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(54) Title: AMORPHOUS SIMEPREVIR POTASSIUM

(57) Abstract: The invention relates to amorphous simeprevir potassium and to a process for the preparation of amorphous simeprevir salts. The invention is further directed to pharmaceutical compositions comprising an effective amount of simeprevir potassium, especially in its amorphous form and to the use of said pharmaceutical compositions as medicament, in particular for the treatment of hepatitis C infections in human.



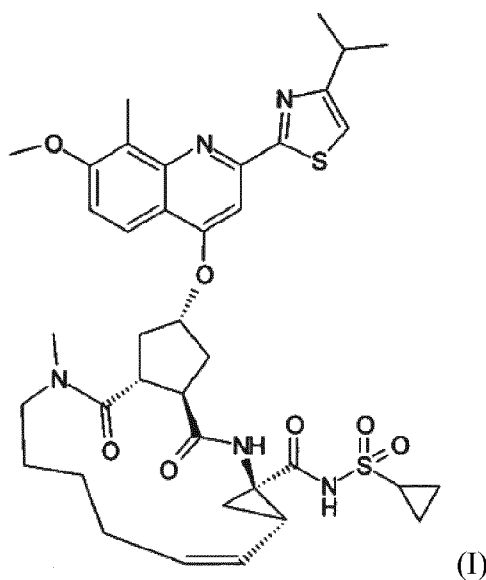
AMORPHOUS SIMEPREVIR POTASSIUM

FIELD OF THE INVENTION

The invention relates to amorphous simeprevir potassium salt and to a process for the preparation of amorphous simeprevir potassium salt. The invention is further directed to pharmaceutical compositions comprising an effective amount of simeprevir potassium salt, especially in its amorphous form and to the use of said pharmaceutical compositions as medicament, in particular for the treatment of hepatitis C infections in human.

BACKGROUND OF THE INVENTION

(1*R*,4*R*,6*S*,15*R*,17*R*)-*cis*-*N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl] (cyclopropyl)sulfonamide (international non-proprietary name: simeprevir) represented by chemical structure (I)



is a specific inhibitor of HCV-NS3/4A serine protease and indicated in combination with other hepatitis C medicaments for the treatment of chronic hepatitis C. The marketed product (OlysioTM) contains the active pharmaceutical ingredient as the amorphous sodium salt.

WO 2007/014926 A1 discloses simeprevir in non-salt form for use in the treatment of hepatitis C virus (HCV) infections. It is mentioned that pharmaceutically acceptable base addition salts can also be used and that the preparations of these salts involve the reaction with an appropriate base.

- 5 WO 2008/092954 A2 discloses crystalline forms of simeprevir in non-salt form for use in the treatment of HCV infections.

WO 2010/097229 A2 discloses an amorphous sodium salt of simeprevir and its preparation via spray drying. According to the application suitable solvents which may be applied in the spray drying process are halogenated hydrocarbons, such as chloroform or dichloromethane
10 (dichloromethane is for example used in example 1 of WO 2010/097229 A2) and ethers such as diethylether or tetrahydrofuran (see page 5, lines 1-2).

It is mentioned in WO 2010/097229 A2 (e.g. on page 6, lines 35-37) that the amorphous sodium salt is highly hygroscopic. This can also be taken from the GMS curve displayed in figure 6 of WO 2010/097229 A2. Water is released to a lesser extent during desorption than adsorbed
15 during sorption, which is indicated by a significant hysteresis between the sorption isotherm and the desorption isotherm. The properties of the amorphous simeprevir sodium salt hence render the production process and the storage of pharmaceutical compositions challenging.

Thus, a first objective of the invention was to provide an amorphous simeprevir salt, which overcomes aforementioned drawbacks associated with the physicochemical properties of the
20 amorphous sodium salt, in particular with regards to its behavior upon contact with water and/or water vapor. A further objective of the invention was to provide a process for the preparation of amorphous simeprevir salts avoiding the use of highly volatile, environmentally problematic and hazardous solvents such as halogenated hydrocarbons and ethers.

SUMMARY OF THE INVENTION

25 In a first aspect, the invention relates to amorphous simeprevir potassium salt. Surprisingly, amorphous simeprevir potassium salt has favorable physical properties upon contact with moisture compared to the amorphous simeprevir sodium salt. The invention is also directed to pharmaceutical compositions comprising an effective amount of amorphous simeprevir potassium salt of the invention and at least one pharmaceutically acceptable excipient. The
30 invention further relates to amorphous simeprevir potassium salt of the invention and

pharmaceutical composition comprising the same for use as a medicament, especially for use in the treatment of hepatitis C virus infections in human.

In a further aspect, the invention relates to a process for the preparation of amorphous simeprevir salts avoiding highly volatile, environmentally problematic and hazardous solvents
5 such as halogenated hydrocarbons and ethers.

Definitions

In the context of the present invention the following abbreviations have the indicated meaning, unless explicitly stated otherwise:

10	PXRD	powder X-ray diffraction
	GMS	gravimetric moisture sorption
	RH	relative humidity
	% w/w	weight percent

As used herein, the term “room temperature” refers to temperatures in the range of from 20 to
15 30 °C.

As used herein, the term “amorphous” is used for a non-crystalline solid which lacks long-range inter-molecular order.

The term “reflection” with regards to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by
20 constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material, which lacks long-range order and only displays short-range order (also see explanation above), thus resulting in broad scattering as for example displayed in figure 1 and
25 figure 3 herein. According to literature, long-range order e.g. extends over approximately 10^3 to 10^{20} atoms, whereas short-range order is over a few atoms only (see “*Fundamentals of Powder Diffraction and Structural Characterization of Materials*” by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003, page 3).

A “peak” caused by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order, is generally a narrow feature in a PXRD pattern. Hence, a peak characteristic of a crystalline phase is regarded as a peak having a width at half of its height from the top to its root, i.e. where the peak starts from the baseline, of less than 1° 2-Theta. Further, the intensity of a peak has a signal to noise ratio of at least 3:1. Additionally, a peak characteristic of a crystalline phase cannot be confused by the person skilled in the art with noise signals of the background, since a peak characteristic of a crystalline phase has an at least 3 times greater intensity than the background noise, preferably at least 10 times greater. Moreover, a “peak” caused by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order is reproducible in that two independent measurements of the same sample will yield a peak at the same position $\pm 0.2^\circ$ 2-Theta.

“No noticeable peak” in the context of the present invention means that the PXRD pattern does not contain any peak that the person skilled in the art would recognize as being characteristic of a crystalline phase.

The term “mother liquor” as used herein, refers to the solution remaining after precipitation of a solid.

