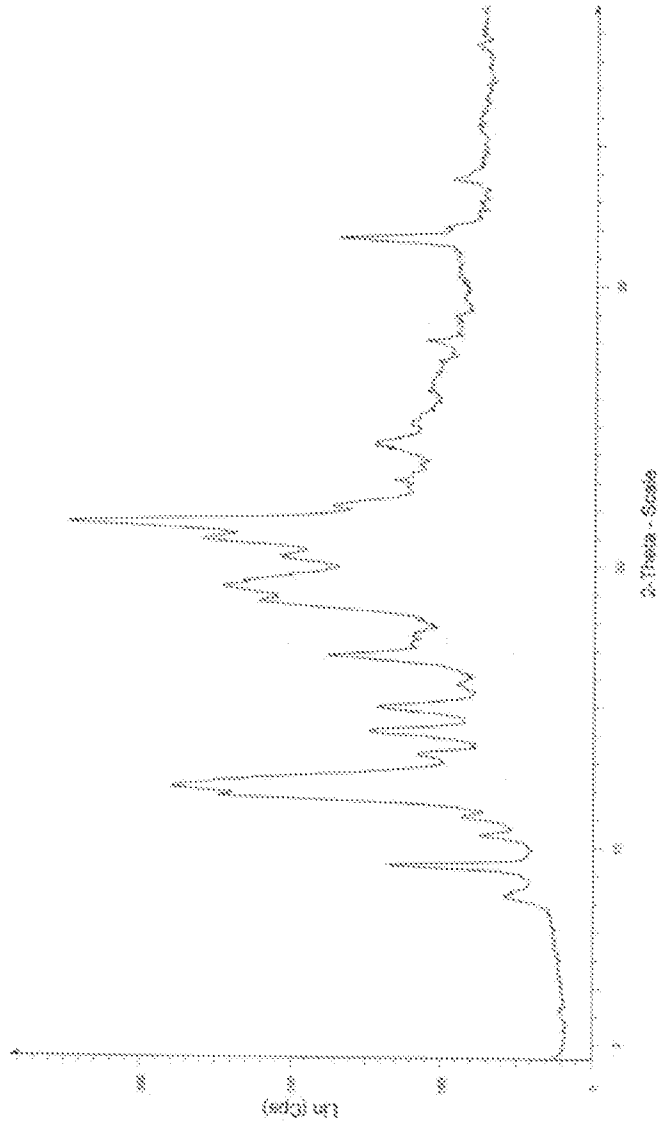


Figure 7.X-ray powder diffractogram of Form III of Ledipasvir.

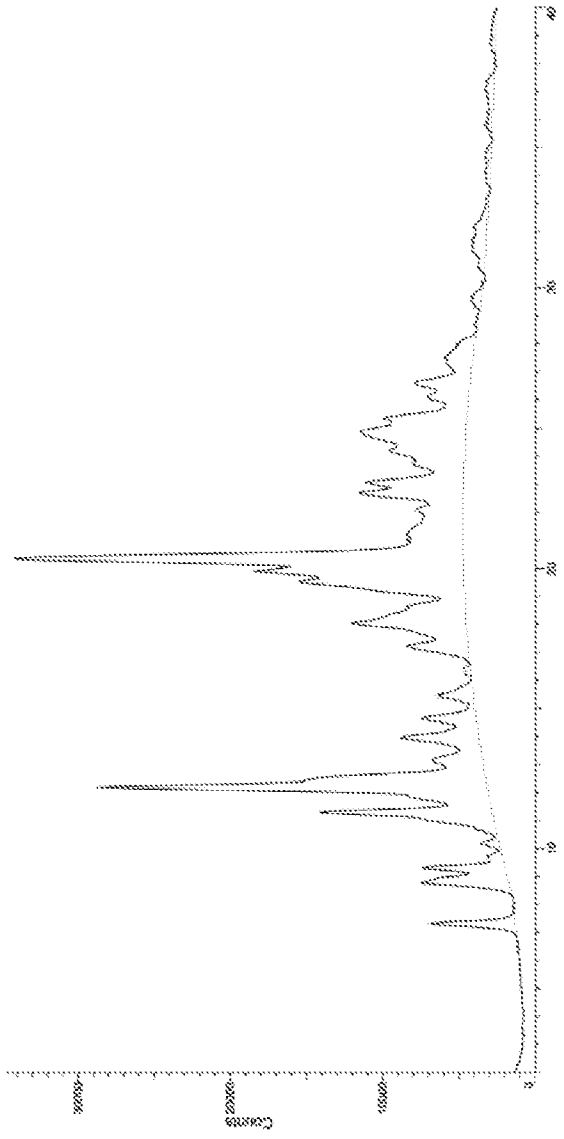
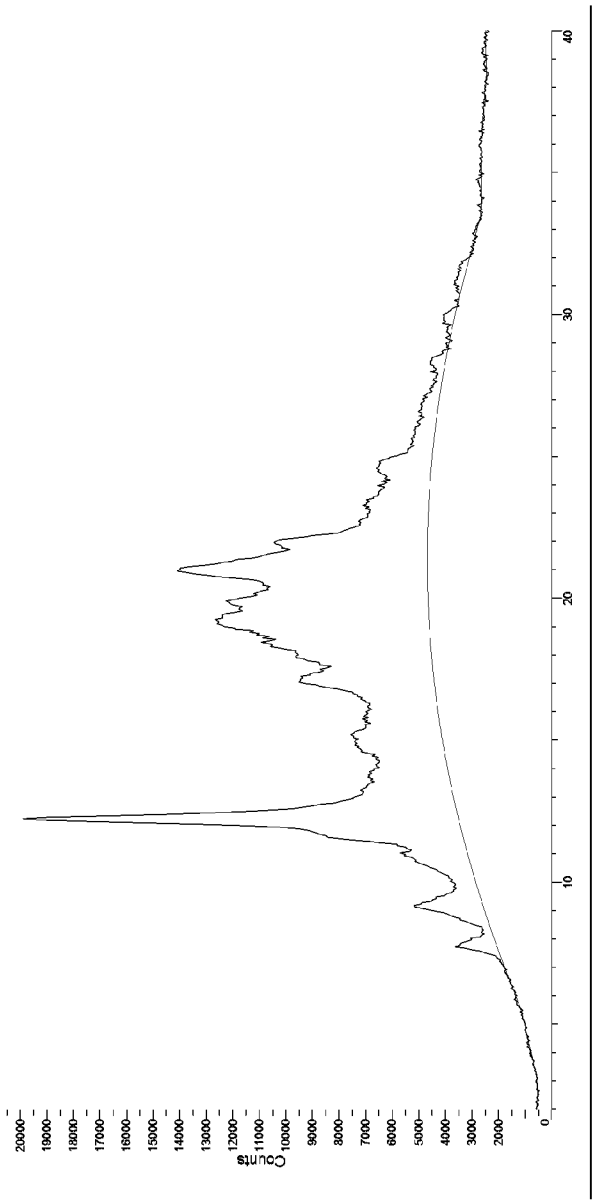



Figure 8.X-ray powder diffractogram of Form G of Ledipasvir.

Figure 9.X-ray powder diffractogram of Form H of Ledipasvir, obtained by example 8.



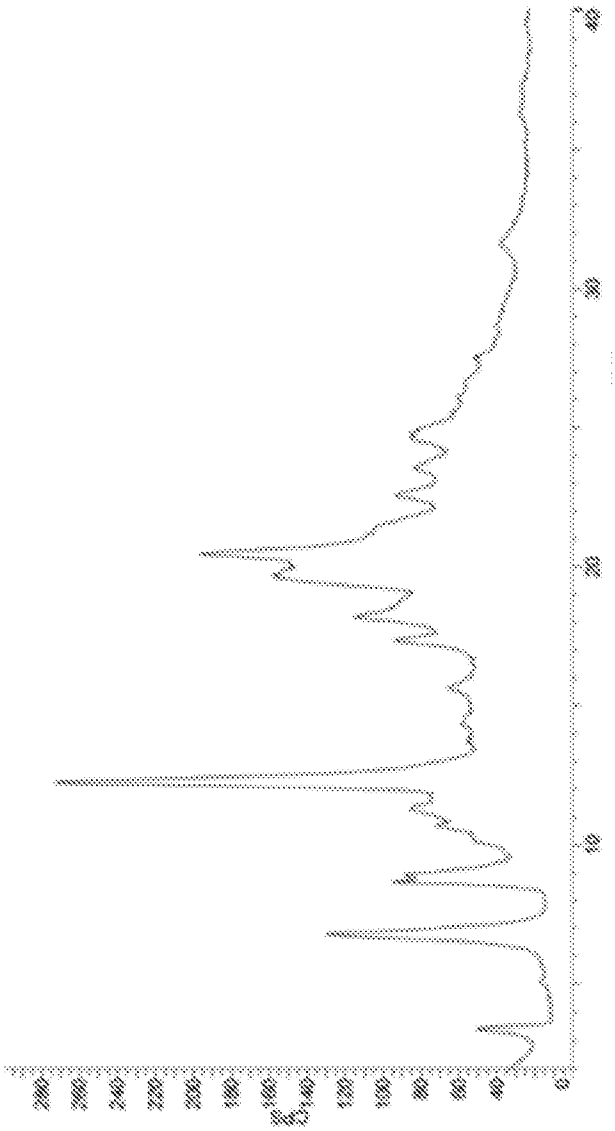


Figure 10. X-ray powder diffractogram of Form C of Ledipasvir.

