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(54) Title: NOVEL POLYMORPH OF RILPIVIRINE HYDROCHLORIDE

(57) Abstract: The present invention relates to a novel polymorph and to novel solvates of rilpivirine hydrochloride, as well as to their preparation. The novel solvates are valuable intermediates for the preparation of the novel polymorph of rilpivirine hydrochloride of the present invention. Moreover the present invention relates to the use of the novel polymorph for the preparation of a medicament. In addition the present invention relates to pharmaceutical compositions comprising an effective amount of the novel polymorph of rilpivirine hydrochloride and to methods of preparing the same. Finally the present invention relates to pharmaceutical combinations comprising an effective amount of the novel polymorph of rilpivirine hydrochloride and additional therapeutic agents.

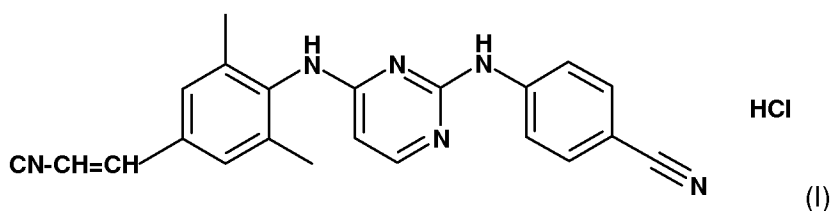


Novel polymorph of rilpivirine hydrochlorideFIELD OF THE INVENTION

The present invention relates to a novel polymorph and to novel solvates of rilpivirine hydrochloride, as well as to their preparation. The novel solvates are valuable intermediates for the preparation of the novel polymorph of rilpivirine hydrochloride of the present invention. Moreover the present invention relates to the use of the novel polymorph for the preparation of a medicament. In addition the present invention relates to pharmaceutical compositions comprising an effective amount of the novel polymorph of rilpivirine hydrochloride and to methods of preparing the same. Finally the present invention relates to pharmaceutical combinations comprising an effective amount of the novel polymorph of rilpivirine hydrochloride and additional therapeutic agents.

BACKGROUND OF THE INVENTION

Rilpivirine hydrochloride, 4-[[4-[[4-(2-Cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) and indicated for the treatment of HIV-1 infection in treatment-naïve adult patients in combination with other antiretroviral agents. Rilpivirine hydrochloride was launched as film coated tablets in Europe and the US (brand name Edurant). In addition rilpivirine hydrochloride was launched as a combination product with nucleoside analog HIV-1 reverse transcriptase inhibitors in the EU (brand name Eviplera) and the US (brand name Complera). Rilpivirine hydrochloride is represented by the following general formula (I):



EP1419152 B1 discloses amongst others rilpivirine base and rilpivirine hydrochloride per se as well as pharmaceutical compositions comprising the same. However, only concrete examples for preparing rilpivirine base are given in said patent but no concrete examples describing the production of the hydrochloride salt are provided.

EP1632232 B1 discloses amongst others a solid pharmaceutical composition comprising crystalline forms A, B, C or D of rilpivirine hydrochloride. In addition said patent discloses a

process for the production of rilpivirine hydrochloride by reacting rilpivirine base with hydrochloric acid in the presence of a suitable acid, such as acetic acid.

Polymorphism is a phenomenon relating to the occurrence of different crystal forms for one molecule. There may be several different crystalline forms for the same molecule with distinct crystal structures and varying in physical properties like melting point, XRPD pattern and FTIR spectrum. These polymorphs are thus distinct solid forms which share the molecular formula of the compound from which the crystals are made up, however they may have distinct advantageous physical properties such as e.g. chemical stability, physical stability, hygroscopicity, solubility, dissolution rate or bioavailability. In addition the preparation process of a crystalline form, especially on large scale, plays an important role in the development of an active pharmaceutical ingredient. It is essential that the crystallization process is robust and reliably produces the desired crystalline form in polymorphically pure form, also on large scale.