As used herein, the term “about” means within 5%, more typically within 1% and most typically within 0.3% of the indicated value or range.

In the context of the invention the term “chemical impurities” are by-products and/or synthetic intermediates used during simeprevir production, other than simeprevir itself. Such chemical impurities may contain structural elements that they have in common with simeprevir, such as a methoxy-methylquinolin ring system or a trisubstituted cyclopropane ring system.

In the context of the invention the term “solid form impurities” are any solid form of simeprevir other than amorphous simeprevir potassium salt, such as crystalline forms of simeprevir potassium or crystalline forms of simeprevir.

The term “antisolvent” as used herein, refers to liquids which reduces the solubility of simeprevir in a solvent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: PXRD pattern of amorphous simeprevir potassium

Figure 2: Gravimetric moisture sorption and desorption isotherms of amorphous simeprevir potassium

5 Figure 3: PXRD pattern of amorphous simeprevir sodium

Figure 4: Gravimetric moisture sorption and desorption isotherms of amorphous simeprevir sodium

DETAILED DESCRIPTION OF THE INVENTION

10 In one aspect, the invention relates to amorphous simeprevir potassium salt. Preferably, the invention relates to solid amorphous simeprevir potassium salt.

Preferably, the invention relates to amorphous simeprevir potassium salt characterized by having a PXRD pattern comprising no reflection in the range of from 2 to 40 ° 2-Theta, when measured at room temperature with CuKalpha_{1,2} radiation having a wavelength of 0.15419 nm.

15 Alternatively, the invention relates to amorphous simeprevir potassium salt characterized by having a PXRD pattern essentially the same as displayed in figure 1 herein, when measured at room temperature with CuKalpha_{1,2} radiation having a wavelength of 0.15419 nm.

It is a further advantage of the amorphous simeprevir potassium salt of the present invention that it is stable at room temperature and/or high relative humidity.

20 The invention therefore also relates to amorphous simeprevir potassium salt which does not have any noticeable peak, especially any peak characteristic of a crystalline form of simeprevir, in a powder X-ray diffraction pattern when measured after 96 hours storage at 20°C. Preferably, the amorphous simeprevir potassium salt has an PXRD pattern substantially as shown in Fig. 1, when measured after 96 hours storage at 20°C.

25 In a further embodiment of the invention, the amorphous simeprevir potassium salt does not have any noticeable peak, especially not any peak characteristic of a crystalline form of simeprevir, in a powder X-ray diffraction pattern when measured after 96 hours storage at 40°C/75% relative humidity. Preferably, the amorphous simeprevir potassium salt has an PXRD pattern substantially as shown in Fig. 1 when measured after 96 hours storage at
30 40°C/75% relative humidity.

Amorphous simeprevir potassium salt of the present invention is preferably chemically pure. "Chemical purity" of the amorphous simeprevir potassium salt can for example be determined by HPLC analysis. The amorphous simeprevir potassium salt of the present invention has a chemical purity of 95% w/w or more, preferably of 98% w/w or more, more preferably of 99.5% w/w or more, based on the total weight of the amorphous simeprevir potassium salt.

The pure amorphous simeprevir potassium salt of the present invention may be further characterized by lack of significant hysteresis in a water vapor sorption / desorption experiment when analyzed by GMS.

Thus, the invention also relates to amorphous simeprevir potassium salt characterized by a GMS curve wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at the same relative humidity is at most 1.3%, preferably at most 1.2%, more preferably at most 1.1%, even more preferably at most 1.0%, even more preferably at most 0.9% and most preferably at most 0.8%, in the range of from 40 to 90% relative humidity at room temperature, preferably at $(25.0 \pm 0.1) ^\circ\text{C}$, for example when measured according to method 2.

The present invention also relates to amorphous simeprevir potassium salt characterized by a GMS curve wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 50% relative humidity is at most 4.0%, preferably at most 3.0%, more preferably at most 2.0%, even more preferably at most 1.0%, for example when measured according to method 2 at $(25.0 \pm 0.1) ^\circ\text{C}$.

The present invention also relates to amorphous simeprevir potassium salt characterized by a GMS curve wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 60% relative humidity is at most 4.0%, preferably at most 3.0%, more preferably at most 2.0%, even more preferably at most 1.0%, for example when measured according to method 2 at $(25.0 \pm 0.1) ^\circ\text{C}$.

The present invention also relates to amorphous simeprevir potassium salt characterized by a GMS curve wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 70% relative humidity is at most 4.0%, preferably at most 3.0%, more preferably at most 2.0%, even more preferably at most 1.0%, for example when measured according to method 2 at $(25.0 \pm 0.1) ^\circ\text{C}$.

Preferably, the invention relates to amorphous simeprevir potassium salt characterized by having a GMS curve, wherein the maximal relative difference between the water content of the sorption isotherm and the water content of the desorption isotherm at the same relative humidity is at most 20%, preferably at most 10% and most preferably at most 8%, in the range of from 5 50 to 70% relative humidity, for example when measured according to method 2 at (25.0 ± 0.1) °C .

Comparative GMS experiments with amorphous simeprevir sodium salt and amorphous simeprevir potassium salt revealed that the amorphous potassium salt of the invention is less hygroscopic. Also, the amorphous simeprevir potassium salt of the invention releases the 10 adsorbed water more easily when the relative humidity decreases. This is an advantage when simeprevir is intended to be formulated in the presence of moisture sensitive excipients, such as microcrystalline cellulose, which might tolerate the short term presence of water, but which are not compatible with the long-term presence of water during storage.

It is known that, for example, tablets with microcrystalline cellulose at a high moisture level 15 can be prone to capping. Moreover, compacted dosage forms comprising microcrystalline cellulose stored under high humidity conditions tend to swell. The amorphous simeprevir potassium salt of the present invention is better suited to being used together with such excipients than amorphous simeprevir sodium.

For example, when water uptake was measured from 0 to 95% at (25 ± 0.1) °C under 20 equilibrium conditions, the amorphous simeprevir sodium salt adsorbed about 33.5% water, whereas the simeprevir potassium salt only adsorbed about 24.8% water in the same relative humidity range.

In addition, water release by the amorphous simeprevir sodium salt during the desorption cycle was more reluctant than water uptake during the adsorption cycle. This is indicated by the 25 significant hysteresis in the GMS curve displayed in figure 4 herein, but also in Figure 6 of WO 2010/097229 A2. In contrast, the amorphous simeprevir potassium salt of the invention releases and adsorbs water almost equally well, which is indicated by the lack of a significant hysteresis between the sorption isotherm and the desorption isotherm (see figure 2 herein). Table 1 again summarizes the observations from the comparative GMS experiments.