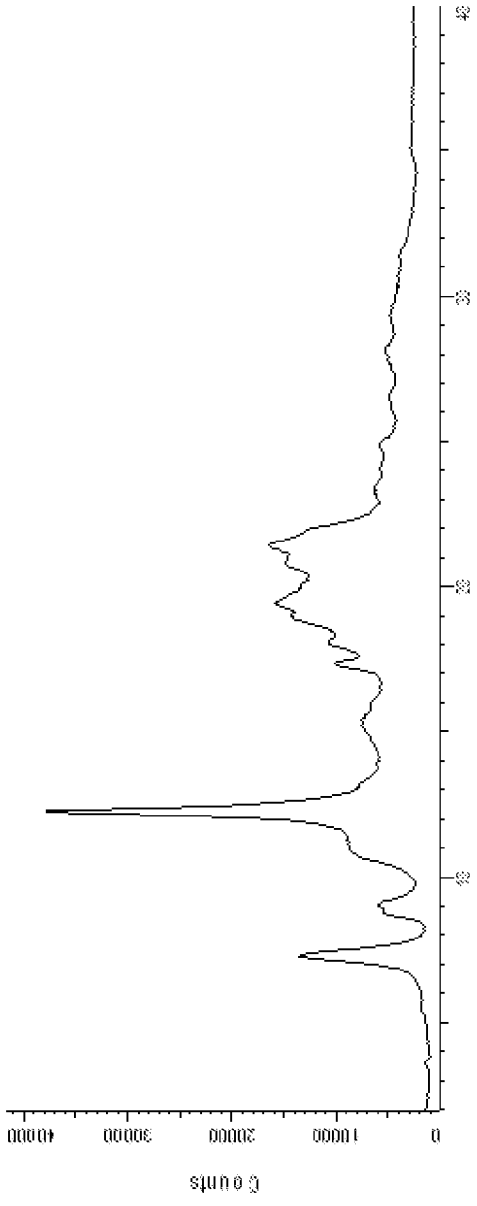



Figure 11. X-ray powder diffractogram of Form J of Ledipasvir.

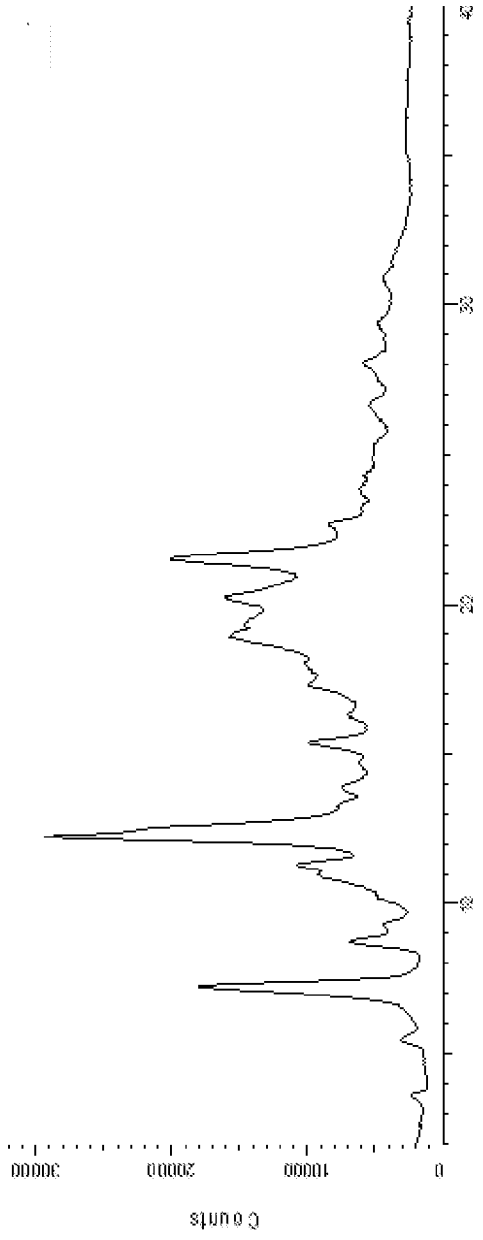



Figure 12. X-ray powder diffractogram of Form K of Ledipasvir.

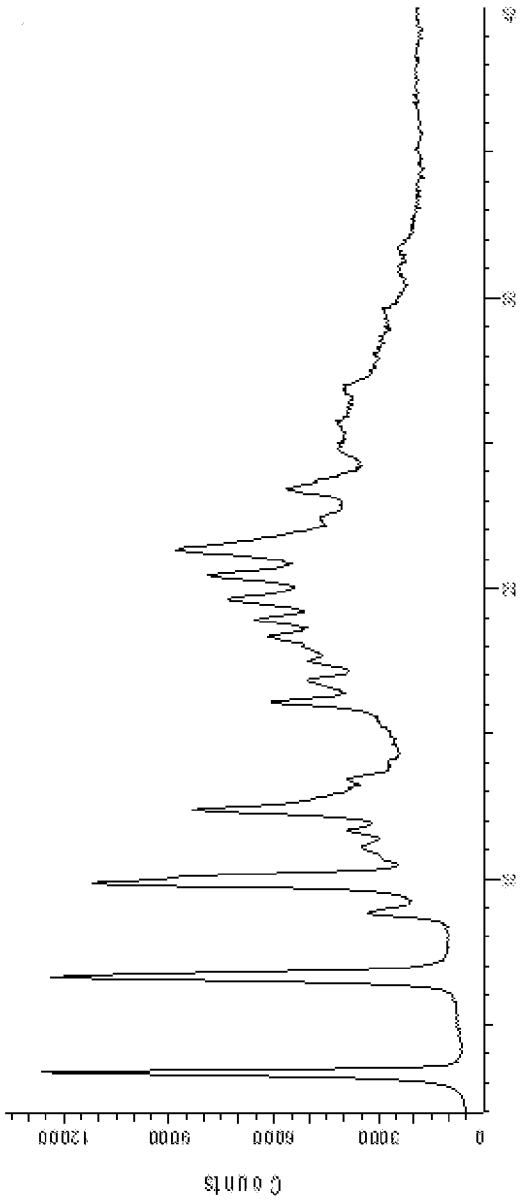
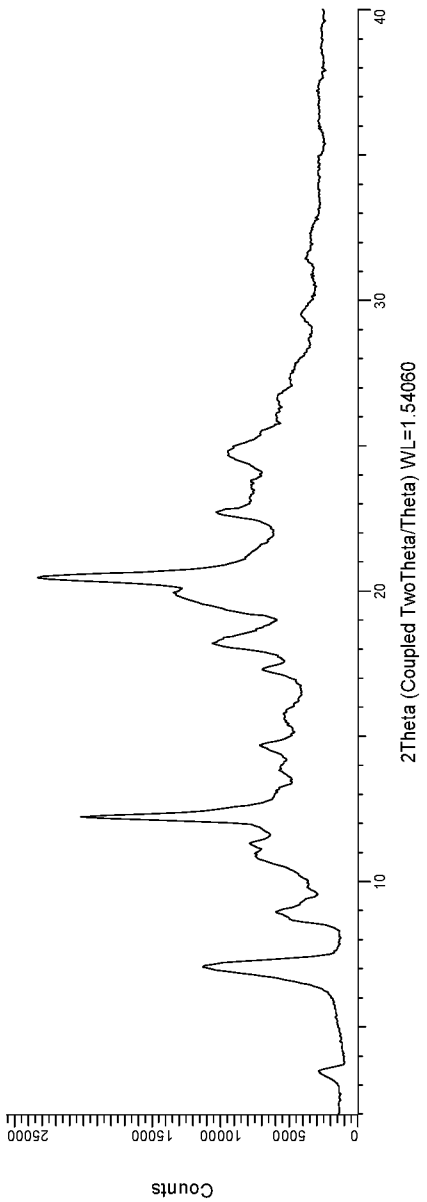



Figure 13. X-ray powder diffractogram of Form L of Ledipasvir.