The bioavailability of a compound intended to be administered orally, is dependent on the compounds solubility in aqueous systems such as e.g. water, as well as the compounds permeability as mentioned in EP1632232 B1. It is known to the person skilled in the art that the solubility of a crystalline solvate form in the solvent, which is incorporated in this form, is smaller than the solubility of a non-solvated form of the same compound. This means that the solubility of a hydrate - wherein water is the incorporated solvent - in water is thus smaller than that of a corresponding non-hydrated form. This is particularly true for badly water soluble active pharmaceutical ingredients such as rilpivirine hydrochloride. Hence an anhydrous form is preferred over a hydrated form for the formulation of an orally administered medicament comprising rilpivirine hydrochloride. Rilpivirine hydrochloride form D of EP1632232 B1 is a hydrate and thus not preferred for the preparation of an orally administered medicament, whereas the novel polymorph of the present invention is an anhydrous form and hence especially suitable for the preparation of an orally administered medicament.

In addition the crystalline forms A and C of EP1632232 B1 are difficult to make in a reliable manner because these forms are obtained from the same solvent system. As the polymorphs A and C of rilpivirine hydrochloride are obtained from the same solvent system, namely acetic acid/water, the production processes are especially critical and sensitive because the single crystalline forms are only obtained in pure form in a quite narrow range of critical parameters, such as the crystallization temperature, as described in the concrete examples A.a) and A.c) of EP1632232 B1. In contrast the novel polymorph of rilpivirine hydrochloride of

the present invention is easily obtained in polymorphically pure form in a reliable manner by applying the novel solvates of rilpivirine hydrochloride of the present invention as intermediates in the production of the novel polymorph.

According to example A.b) of EP1632232 B1 form B is obtained by recrystallizing rilpivirine hydrochloride from propanone using an initial rilpivirine hydrochloride concentration of 0.3 g/L. However, this concentration is not suitable for up-scaling as larger amounts of rilpivirine hydrochloride would require tremendous solvent volumina and hence the usage of tremendously large reaction vessels. In contrast the novel polymorph of the present invention is obtained by applying higher initial concentrations of the novel solvates of rilpivirine hydrochloride of the present invention, which are employed as intermediates for the production of the novel polymorph of the present invention and is thus suitable for large scale production.

Hence the aim of the present invention is to circumvent the drawbacks of the known forms A, B, C and D of EP1632232 B1 by providing an anhydrous polymorph of rilpivirine hydrochloride, which is obtained in polymorphically pure form in an easy and reliable manner, also on large scale.

SUMMARY OF THE INVENTION

The inventors of the present invention have found a novel polymorph of rilpivirine hydrochloride, in the following named rilpivirine hydrochloride form F. Polymorph F is an anhydrous and non-solvated crystalline form and shows certain advantages compared to the known forms A, B, C and D of rilpivirine hydrochloride of EP1632232 B1 making it especially suitable for the preparation of an orally administered medicament.

Hence in a preferred embodiment the present invention relates to a novel polymorph of rilpivirine hydrochloride, in the following named rilpivirine hydrochloride form F. Form F of rilpivirine hydrochloride can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $5.6 \pm 0.2^\circ$, $6.1 \pm 0.2^\circ$, $6.9 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$ and $13.8 \pm 0.2^\circ$.

In a further preferred embodiment, the present invention relates to processes of preparing form F of rilpivirine hydrochloride in which the novel crystalline solvates of rilpivirine hydrochloride of the present invention are employed as intermediates.

Thus in an additional preferred embodiment, the present invention relates to novel solvates of rilpivirine hydrochloride.

In one embodiment the present invention relates to solvates of rilpivirine hydrochloride which are isomorphic and can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.8 \pm 0.2^\circ$.

In a further embodiment the present invention relates to additional solvates of rilpivirine hydrochloride which are isomorphic and can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $16.1 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$.

In still another embodiment the present invention relates to a dichloromethane solvate of rilpivirine hydrochloride which can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$ and $24.1 \pm 0.2^\circ$.

Moreover in another embodiment the present invention relates to a cyclohexanone solvate of rilpivirine hydrochloride which can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $17.3 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$, $20.8 \pm 0.2^\circ$ and $23.3 \pm 0.2^\circ$.

The present invention also relates to a method of preparing the novel solvates of rilpivirine hydrochloride comprising the steps of:

- a) providing a suspension or solution of rilpivirine free base in a solvent selected from alcohols, ketones, ethers, or chlorinated hydrocarbons,
- b) adding hydrochloric acid to the suspension or solution and
- c) recovering the novel solvate of rilpivirine hydrochloride.

Furthermore the present invention relates to the use of the novel solvates of rilpivirine hydrochloride as intermediates for the preparation of rilpivirine hydrochloride form F.