Amorphous Simeprevir Na	Amorphous Simeprevir K
water uptake from 0 to 95% RH: 33.5% significant hysteresis from 40 to 90% RH	water uptake from 0 to 95% RH: 24.8% no significant hysteresis

Table 1: Comparison of physical properties of amorphous simeprevir sodium and potassium at different relative humidity at 25.0 ± 0.1 °C

It is surprising that the amorphous potassium salt of the invention is less hygroscopic compared to amorphous simeprevir sodium salt. In addition, the adsorbed water is only weakly bound by the amorphous simeprevir potassium salt of the present invention, allowing a reproducible equilibration of the water content irrespective of the previous sample history. This is also in contrast to what could have been expected based on the behavior of the amorphous simeprevir sodium salt.

These properties make the use of the amorphous simeprevir potassium salt of the invention in pharmaceutical compositions attractive, as the material is easier to handle during pharmaceutical processing, and requirements with regards to metering accuracy are met more easily.

Therefore, the invention also relates to pharmaceutical compositions comprising an effective amount of amorphous simeprevir potassium salt of the invention and at least one pharmaceutically acceptable excipient.

Preferably, the effective amount of amorphous simeprevir potassium of the invention is in the range of from about 25 to 500 mg, more preferably from about 50 to 250 mg, even more preferably from about 100 to 200 mg and most preferably the effective amount is about 150 mg, calculated as simeprevir.

Preferably, pharmaceutical compositions of the invention comprise an effective amount of amorphous simeprevir potassium of the invention and one or more pharmaceutically acceptable excipients selected from the group of wetting agents lubricants, glidants, disintegrants and fillers.

In particular, pharmaceutical compositions of the invention comprise an effective amount of amorphous simeprevir potassium of the invention and one or more pharmaceutically acceptable excipients selected from sodium lauryl sulfate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium and lactose monohydrate.

Pharmaceutical compositions of the invention comprising an effective amount of amorphous simeprevir potassium of the invention are preferably oral dosage forms, more preferably tablets or capsules and most preferably capsules.

5 In addition, the invention relates to amorphous simeprevir potassium of the invention and to pharmaceutical compositions comprising an effective amount of amorphous simeprevir potassium of the invention, for use as medicament.

10 In particular, the invention relates to amorphous simeprevir potassium of the invention and to pharmaceutical compositions comprising an effective amount of simeprevir potassium, in particular of amorphous simeprevir potassium of the invention, for use in the treatment of hepatitis C infections in human.

Moreover, the present invention relates to a process for the preparation of amorphous simeprevir alkali metal salt, preferably of amorphous simeprevir potassium salt or amorphous simeprevir sodium salt, comprising:

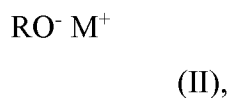
- 15 (i) combining simeprevir with an alkali metal alcoholate in the presence of a solvent;
- (ii) obtaining solid amorphous simeprevir salt by
 - (ii.1) combining the reaction mixture of (i) with an antisolvent or
 - (ii.2) lyophilizing the reaction mixture of (i);
- (iii) optionally separating at least a part of the solid amorphous simeprevir alkali metal salt obtained in (ii.1) from its mother liquor;
- 20 (iv) optionally drying the amorphous simeprevir salt obtained in (iii);

Simeprevir, which is used as starting material in step (i) can for example be prepared according to the process disclosed in example 5 of WO 2007/014926 A1 or according to the process disclosed in examples 1 and 2 of WO 2008/092954 A2. Any solid form of simeprevir may be applied as starting material such as amorphous simeprevir, crystalline simeprevir or mixtures
25 of amorphous and crystalline simeprevir. Suitable crystalline forms may be selected from forms I, II, III, IV, V and VI of WO 2008/092954 A2 or any mixtures thereof. Amorphous simeprevir may for example be prepared according to the procedure disclosed in example 4 of WO 2008/092954 A2, whereas crystalline forms I, II, III, IV, V and VI may be prepared according to the processes disclosed in examples 3 and 5 to 9 of WO 2008/092954 A2 respectively.

30 Solvents which may be used in the process of the invention are preferably selected from alcohols such as methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, 2-butanol, isobutanol,

tert-butanol, amylalcohol, isoamylalcohol, *tert*-amylalcohol, hexanol, octanol or mixtures thereof, whereas most preferably *tert*-butanol is used. The solvent is used in an amount that is sufficient to dissolve simeprevir.

Suitable alkali metal alcoholates which may be applied in the process of the invention are represented by the general formula (II)



wherein R represents branched or non-branched C₁-C₁₀ alkyl and M⁺ represents an alkali metal cation preferably selected from potassium, sodium and lithium, more preferably from potassium and sodium and most preferably the alkali metal cation is potassium. Concrete examples for suitable alkali metal alcoholates are sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, sodium *n*-propylate, potassium *n*-propylate, sodium *iso*-propylate, potassium *iso*-propylate, sodium *n*-butoxide, potassium *n*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, sodium *tert*-amylate, potassium *tert*-amylate, sodium 3,7-dimethyl-3-octylate, potassium 3,7-dimethyl-3-octylate, whereat sodium methoxide, potassium methoxide, sodium *tert*-butoxide and potassium *tert*-butoxide are most preferred. In step (i) of the process a mixture of simeprevir and the applied alkali metal alcoholate in a suitable solvent is prepared. Preferably, the simeprevir concentration of the mixture is in the range of from about 1 to 50 g, more preferably from about 10 to 40 g and most preferably from about 15 to 25 g per liter solvent. The molar ratio of simeprevir and the applied alkali metal alcoholate is preferably in the range of from about 1 : 1 to 6, more preferably from about 1 : 1 to 4 and most preferably from about 1 : 1 to 2. Preferably, the amount of alkali metal alcoholate is chosen such that at the end of the acid base reaction a solution, preferably a clear solution, more preferably a clear solution free of any solid material is obtained. Optionally, the reaction mixture may be heated for example to a temperature of about 40 °C or more, preferably of about 50 °C or more, more preferably of about 60 °C or more, for example the mixture may be heated to reflux temperature. The reaction mixture is kept, preferably under stirring, at the applied temperature for a period that is long enough to allow a complete acid-base reaction, for example a period in the range of from about 0.5 to 48 hours, preferably from about 1 to 24 hours, more preferably from about 2 to 12 hours.

Suitable antisolvents, which may be used in step (ii) of the process are selected from alkanes such as *n*-pentane, *n*-hexane, cyclohexane, *n*-heptane or mixtures thereof, whereat *n*-heptane is most preferred.