Figure 14. X-ray powder diffractogram of Form M of Ledipasvir, obtained by procedure 1 of example 14



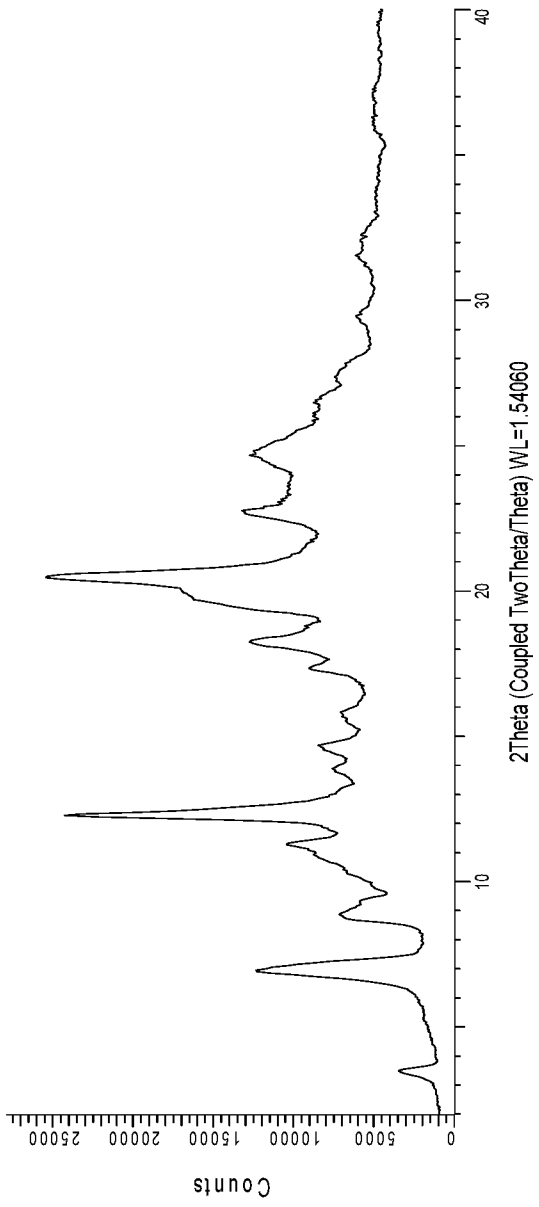



Figure 15. X-ray powder diffractogram of Form M of Ledipasvir, obtained by procedure 2 of example 14

Figure 16. X-ray powder diffractogram of Form N of Ledipasvir, obtained by procedure 1 of example 15

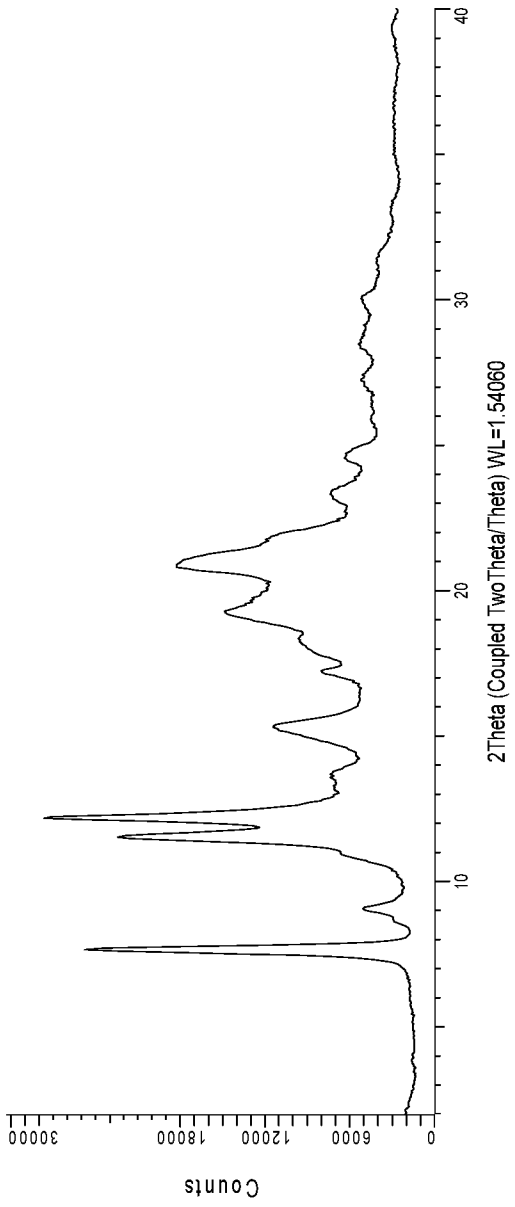
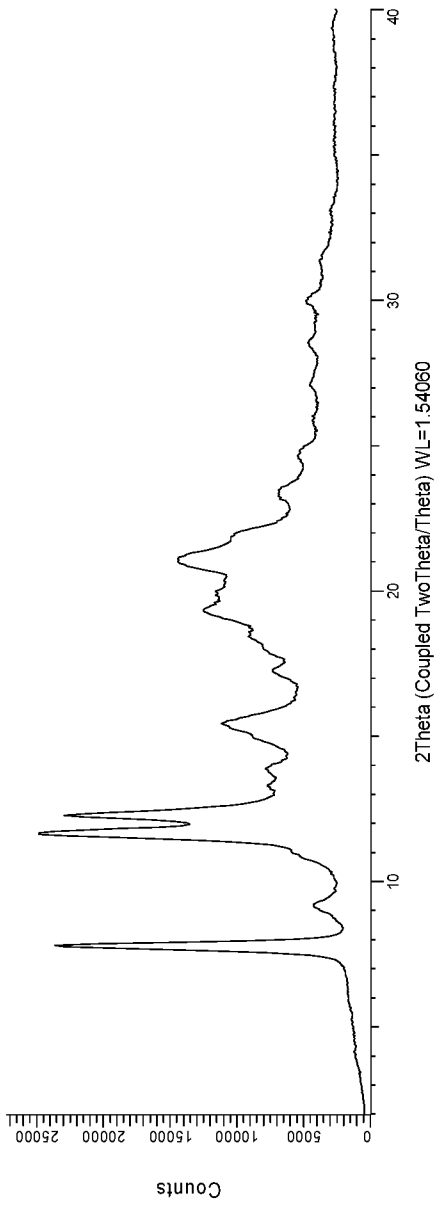


Figure 17. X-ray powder diffractogram of Form N of Ledipasvir, obtained by procedure 2 of example 15



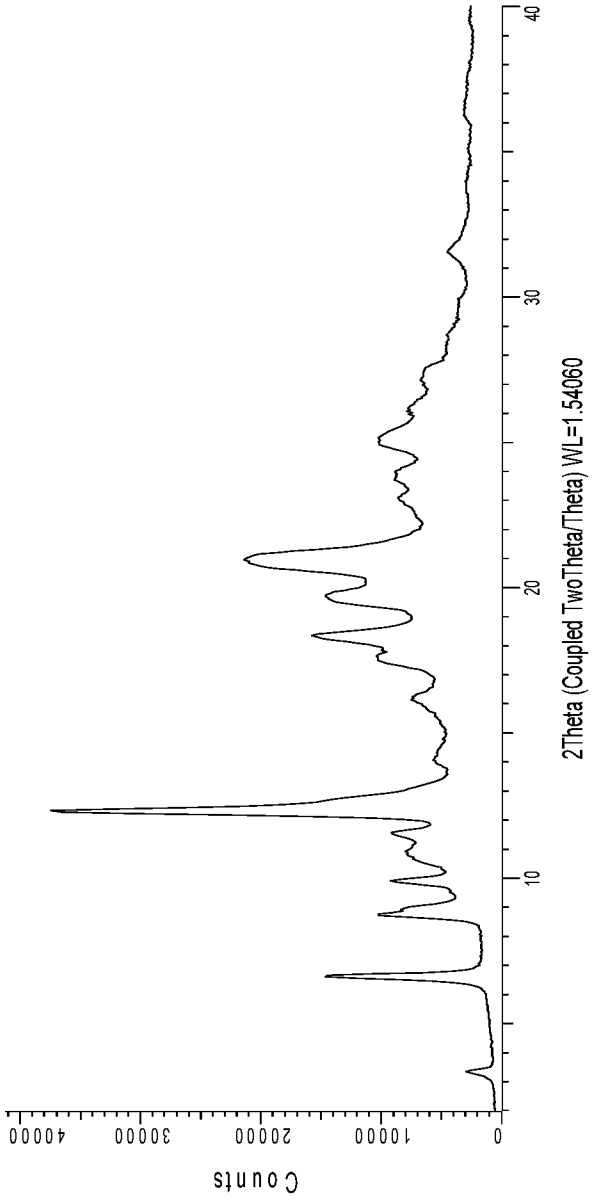



Figure 18. X-ray powder diffractogram of Form O of Ledipasvir.