In addition the present invention relates to the use of the novel polymorph F of rilpivirine hydrochloride for the preparation of a medicament.

In another embodiment the present invention relates to pharmaceutical compositions comprising an effective amount of the novel polymorph F of rilpivirine hydrochloride and a pharmaceutically acceptable carrier and to processes of preparing the same.

Finally the present invention relates to pharmaceutical combinations comprising an effective amount of the novel polymorph F of rilpivirine hydrochloride and additional therapeutic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: X-ray powder diffractogram (XRPD) of rilpivirine hydrochloride form F

Figure 2: Fourier transform infrared (FTIR) spectrum of rilpivirine hydrochloride form F

Figure 3: Overlay X-ray powder diffractograms (XRPD) of rilpivirine hydrochloride 1-propanol, 2-propanol, acetone, tetrahydrofuran and chloroform solvates

Figure 4: Overlay X-ray powder diffractograms (XRPD) of rilpivirine hydrochloride 1,4-dioxane and 2-butanone solvates

Figure 5: X-ray powder diffractogram (XRPD) of rilpivirine hydrochloride dichloromethane solvate

Figure 6: X-ray powder diffractogram (XRPD) of rilpivirine hydrochloride cyclohexanone solvate

Figure 7: Overlay Fourier transform infrared spectra (FTIR) of rilpivirine hydrochloride 1-propanol, 2-propanol, acetone, tetrahydrofuran and chloroform solvates

Figure 8: Overlay Fourier transform infrared spectra (FTIR) of rilpivirine hydrochloride 1,4-dioxane, 2-butanone, dichloromethane and cyclohexanone solvates

Figure 9: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride 1-propanol solvate

Figure 10: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride 2-propanol solvate

Figure 11: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride acetone solvate

Figure 12: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride 2-butanone solvate

Figure 13: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride tetrahydrofuran solvate

Figure 14: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride 1,4-dioxane solvate

Figure 15: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride dichloromethane solvate

Figure 16: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride chloroform solvate

Figure 17: Thermogravimetric analysis (TGA) curve of rilpivirine hydrochloride cyclohexanone solvate

DETAILED DESCRIPTION OF THE INVENTION

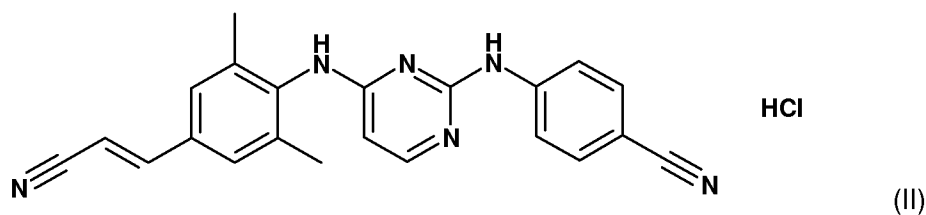
As used herein the term “room temperature” indicates that the applied temperature is not critical and that no exact temperature value has to be kept. Usually, “room temperature” is understood to mean temperatures of about 15 °C to about 25 °C [see e.g. EU Pharmacopoeia 7.5, 1.2 (2012)].

The term “solvate” as used herein describes a crystalline compound in which solvent molecules are incorporated into the crystal lattice of the compound in a stoichiometric or non-stoichiometric manner.

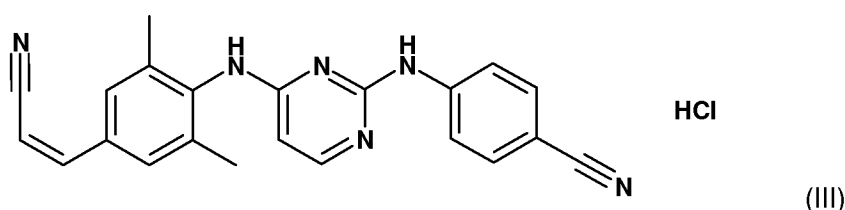
The term “concentrated hydrochloric acid” as used herein means aqueous hydrochloric acid having a concentration of about 37 %.

Rilpivirine hydrochloride exists in two stereoisomeric forms, namely an E-isomeric form and a Z-isomeric form. The novel crystalline forms of rilpivirine hydrochloride of the present invention are preferably present as the pure E-isomer, whereat pure in this context refers to an E-isomer content of at least about 95 %, more preferably of at least about 98 % and most preferably of at least about 99 %.