In the successive step (ii.1) the reaction mixture obtained in (i) is combined with an antisolvent by adding the antisolvent to the reaction mixture or *vice versa*. The applied solvent/antisolvent ratio may be in the range of from about 1 : 2 to 10, preferably from about 1 : 2 to 8, more preferably from about 1 : 2 to 6 and most preferably from about 1 : 2 to 4. After complete antisolvent addition the obtained suspension may optionally be cooled, for example to a temperature of about 10 °C or less, preferably of about 0 °C or less, more preferably of about -10 °C or less, in order to improve the yield. The suspension is optionally kept, preferably under stirring, at the applied temperature for a period in the range of from about 0.5 to 48 hours, preferably from about 1 to 24 hours, more preferably from about 2 to 12 hours.

Subsequently, the solid obtained from step (ii.1) may be separated from its mother liquor by any conventional method such as filtration, centrifugation, evaporation of the solvent, decantation of the solvent or by two or more of these methods. Most preferably, the solid is collected by filtration.

Finally, the amorphous simeprevir salt obtained in step (iii) may be dried at a temperature of about 100 °C or less, preferably at a temperature of about 40 °C or less, for example at about room temperature. Drying may be performed at atmospheric or at reduced pressure for a period of about 72 hours or less.

Alternatively, the reaction mixture obtained in (i) may be lyophilized. Lyophilization may for example be performed according to the procedures described in examples 3 and 4 herein.

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

1. Amorphous simeprevir potassium salt.
2. The amorphous simeprevir potassium salt according to item 1 characterized by having a powder X-ray diffractogram comprising no reflection in the range of from 2 to 40 ° 2-Theta, when measured at 20 °C with CuK α _{1,2} radiation having a wavelength of 0.15419 nm.

3. The amorphous simeprevir potassium salt according to item 2 characterized by having a powder X-ray diffractogram essentially the same as displayed in Figure 1 herein.
4. The amorphous simeprevir potassium salt according to any one of items 1 to 3 characterized by having a gravimetric moisture sorption curve, wherein the absolute
5 difference in the water content between the sorption isotherm and the desorption isotherm at the same relative humidity is at most 1.3%, when measured in the range of from 40 to 90% relative humidity at (25.0 ± 0.1) °C.
5. The amorphous simeprevir potassium salt according to items 4, wherein the absolute
10 difference in the water content between the sorption isotherm and the desorption isotherm at the same relative humidity is at most 1.0%.
6. The amorphous simeprevir potassium salt according to items 4 or 5, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at the same relative humidity is at most 0.8%.
7. The amorphous simeprevir potassium salt according to any one of items 1 to 3
15 characterized by having a gravimetric moisture sorption curve, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 50% relative humidity is at most 4.0%, when measured according to method 2 at (25.0 ± 0.1) °C.
8. The amorphous simeprevir potassium salt according to item 7, wherein the absolute
20 difference in the water content between the sorption isotherm and the desorption isotherm at 50% relative humidity is at most 2.0%.
9. The amorphous simeprevir potassium salt according to any one of items 1 to 3 characterized by having a gravimetric moisture sorption curve, wherein the absolute
25 difference in the water content between the sorption isotherm and the desorption isotherm at 60% relative humidity is at most 4.0%, when measured according to method 2 at (25.0 ± 0.1) °C.
10. The amorphous simeprevir potassium salt according to item 9, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 60% relative humidity is at most 2.0%.

11. The amorphous simeprevir potassium salt according to any one of items 1 to 3 characterized by having a gravimetric moisture sorption curve, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 70% relative humidity is at most 4.0%, when measured according to method 2 at $(25.0 \pm 0.1) ^\circ\text{C}$.
12. The amorphous simeprevir potassium salt according to item 11, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at 70% relative humidity is at most 2.0%.
13. The amorphous simeprevir potassium salt according to any one of items 1 to 12 characterized by having a gravimetric moisture sorption curve, wherein the relative difference between the water content of the sorption isotherm and the desorption isotherm at same relative humidity is at most 20%, when measured in the range of from 40 to 80% relative humidity at $(25.0 \pm 0.1) ^\circ\text{C}$.
14. The amorphous simeprevir potassium salt according to item 13, wherein the relative difference is at most 10%.
15. The amorphous simeprevir potassium salt according to any one of items 1 to 14 wherein the water content at 95% relative humidity and $(25.0 \pm 0.1) ^\circ\text{C}$ is at most 30%.
16. The amorphous simeprevir potassium salt according to any one of items 1 to 15 wherein the content of chemical impurities is at most 2%.
17. The amorphous simeprevir potassium salt according to any one of items 1 to 16 wherein the content of solid forms other than amorphous simeprevir potassium salt is at most 2%.
18. The amorphous simeprevir potassium salt according to item 17 wherein the content of solid forms other than amorphous simeprevir potassium salt is at most 1%.
19. A pharmaceutical composition comprising an effective amount of amorphous simeprevir potassium salt, and at least one pharmaceutically acceptable excipient.
20. The pharmaceutical composition according to item 19, wherein the amorphous simeprevir potassium salt is amorphous simeprevir potassium salt according to any one of items 1 to 18.

21. The pharmaceutical composition according to item 20 comprising a pharmaceutically acceptable excipient which is moisture sensitive.
22. The pharmaceutical composition according to item 21, wherein the moisture sensitive excipient is selected from the group consisting of microcrystalline cellulose, XX, YY, ZZ.
23. The pharmaceutical composition according to any one of items 19 to 22, which is an oral dosage form.
24. The pharmaceutical composition according to any one of items 19 to 23, which is a capsule or a tablet.
25. The pharmaceutical composition according to any one of items 19 to 24, which is packaged in a pharmaceutically acceptable packaging material.
26. The amorphous simeprevir potassium salt according to any one of items 1 to 18 or the pharmaceutical composition according to any one of items 19 to 25 for use as a medicament.
27. The amorphous simeprevir potassium salt according to any one of items 1 to 18 or the pharmaceutical composition according to any one of items 19 to 25 for use in the treatment of hepatitis C infections in human.
28. A process for the preparation of an amorphous simeprevir alkali metal salt comprising:
- (i) combining simeprevir with an alkali metal alcoholate in the presence of a solvent; and
 - (ii) obtaining solid amorphous simeprevir alkali metal salt by
 - (ii.1) combining the reaction mixture of (i) with an antisolvent or
 - (ii.2) lyophilizing the reaction mixture of (i).
29. The process according to item 28, wherein the amorphous simeprevir alkali metal salt is selected from amorphous simeprevir potassium salt and amorphous simeprevir sodium salt.
30. The process according to items 28 or 29, wherein in step (i) simeprevir in non-salt form is used as the starting material.