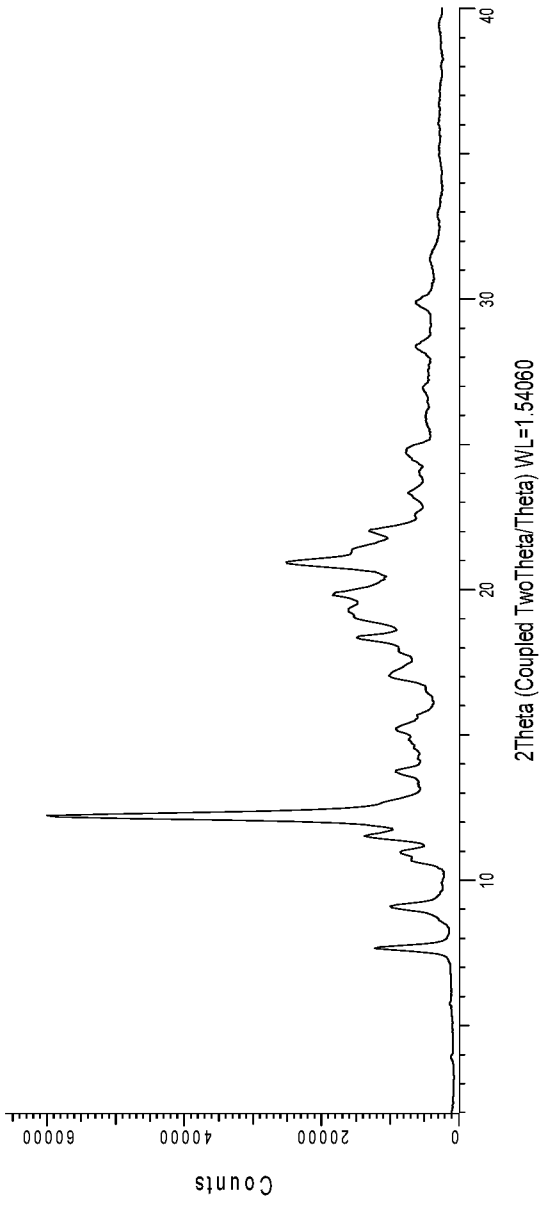



Figure 19. X-ray powder diffraction of form H of Ledipasvir obtained by example 17.

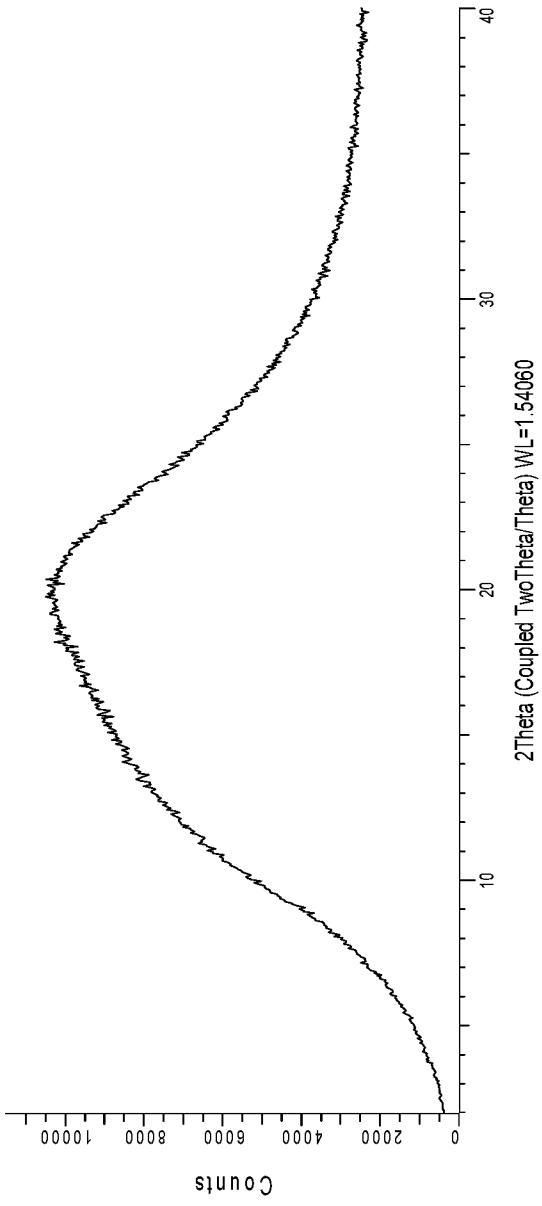



Figure 20. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 1 of example 18.

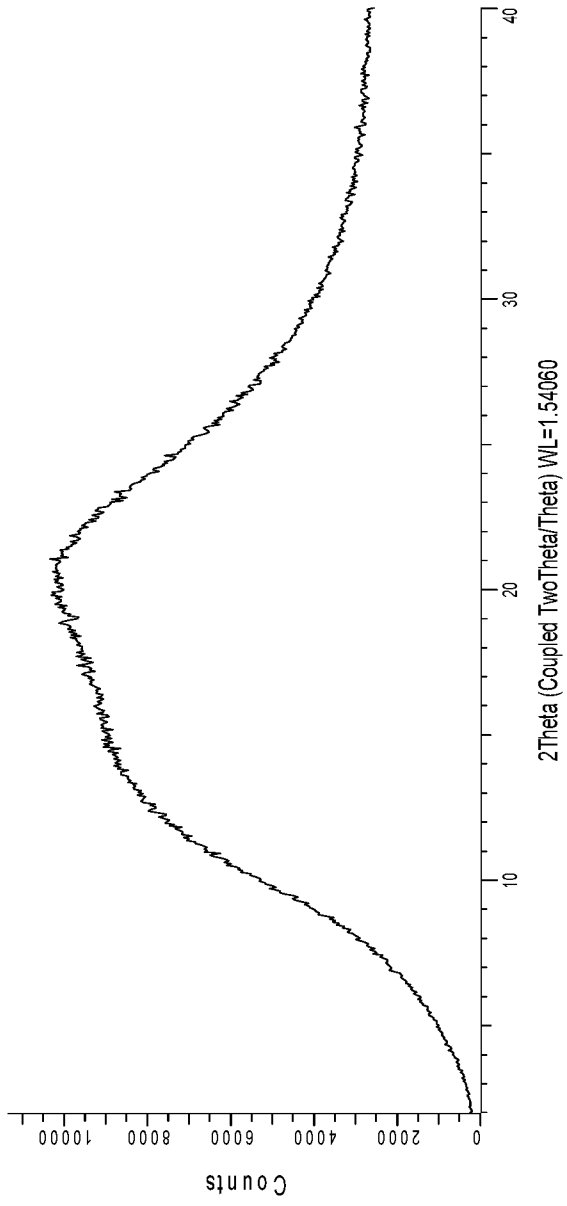



Figure 21. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 2 of example 18.

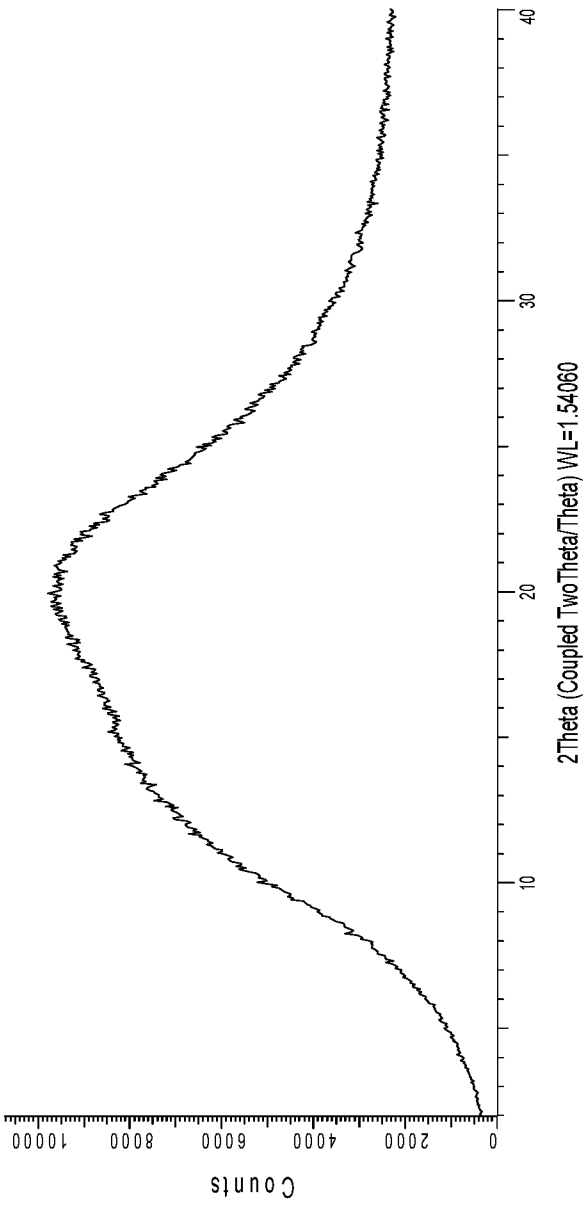



Figure 22. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 3 of example 18.