The chemical structure of the E-isomeric form of rilpivirine hydrochloride is represented by the following general formula (II):



The chemical structure of the Z-isomeric form of rilpivirine hydrochloride is represented by the following general formula (III):



In a first aspect, the present invention relates to a novel polymorph of rilpivirine hydrochloride (hereinafter also referred to as rilpivirine hydrochloride form F).

Form F of rilpivirine hydrochloride can be characterized by showing an X-ray powder diffractogram comprising characteristic peaks at 2-theta angles of $5.6 \pm 0.2^\circ$, $6.1 \pm 0.2^\circ$, $6.9 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$ and $13.8 \pm 0.2^\circ$. The X-ray powder diffractogram of form F of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $15.9 \pm 0.2^\circ$, $16.6 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $17.9 \pm 0.2^\circ$, $18.5 \pm 0.2^\circ$, $19.6 \pm 0.2^\circ$, $20.9 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.8 \pm 0.2^\circ$, $22.0 \pm 0.2^\circ$, $22.8 \pm 0.2^\circ$, $23.5 \pm 0.2^\circ$, $23.8 \pm 0.2^\circ$, $24.2 \pm 0.2^\circ$, $24.6 \pm 0.2^\circ$, $24.9 \pm 0.2^\circ$, $25.5 \pm 0.2^\circ$, $26.6 \pm 0.2^\circ$ and $27.4 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 1.

In addition form F of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3223 \pm 2 \text{ cm}^{-1}$, $2222 \pm 2 \text{ cm}^{-1}$, $1652 \pm 2 \text{ cm}^{-1}$, $966 \pm 2 \text{ cm}^{-1}$ and $811 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of form F of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3176 \pm 2 \text{ cm}^{-1}$, $3055 \pm 2 \text{ cm}^{-1}$, $2961 \pm 2 \text{ cm}^{-1}$, $2862 \pm 2 \text{ cm}^{-1}$, $1635 \pm 2 \text{ cm}^{-1}$, $1598 \pm 2 \text{ cm}^{-1}$, $1566 \pm 2 \text{ cm}^{-1}$, $1541 \pm 2 \text{ cm}^{-1}$, $1522 \pm 2 \text{ cm}^{-1}$, $1503 \pm 2 \text{ cm}^{-1}$, $1444 \pm 2 \text{ cm}^{-1}$, $1416 \pm 2 \text{ cm}^{-1}$, $1386 \pm 2 \text{ cm}^{-1}$, $1357 \pm 2 \text{ cm}^{-1}$, $1338 \pm 2 \text{ cm}^{-1}$, $1308 \pm 2 \text{ cm}^{-1}$, $1273 \pm 2 \text{ cm}^{-1}$, $1241 \pm 2 \text{ cm}^{-1}$, $1213 \pm 2 \text{ cm}^{-1}$, $1178 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1097 \pm 2 \text{ cm}^{-1}$, $1072 \pm 2 \text{ cm}^{-1}$, $1031 \pm 2 \text{ cm}^{-1}$, $1018 \pm 2 \text{ cm}^{-1}$, $985 \pm 2 \text{ cm}^{-1}$, $869 \pm 2 \text{ cm}^{-1}$, $851 \pm 2 \text{ cm}^{-1}$, $794 \pm 2 \text{ cm}^{-1}$, $713 \pm 2 \text{ cm}^{-1}$, $680 \pm 2 \text{ cm}^{-1}$, $666 \pm 2 \text{ cm}^{-1}$ and $623 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 2.

Furthermore form F of rilpivirine hydrochloride can be characterized as being an anhydrous form containing less than about 1.5 %, preferably less than about 1.0 % water.

The present invention also relates to a process for the preparation of form F of rilpivirine hydrochloride comprising slurring a novel solvate of rilpivirine hydrochloride of the present invention in water, collecting the obtained crystals and drying the crystals at about 80°C to about 180°C and/or below about 5 % relative humidity.