31. The process according to any one of items 28 to 30, wherein in step (i) simeprevir is dissolved to form a solution.
32. The process of item 31, wherein after step (i) a clear solution free of any solid material is obtained.
- 5 33. The process according to any one of items 28 to 32, wherein in step (i) the simeprevir concentration in the solvent is from 1 g/l to 50g/l.
34. The process according to any one of items 28 to 33, wherein in step (i) the molar ratio of simeprevir and alkali metal alcoholate is from 1:1 to 1:6.
35. The process according to item 34, wherein the molar ration is from 1:1 to 1:2.
- 10 36. The process according to any one of items 28 to 35, wherein in step (i) the alkali metal alcoholate is a branched or non-branched alkali metal alkanolate comprising one to ten carbon atoms.
37. The process according to any one of items 28 to 36, wherein in step (i) the alkali metal alcoholate is selected from the group of potassium methoxide, sodium methoxide,
15 potassium *tert*-butoxide, sodium *tert*-butoxide.
38. The process according to any one of items 28 to 37, wherein the solvent is an alcohol
39. The process according to item 38, wherein the alcohol is *tert*-butanol.
40. The process according to any one of items 27 to 39, wherein in step (ii-1) the antisolvent is an alkane.
- 20 41. The process according to item 39 wherein the alkane is *n*-heptane.
42. The process according to any one of items 40 to 41, wherein the solvent / antivolvent ratio (v/v) is from 1:2 to 1:10.
43. The process according to item 42, wherein the solvent / antivolvent ratio (v/v) is from 1:2 to 1:4.
- 25 44. The process according to any one of items 40 to 43, wherein, after antisolvent addition, the reaction is brought to a temperature of from -10°C to 10°C.

45. The process according to any one of items 28 to 44 further comprising (iii) separating at least a part of the amorphous simeprevir alkali metal salt obtained in step (ii.1) from its mother liquor.

46. The process according to item 45 further comprising (iv) drying the amorphous simeprevir alkali metal salt obtained in (iii).

47. The process according to item 46, wherein drying is performed at a pressure of from 5 mbar to 100 mbar.

The following non-limiting examples are illustrative for the disclosure and are not to be construed to be limiting for the scope of the claims.

Methods

Method 1:

Powder X-ray diffractograms were obtained with a PANalytical X'Pert PRO diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-K α _{1,2} radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. The diffractograms were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a stepsize of 0.013° 2-Theta with 40s per step (255 channels) in the angular range of 2° to 40° 2-Theta at ambient conditions.

Method 2:

Moisture sorption and desorption isotherms were recorded with an SPSx-1 μ moisture sorption analyzer (ProUmid, Ulm). The measurement cycle was started at 40% RH and first decreased to 3% RH, then to 0% RH. Subsequently, the relative humidity was increased to 5% and 10%, then to 90% in 10% steps. It was further increased to 95%. Then it was decreased back to 90% and to 0% in 10% steps. Finally, it was increased again to 40% RH in 10% steps. The time per step was set to a minimum of 2 hours and a maximum of 10 hours. If an equilibrium condition with a constant mass of $\pm 0.01\%$ within 1 hour was reached before the maximum time for all examined samples the sequential humidity step was applied before the maximum time of 10 hours. If no equilibrium was achieved the consecutive humidity step was applied after the maximum time of 10 hours. The temperature was 25 ± 0.1 °C.

At the end of the GMS experiment the water content of the samples was determined by Karl Fischer coulometry using a Metrohm 831 KF Coulometer. The so determined values were then used to calculate the water content of the samples at the respective RH values, which are displayed in Figures 2 and 4.

5

Examples

Example 1: Preparation of amorphous simeprevir potassium by precipitation

Simeprevir in non-salt form (107 mg, 143 mmol; prepared according to the process disclosed in examples 1 and 2 of WO 2008/092954 A2) was suspended in *tert*-butanol (1 mL) and heated to 82 °C. A suspension of potassium *tert*-butoxide (24 mg, 214 mmol) in *tert*-butanol (3.5 mL) was heated to 60 °C and added to the simeprevir suspension. A slightly turbid solution was obtained. After 0.5 h of stirring at 82 °C the solution was cooled to 25 °C over 2 h and subsequently *n*-heptane (15 mL) was added causing precipitation of a colorless solid. The obtained suspension was further cooled to -10 °C over 2 h and stirred at this temperature for additional 15 h. Finally, the solid was collected by filtration and dried under vacuum at 20-30 mbar) for 28 h.

Yield: 47 mg (42% of theory)

Amorphous simeprevir potassium salt from example 1 was analyzed by method 1 (figure 1) and method 2 (figure 2).

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Example 2: Preparation of amorphous simeprevir sodium by precipitation

Simeprevir (107 mg, 143 mmol; prepared according to the process disclosed in examples 1 and 2 of WO 2008/092954 A2) was suspended in *tert*-butanol (1 mL) and heated to 82 °C. A suspension of sodium *tert*-butoxide (21 mg, 219 mmol) in *tert*-butanol (3 mL) was heated to 60 °C and added to the simeprevir suspension. A clear solution was obtained. After 0.5 h of stirring at 82 °C the solution was cooled to 25 °C over 2 h and subsequently *n*-heptane (15 mL) was added causing precipitation of a colorless solid. The obtained suspension was further cooled to -10 °C over 2 h and stirred at this temperature for additional 15 h. Finally, the solid was collected by filtration and dried under vacuum (20-30 mbar) for 28 h.

Yield: 75 mg (68% of theory)

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Amorphous simeprevir sodium salt from example 2 was analyzed by method 1 (figure 3) and method 2 (figure 4).

Example 3: Preparation of amorphous simeprevir potassium by lyophilization

- 5 A solution of simeprevir (65 mg, 87 mmol; prepared as described in example 1) and ethanolic potassium ethoxide solution (22 microL, 24% w/w) in *tert*-butanol (4mL) was prepared by heating to 82 °C. The resulting clear solution was lyophilized using a Christ alpha 2 4 LSC plus freeze dryer and applying the settings according to table 2.