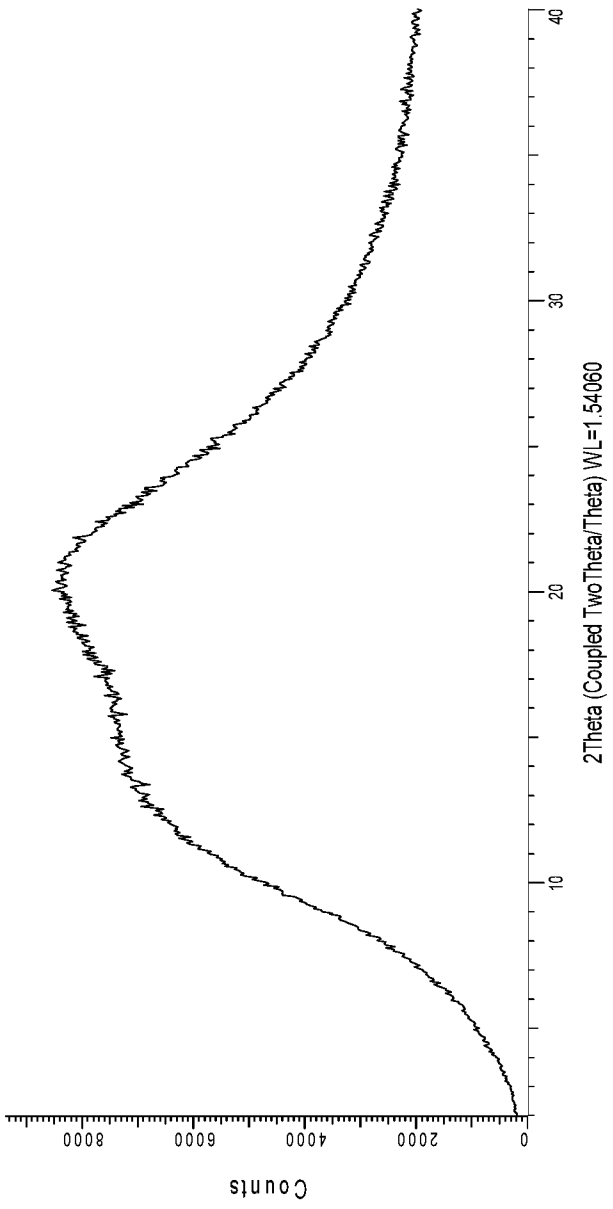



Figure 23. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 4 of example 18.

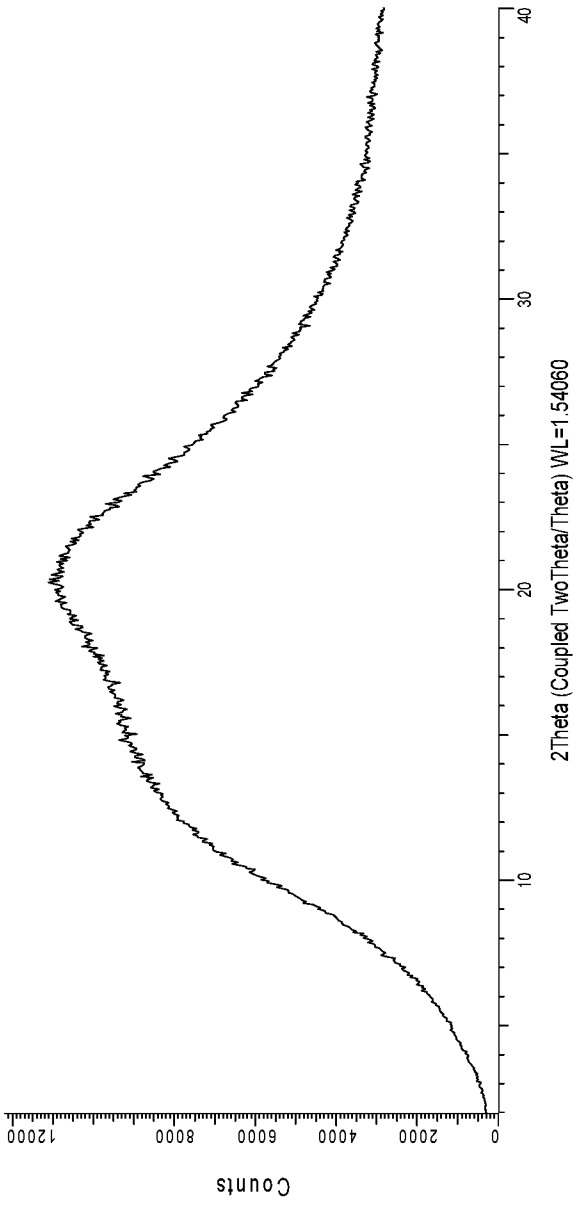



Figure 24. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 5 of example 18.

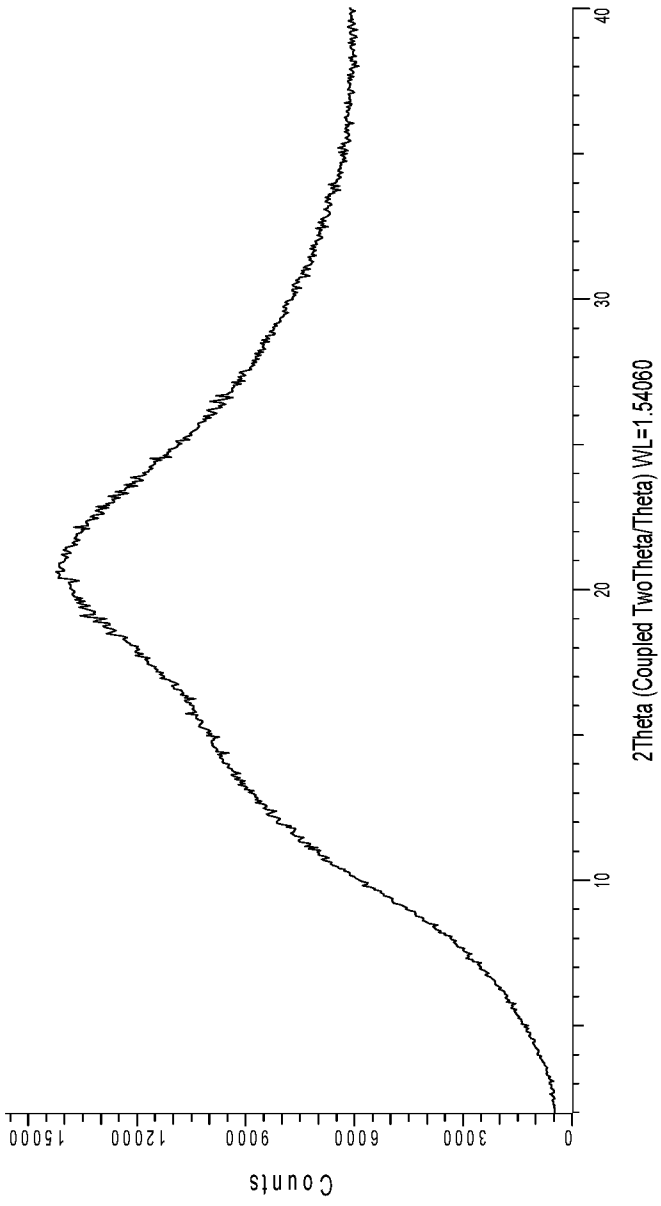



Figure 25. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 6 of example 18.