In a first step a suspension of a novel solvate of rilpivirine hydrochloride of the present invention in water is provided. Any crystalline solvate of rilpivirine hydrochloride of the

present invention may be applied e.g. crystalline rilpivirine hydrochloride 1-propanol solvate, crystalline rilpivirine hydrochloride 2-propanol solvate, crystalline rilpivirine hydrochloride acetone solvate, crystalline rilpivirine hydrochloride 2-butanone solvate, crystalline rilpivirine hydrochloride cyclohexanone solvate, crystalline rilpivirine hydrochloride tetrahydrofuran solvate, crystalline rilpivirine hydrochloride 1,4-dioxane solvate, crystalline rilpivirine hydrochloride dichloromethane solvate, crystalline rilpivirine hydrochloride chloroform solvate or mixtures thereof.

The initial rilpivirine hydrochloride concentration applied in the process may range from about 1 to 200 g/L, preferably from about 5 to 150 g/L, more preferably from about 10 to 100 g/L and most preferably from about 15 to 30 g/L.

The suspension is stirred, at a temperature preferably ranging from about 0 to 40 °C, more preferably from about 10 to 30 °C and most preferably the suspension is stirred at about room temperature, for a time preferably ranging from about 1 to 72 hours, more preferably from about 6 to 60 hours, and most preferably from about 12 to 48 hours.

The obtained crystals are then collected by any conventional methods such as filtration, centrifugation or evaporation of the solvent, preferably by filtration.

Thereafter the crystals are dried preferably under vacuum at a temperature preferably ranging from about 80 °C to 180 °C, more preferably from about 90 °C to 140 °C and most preferably from about 100 °C to 110 °C for a time preferably ranging from about 1 to 72 hours, more preferably from about 6 to 48 hours and most preferably from about 12 to 24 hours.

Alternatively the crystals can be dried at room temperature by storing them at an atmosphere having a relative humidity of $\leq 5\%$ e.g. by storing the crystals in a closed containment over a desiccant such as e.g. P_2O_5 or silica gel, whereat the storing time may range from about 1 to 72 hours, more preferably from about 6 to 48 hours and most preferably from about 12 to 24 hours. The storing time may be decreased by storing the crystals at $\leq 5\%$ relative humidity and applying elevated temperatures preferably ranging from about 30 to 180 °C, more preferably from about 40 to 140 °C and most preferably from about 50 to 110 °C.

The particle size of rilpivirine hydrochloride form F obtained according to the processes of the present invention typically ranges from about 10 to 150 μm determined by optical light microscopy. However, the particle size can be decreased by any conventional method such

as e.g. milling or grinding. In addition the particle size can be homogenized by applying an additional sieving step. Preferably milling and sieving are performed in such a manner that rilpivirine hydrochloride form F having a particle size ranging from about 0.1 to 50 μm , more preferably from about 0.1 to 25 μm and most preferably from about 0.1 to 15 μm is obtained.

The bioavailability of a compound intended to be administered orally, is dependent on the compounds solubility in aqueous systems such as e.g. water, as well as the compounds permeability as mentioned in EP1632232 B1. It is known to the person skilled in the art that the solubility of a crystalline solvate form in the solvent, which is incorporated in this form, is smaller than the solubility of a non-solvated form of the same compound. This means that the solubility of a hydrate - wherein water is the incorporated solvent - in water is thus smaller than that of a corresponding non-hydrated form. This is particularly true for badly water soluble active pharmaceutical ingredients such as rilpivirine hydrochloride. Hence, an anhydrous form is preferred over a hydrated form for the formulation of an orally administered medicament comprising rilpivirine hydrochloride. Rilpivirine hydrochloride form D of EP1632232 B1 is a hydrate and thus not preferred for the preparation of an orally administered medicament, whereas the novel polymorph F of the present invention is an anhydrous form and hence especially suitable for the preparation of an orally administered medicament.

In addition, the crystalline forms A and C of EP1632232 B1 are difficult to make in a reliable manner because these forms are obtained from the same solvent system. As the polymorphs A and C of rilpivirine hydrochloride are obtained from the same solvent system, namely acetic acid/water, the production processes are especially critical and sensitive because the single crystalline forms are only obtained in pure form in a quite narrow range of critical parameters, such as the crystallization temperature, as described in the concrete examples A.a) and A.c) of EP1632232 B1. In contrast, the novel polymorph F of rilpivirine hydrochloride of the present invention is easily obtained in polymorphically pure form in a reliable manner by applying the novel solvates of rilpivirine hydrochloride of the present invention as intermediates in the process for the production of the novel polymorph F. The novel solvates are slurried in water and dried at $\geq 80\text{ }^{\circ}\text{C}$ and or at $\leq 5\%$ relative humidity to obtain polymorphically pure form F of rilpivirine hydrochloride.