Step	Temperature [°C]	Time [hh:mm]	Pressure [mbar]
freezing	-10	02:30	1000
main drying	-10	03:00	0.120
	-10 to 0	01:30	0.120
	0	03:00	0.120
	0 to 10	01:30	0.120
	10	03:00	0.120
	10 to 20	01:30	0.120
	20	03:00	0.120
	20 to 25	00:45	0.120
	25	03:00	0.120
	25 to 30	00:45	0.120
	30	03:00	0.120
final drying	30	15:00	0.0010

Table 2: Applied settings for freeze drying

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Comparative Example 1: Preparation of amorphous simeprevir sodium by lyophilization

A solution of simeprevir (60 mg, 80 mmol; prepared as described in example 1) and ethanolic sodium ethoxide solution (30 microL, 21% w/w) in *tert*-butanol (4 mL) was prepared by heating to 82 °C. The resulting clear solution was lyophilized using a Christ alpha 2 4 LSC plus freeze
 15 dryer and applying the same settings as outlined in table 2 of example 3.

CLAIMS

- 1) Amorphous simeprevir potassium salt.
- 2) The amorphous simeprevir potassium salt according to claim 1 characterized by having a powder X-ray diffractogram comprising no reflection in the range of from 2 to 40 ° 2-Theta, when measured at 15 to 30 °C with CuKalpha_{1,2} radiation having a wavelength of 0.15419 nm.
- 3) The amorphous simeprevir potassium salt according to claim 1 or 2 characterized by having a gravimetric moisture sorption curve, wherein the absolute difference in the water content between the sorption isotherm and the desorption isotherm at same relative humidity is not more than 1.3%, when measured in the range of from 40 to 90% relative humidity at (25.0 ± 0.1) °C.
- 4) The amorphous simeprevir potassium salt according to any one of the preceding claims characterized by having a gravimetric moisture sorption curve, wherein the relative deviation of the water content of the sorption isotherm and the desorption isotherm at same relative humidity is not more than 20%, when measured in the range of from 40 to 80% relative humidity at (25.0 ± 0.1) °C.
- 5) A pharmaceutical composition comprising an effective amount of amorphous simeprevir potassium salt, preferably of amorphous simeprevir potassium salt according to any one of the preceding claims, and at least one pharmaceutically acceptable excipient.
- 6) The pharmaceutical composition according to claim 5, which is an oral dosage form.
- 7) The amorphous simeprevir potassium salt according to any one of claims 1 to 4 or the pharmaceutical composition according to claim 5 or 6 for use as a medicament.
- 8) The amorphous simeprevir potassium salt according to any one of claims 1 to 4 or the pharmaceutical composition according to claim 5 or 6 for use in the treatment of hepatitis C infections in human.
- 9) A process for the preparation of an amorphous simeprevir alkali metal salt comprising:
 - (i) combining simeprevir with an alkali metal alcoholate in the presence of a solvent;
 - (ii) obtaining solid amorphous simeprevir alkali metal salt by

- (ii.1) combining the reaction mixture of (i) with an antisolvent or
- (ii.2) lyophilizing the reaction mixture of (i).

- 5 10) The process according to claim 9, wherein the amorphous simeprevir alkali metal salt is selected from amorphous simeprevir potassium salt and amorphous simeprevir sodium salt.
- 11) The process according to claim 9 or 10, wherein the alkali metal alcoholate is selected from the group of potassium methoxide, sodium methoxide, potassium *tert*-butoxide, sodium *tert*-butoxide.
- 12) The process according to any one of claims 9 to 11, wherein the alcohol is *tert*-butanol.
- 10 13) The process according to any one of claims 9 to 12, wherein the antisolvent is *n*-heptane.
- 14) The process according to any one of claims 9 to 13 further comprising (iii) separating at least a part of the amorphous simeprevir alkali metal salt obtained in step (ii.1) from its mother liquor.
- 15 15) The process according to claim 14 further comprising (iv) drying the amorphous simeprevir alkali metal salt obtained in (iii).