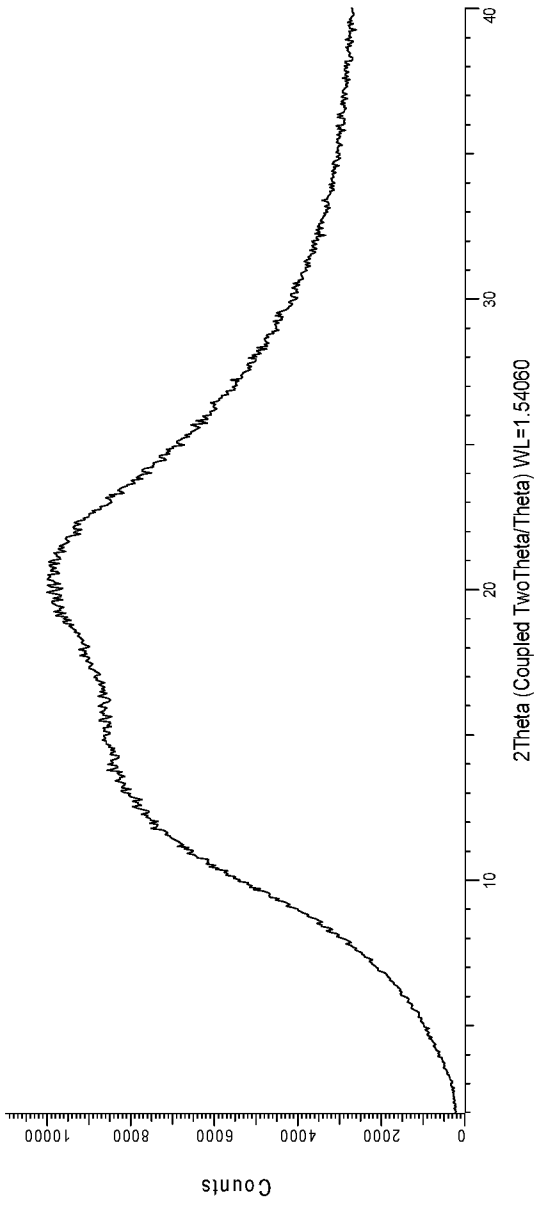



Figure 26. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 7 of example 18.

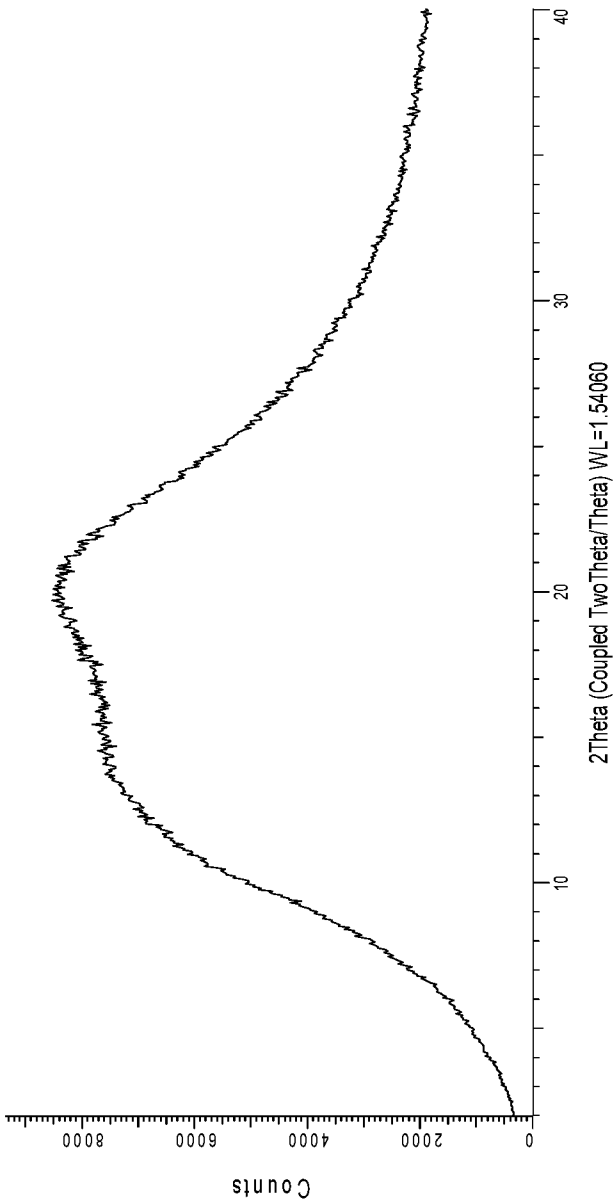



Figure 27. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 8 of example 18.

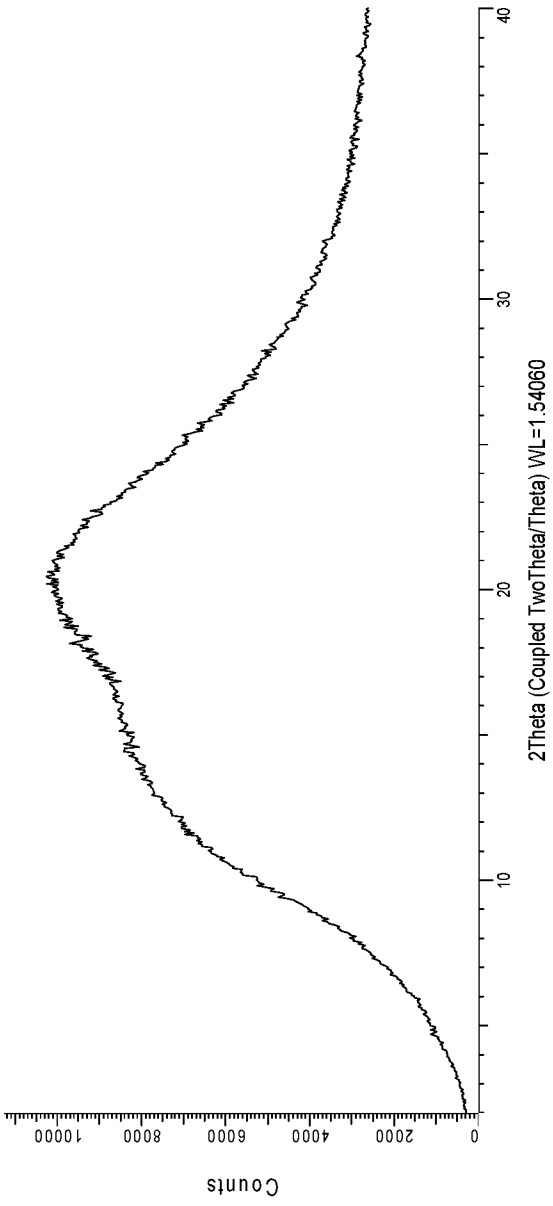



Figure 28. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 9 of example 18.

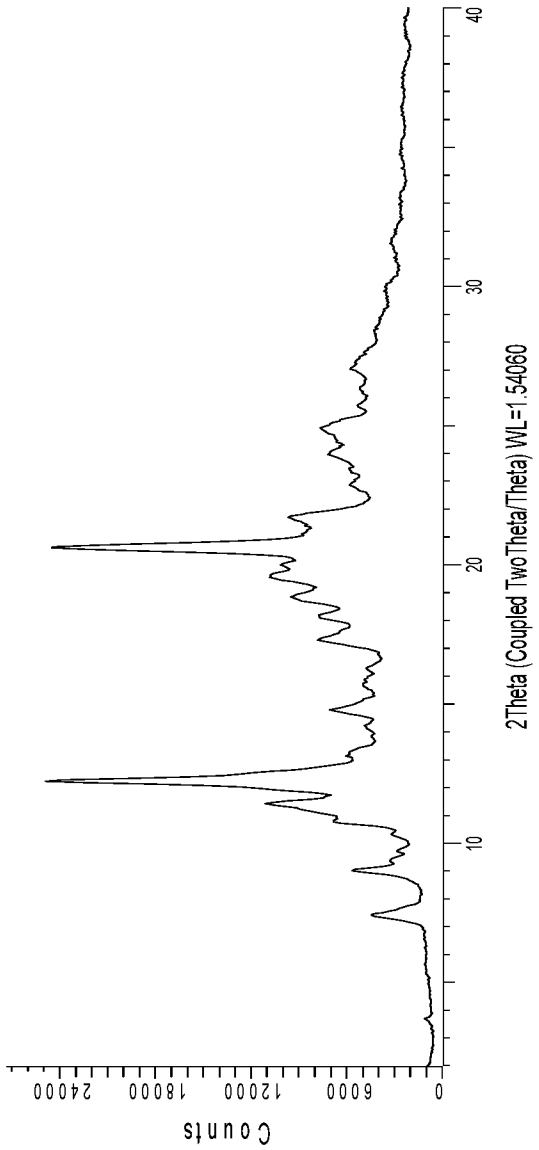



Figure 29. X-ray powder diffraction of form P of Ledipasvir obtained by example 19.

Figure 30. X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 1 of example 21.

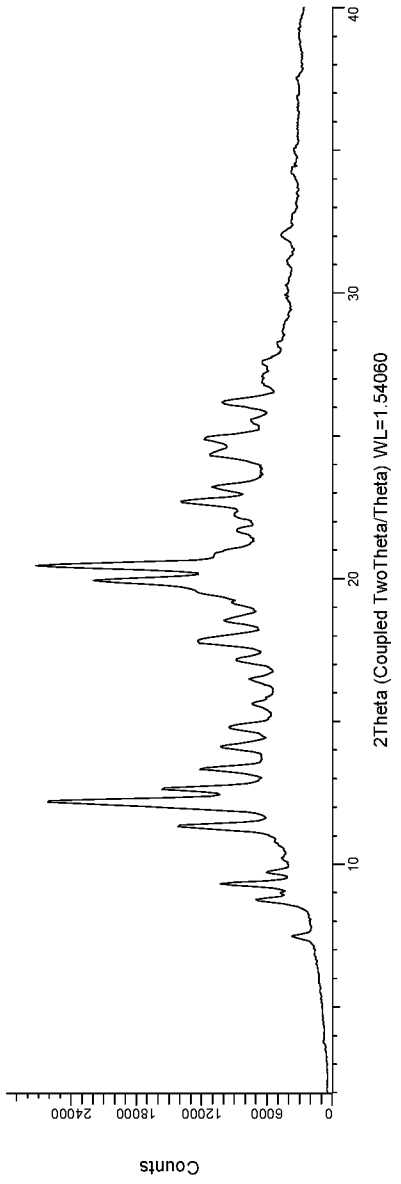


Figure 31. X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 2 of example 21.

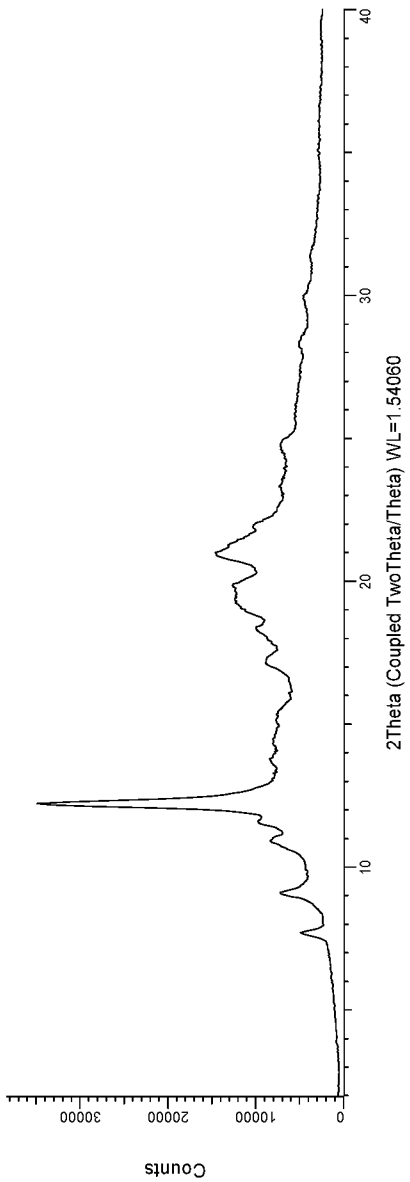


Figure 32. X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 3 of example 21.

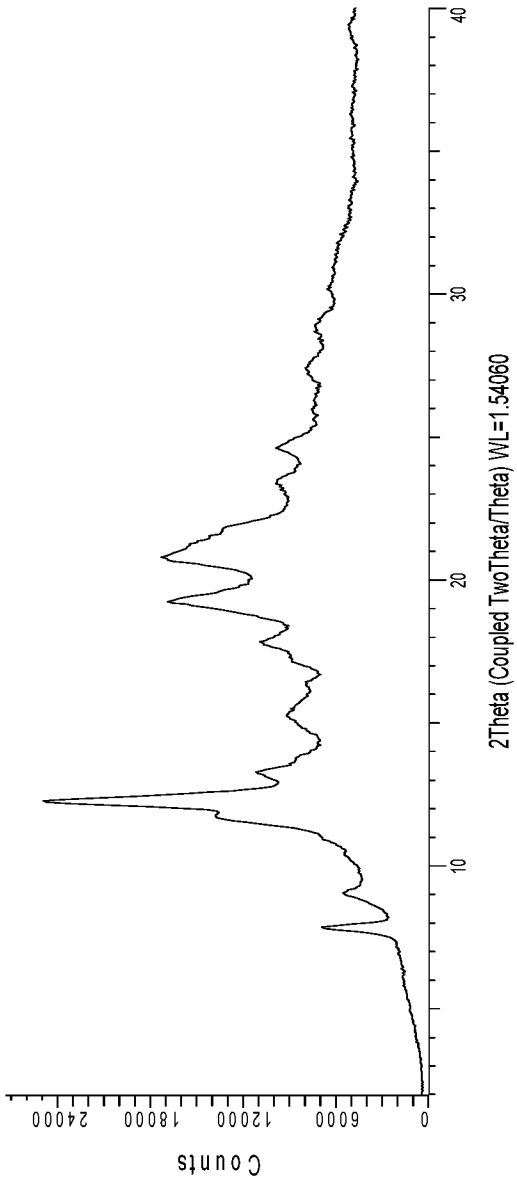
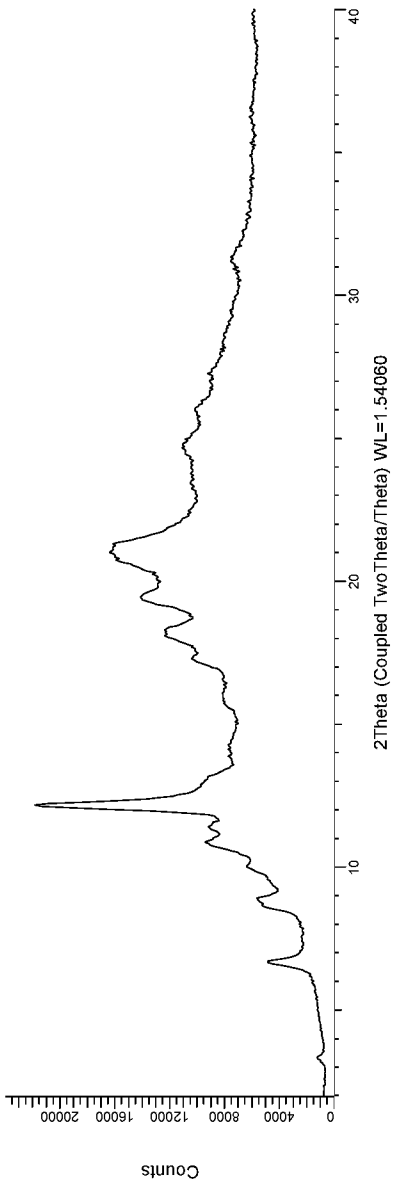


Figure 33. X-ray powder diffraction of Ledipasvir crystalline Premix obtained by procedure 4 of example 21.



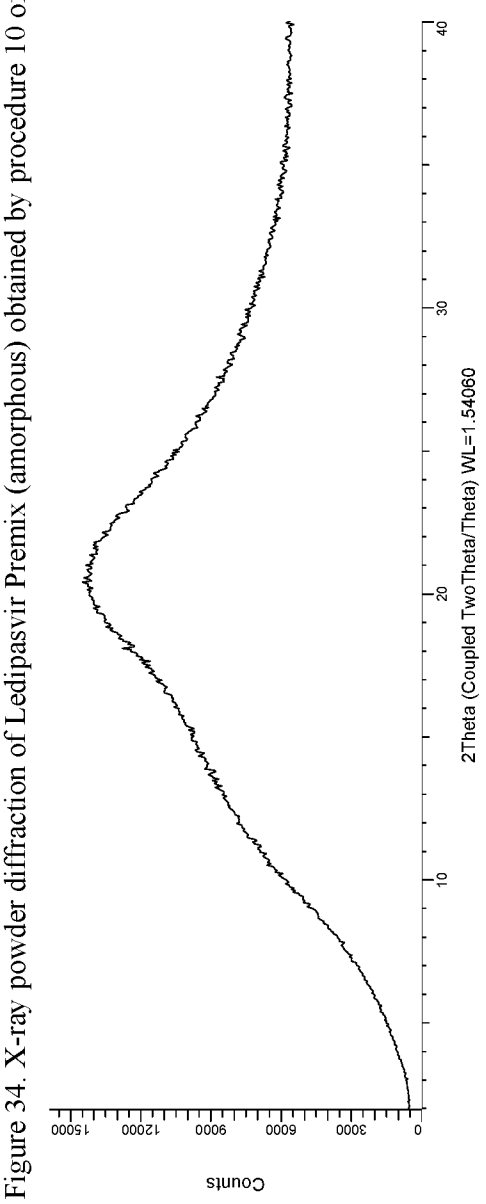



Figure 34. X-ray powder diffraction of Ledipasvir Premix (amorphous) obtained by procedure 10 of example 18.