Figure 1

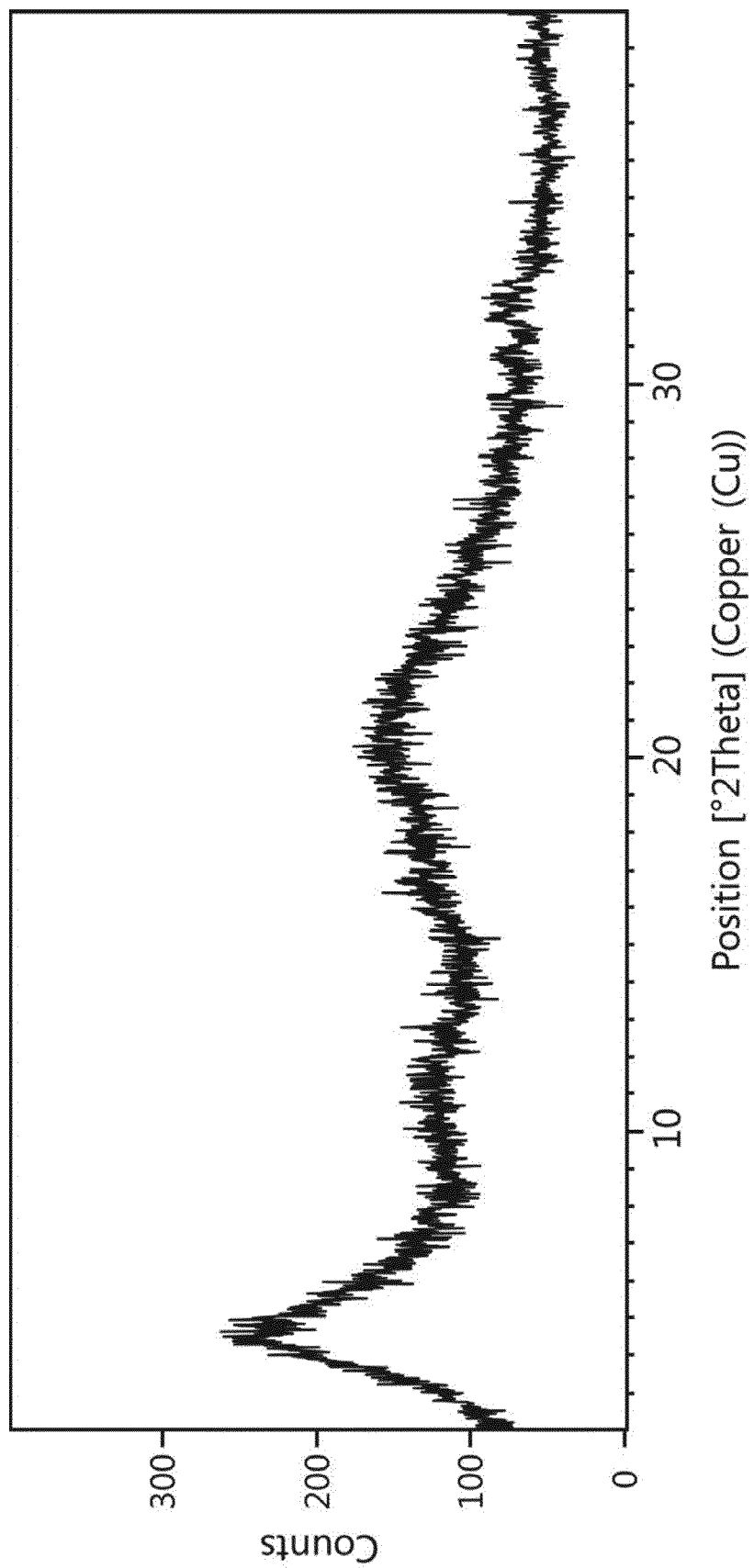


Figure 2

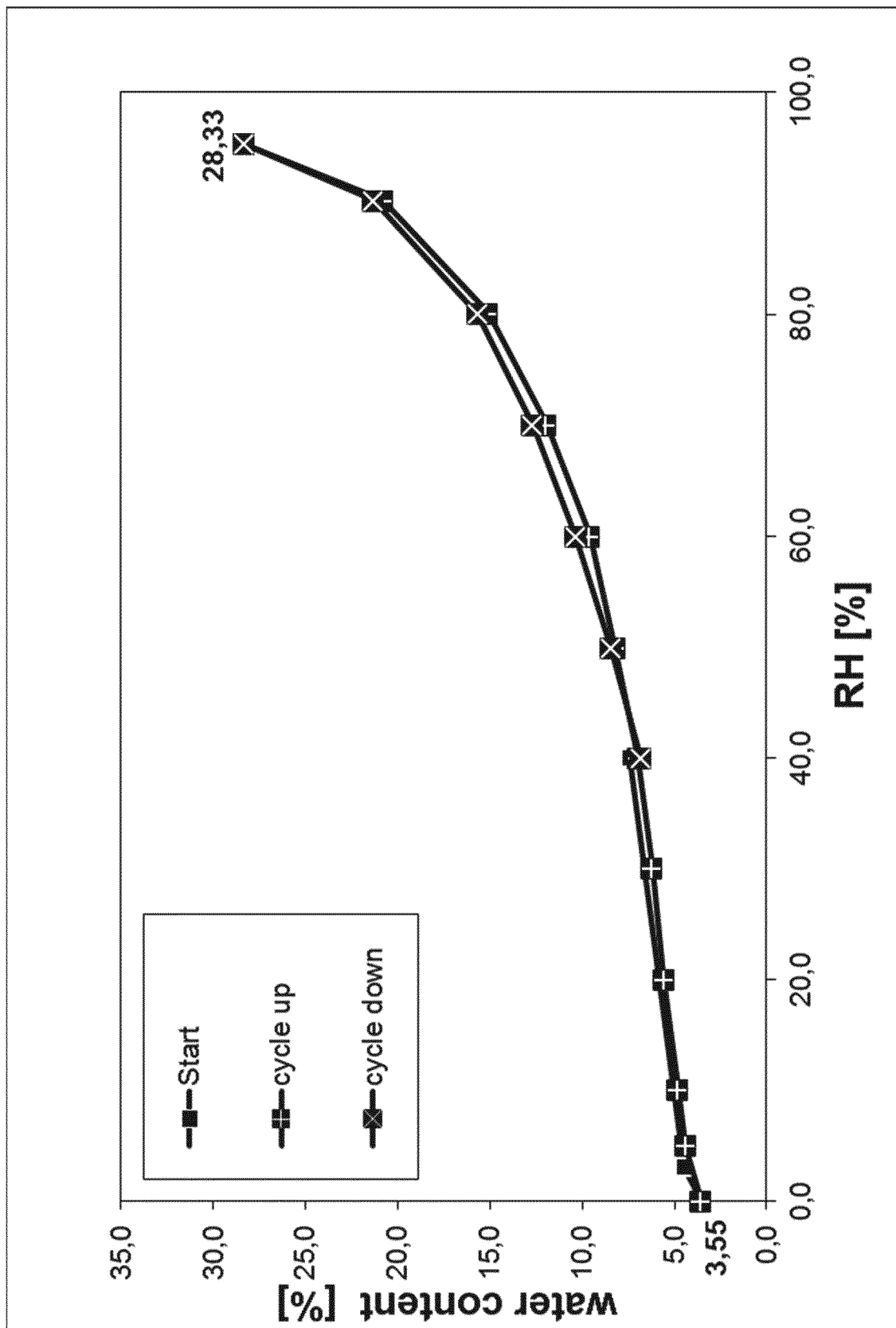


Figure 3

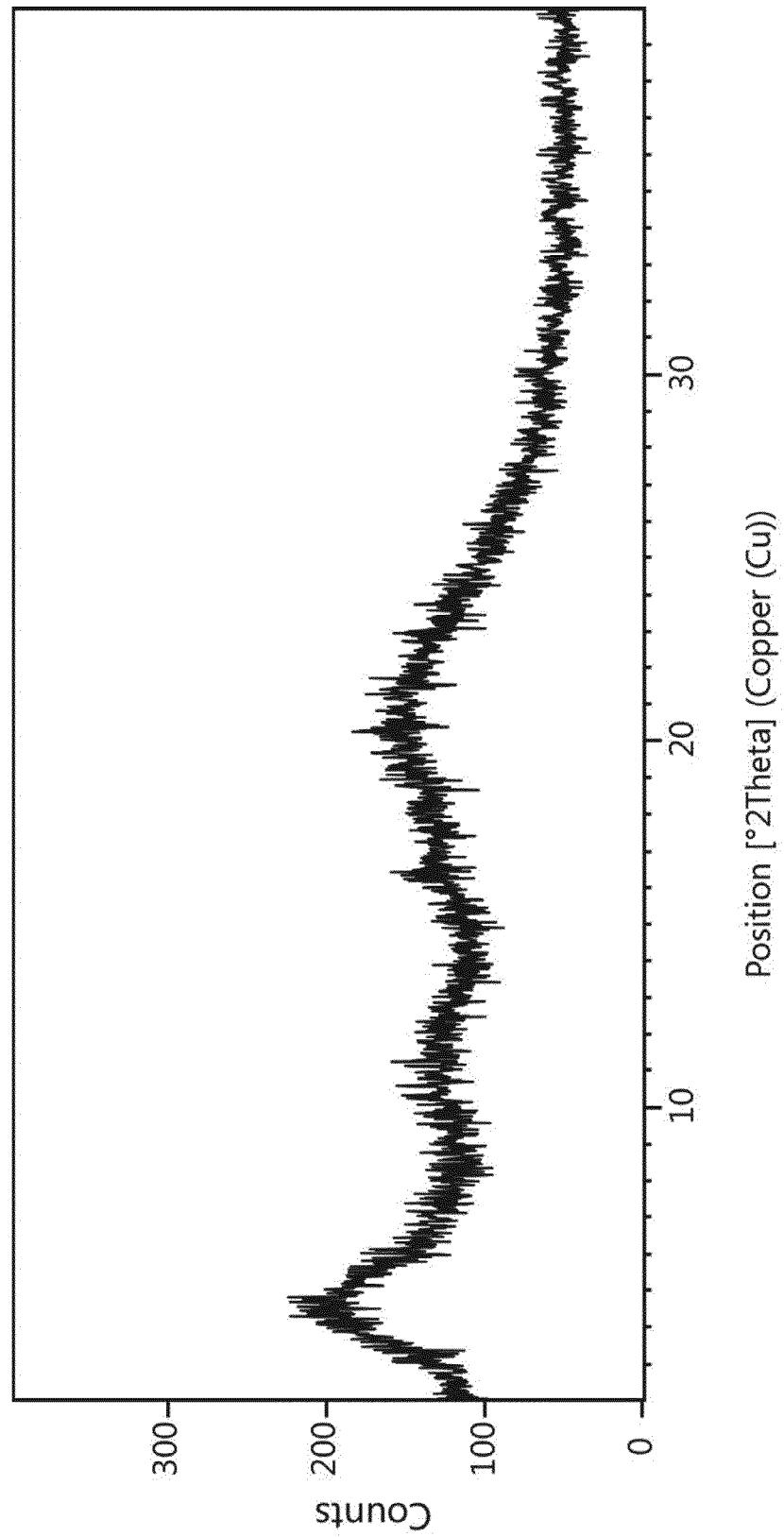
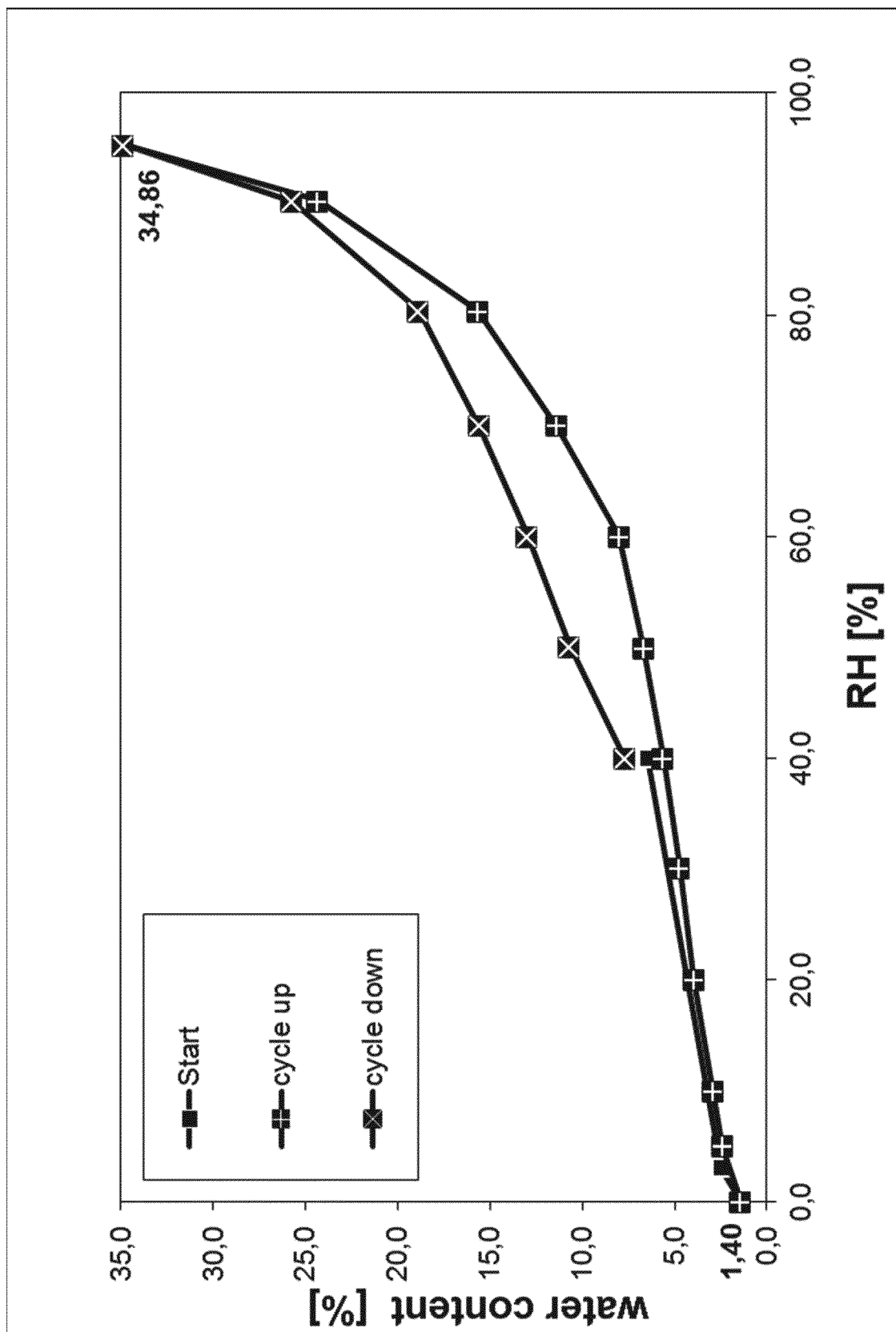


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/059505

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/04 A61K31/438 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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/014926 A1 (TIBOTEC PHARM LTD [IE]; MEDIVIR AB [SE]; RABOISSON PIERRE JEAN-MARIE B) 8 February 2007 (2007-02-08) cited in the application compound 47 in p. 132, salts p. 11 -----	1-15
A	WO 2010/097229 A2 (ORTHO MCNEIL JANSSEN PHARM [US]; VAN REMOORTERE PETER JOZEF MARIA [US]) 2 September 2010 (2010-09-02) cited in the application the whole document -----	1-15



Further documents are listed in the continuation of Box C.



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

16 June 2016

Date of mailing of the international search report

08/09/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/059505

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.:
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.:

1-8(completely); 9-15(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-8(completely); 9-15(partially)

Amorphous simeprevir potassium salt, uses and process of preparation thereof. Also preparation of other alkali metal salts different from sodium.

2. claims: 9-15(partially)

Process of preparation of amorphous simeprevir sodium salt

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/059505

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Information on patent family members

International application No

PCT/EP2016/059505

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