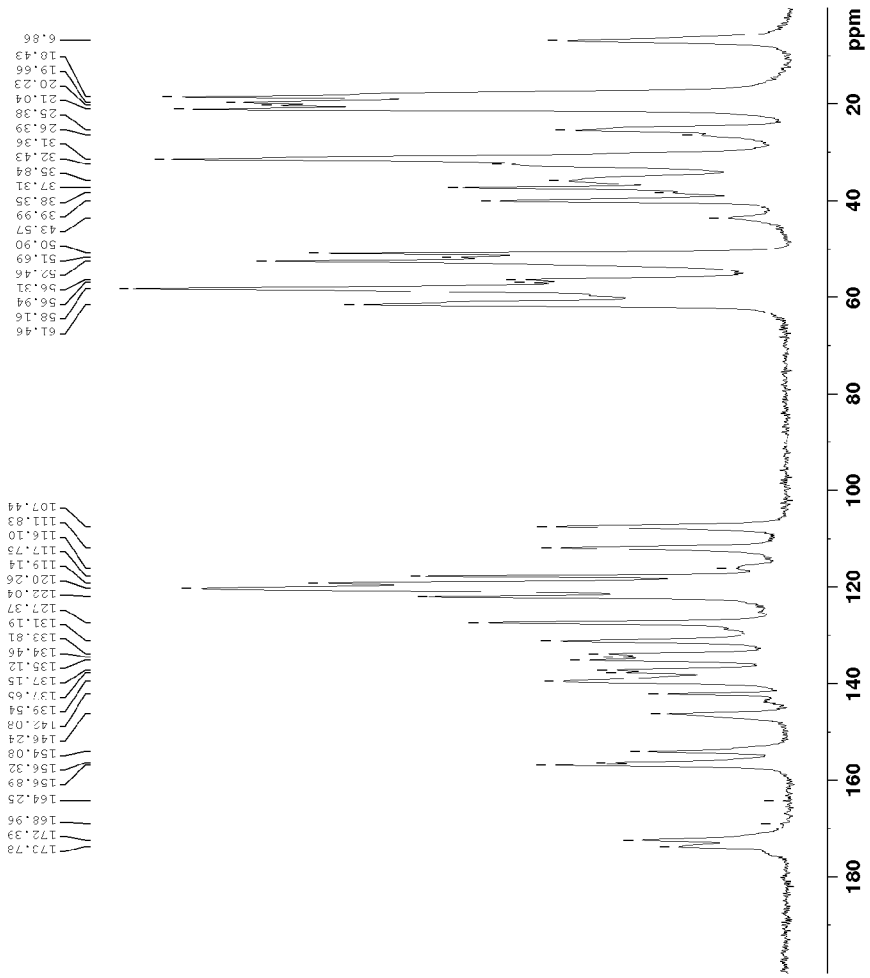



Figure 35. Solid-state 13C NMR spectrum of form G

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/021905

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/4184 A61P31/12
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)
C07D

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

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

EPO-Internal, 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. |
|---|---|---|
| X | WO 2013/184698 A1 (GILEAD SCIENCES INC [US]) 12 December 2013 (2013-12-12)<br>cited in the application<br>claims 1, 6, 11, 21, 26, 29, 34, 37, 42, 47, 50, 53, 56<br>claims 61, 66, 69, 81<br>tables 8, 10<br>paragraph [0128]<br>paragraph [0172]<br>-----<br>-/-- | 1-75,83, 84 |

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 June 2016 | 15/06/2016 |

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

3

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

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/021905

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-75, 83, 84(all partially)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CAIRA: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP008166276, ISSN: 0340-1022 paragraph bridging pages 165-166 chapter 3.1 | 1-75,83, 84 |
| X | WO 2013/184702 A1 (GILEAD SCIENCES INC [US]) 12 December 2013 (2013-12-12) cited in the application paragraph [0207] - paragraph [0208] | 18-22, 24,25 |
| X | US 2011/306541 A1 (DELANEY IV WILLIAM E [US] ET AL) 15 December 2011 (2011-12-15) paragraph [0234] | 18-22, 24,25 |
| X,P | CN 104 961 733 A (SHANGHAI FOREFRONT PHARMACEUTICAL CO LTD) 7 October 2015 (2015-10-07) cited in the application figures 1-12 tables on pages 13-20 | 1-75,83, 84 |
| X,P | CN 105 237 517 A (NJCTT PHARMACEUTICAL CO) 13 January 2016 (2016-01-13) cited in the application figure 3 tables on pages 4-7 | 1-75,83, 84 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/021905

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2013184698 A1 | 12-12-2013 | AR 091259 A1 | 21-01-2015 |
| | | AU 2013271768 A1 | 15-01-2015 |
| | | CA 2875507 A1 | 12-12-2013 |
| | | CN 104379584 A | 25-02-2015 |
| | | CN 105524050 A | 27-04-2016 |
| | | EP 2855478 A1 | 08-04-2015 |
| | | HK 1205127 A1 | 11-12-2015 |
| | | JP 2015518891 A | 06-07-2015 |
| | | KR 20150028971 A | 17-03-2015 |
| | | SG 11201408013W A | 29-01-2015 |
| | | TW 201408661 A | 01-03-2014 |
| | | US 2013324496 A1 | 05-12-2013 |
| | | US 2015141659 A1 | 21-05-2015 |
| | | US 2015344488 A1 | 03-12-2015 |
| | | UY 34844 A | 31-12-2013 |
| | | WO 2013184698 A1 | 12-12-2013 |
| WO 2013184702 A1 | 12-12-2013 | AU 2013271772 A1 | 15-01-2015 |
| | | CA 2875508 A1 | 12-12-2013 |
| | | CN 104520293 A | 15-04-2015 |
| | | EP 2855454 A1 | 08-04-2015 |
| | | HK 1208670 A1 | 11-03-2016 |
| | | HK 1209124 A1 | 24-03-2016 |
| | | JP 2015518892 A | 06-07-2015 |
| | | KR 20150027158 A | 11-03-2015 |
| | | SG 11201408011S A | 29-01-2015 |
| | | US 2013324740 A1 | 05-12-2013 |
| | | US 2015232453 A1 | 20-08-2015 |
| | | WO 2013184702 A1 | 12-12-2013 |
| US 2011306541 A1 | 15-12-2011 | AR 084393 A1 | 15-05-2013 |
| | | TW 201211047 A | 16-03-2012 |
| | | US 2011306541 A1 | 15-12-2011 |
| | | UY 33445 A | 31-01-2012 |
| | | WO 2011156757 A1 | 15-12-2011 |
| CN 104961733 A | 07-10-2015 | NONE | |
| CN 105237517 A | 13-01-2016 | NONE | |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/** 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17, 23, 26-63, 71, 84(completely); 18-22, 24, 25, 64-70, 72-75, 83(partially)

ledipasvir form B and subject-matter referring to it
ledipasvir form G and subject-matter referring to it
ledipasvir form H and subject-matter referring to it
ledipasvir form M and subject-matter referring to it
ledipasvir form N and subject-matter referring to it
ledipasvir form O and subject-matter referring to it
ledipasvir form P and subject-matter referring to it

1.1. claims: 2, 3, 23, 26-31, 71(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83(partially)

ledipasvir form B and subject-matter referring to it

1.2. claims: 4-9, 32-38(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83, 84(partially)

ledipasvir form G and subject-matter referring to it

1.3. claims: 10, 44-46(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83(partially)

ledipasvir form H and subject-matter referring to it

1.4. claims: 11, 12, 47-52(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83, 84(partially)

ledipasvir form M and subject-matter referring to it

1.5. claims: 13, 61-63(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83(partially)

ledipasvir form N and subject-matter referring to it

1.6. claims: 14, 15, 53-60(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83, 84(partially)

ledipasvir form O and subject-matter referring to it

1.7. claims: 16, 17, 39-43(completely); 1, 18-22, 24, 25, 64-70, 72-75, 83, 84(partially)

ledipasvir form P and subject-matter referring to it

---

2. claims: 18, 19, 22, 64-70, 72-75(all partially)

ledipasvir hydrate and subject-matter referring to it not being part of invention 1

---

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

3. claims: 20, 21, 64-70, 72-75(all partially)

ledipasvir having a specific surface area of not less than 10m2/g not being part of inventions 1-2

---

4. claims: 24, 25, 64-70, 72-75(all partially)

ledipasvir having a content of the keto impurity of not more than 0.1% area as measured by HPLC or a total impurity content of not more than 0.2% area percent as measured by HPLC not being part of inventions 1-3

---

5. claims: 76-82

processes for the preparation of ledipasvir using precursors of formulae 7-10

---

6. claim: 83(partially)

purification processes comprising crystallizing ledipavir from a solvent system selected from the group consisting of acetonitrile/toluene, acetonitrile/MDC, THF/toluene and acetone/MDC not being part of the inventions 1-4

---