According to example A.b) of EP1632232 B1 form B is obtained by recrystallizing rilpivirine hydrochloride from propanone using an initial rilpivirine hydrochloride concentration of 0.3 g/L. However, this concentration is not suitable for up-scaling as larger amounts of rilpivirine hydrochloride would require tremendous solvent volumina and hence the usage of

tremendously large reaction vessels. In contrast the novel polymorph F of the present invention is obtained by applying higher initial concentrations of the novel solvates of rilpivirine hydrochloride of the present invention, which are employed as intermediates for form F production, such as e.g. 20 mg/mL (see example 1) and is thus suitable for large scale production.

The novel polymorph F of rilpivirine hydrochloride of the present invention circumvents the drawbacks of the known forms A, B, C and D of EP1632232 B1 as it is an anhydrous form obtained in polymorphically pure form in an easy and reliable manner according to the processes of the present invention, also on large scale.

Thus polymorph F of rilpivirine hydrochloride is the most favored form to be used in an oral antiviral pharmaceutical composition and may advantageously be employed in various pharmaceutical formulations for use in the treatment of HIV-1 infection. The present invention therefore also relates to pharmaceutical compositions comprising rilpivirine hydrochloride form F as described above and a pharmaceutically acceptable carrier.

Preferably, the present invention relates to pharmaceutical compositions, wherein more than 95 % of rilpivirine hydrochloride are stably present as rilpivirine hydrochloride form F, more preferably wherein rilpivirine hydrochloride form F is the only detectable crystalline form of rilpivirine hydrochloride. The absence of other crystalline forms of rilpivirine hydrochloride, such as forms A, B, C and D of EP1632232 B1 can be tested by comparing an XRPD taken of any crystalline rilpivirine hydrochloride with the XRPD of form F as obtained from example 1 and shown in figure 1, which for this comparison is to be taken as an XRPD of 100 % form F.

“Stably present” as defined herein means that even after storage of the pharmaceutical composition for 180 days and preferably even after storage for 3 years, the crystalline form of rilpivirine hydrochloride designated as rilpivirine hydrochloride form F initially comprised in the pharmaceutical composition is still present as rilpivirine hydrochloride form F after storage for the indicated period.

The pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F may further comprise one or more pharmaceutically acceptable excipients. Such excipients are preferably selected from the group consisting of fillers, sweeteners, buffering agents, glidants, flowing agents, flavouring agents, lubricants, preservatives, surfactants, wetting agents, binders, disintegrants and thickeners. Other excipients known in the field of

pharmaceutical compositions may also be used. Furthermore, the pharmaceutical composition may comprise a combination of two or more excipients also within one of the members of the above mentioned group.

Examples of suitable excipients for pharmaceutical compositions of the invention comprising rilpivirine hydrochloride form F are given e.g. in EP1632232 B1, which is herein incorporated by reference in paragraphs [0063] to [0080].

Paragraph [0063] of EP1632232 B1 discloses examples of wetting agents for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred wetting agents, which can also be used for the pharmaceutical compositions of the present invention, comprise sodium lauryl sulphate, sodium dioctyl sulfosuccinate or wetting agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60 and 80, whereat Tween 20 (= polysorbate 20) is most preferred.

Paragraphs [0065] to [0072] of EP1632232 B1 disclose examples of binders for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred binders, which can also be used for the pharmaceutical compositions of the present invention, comprise e.g. alkylcelluloses such as methylcellulose, hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose, hydroxyalkylalkylcelluloses such as hydroxyethylmethylcellulose and hydroxypropylmethylcellulose, carboxyalkylcelluloses such as carboxymethylcellulose, alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose, carboxyalkylalkylcelluloses such as carboxymethylethylcellulose, carboxyalkylcellulose esters, starches such as starch 1551, pectins such as sodium carboxymethylamylopectin, chitin derivatives such as chitosan, heparin and heparinoids, polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guar gum and xanthan gum, polyacrylic acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate, polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines, copovidone, whereat starch, polyvinylpyrrolidone or a cellulose ether e.g. PVP K29-32, PVP K90, methyl cellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose or hydroxypropyl methylcellulose (HPMC) are preferred.

Paragraph [0075] of EP1632232 B1 discloses examples of suitable diluents for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred diluents, which can also be used for the pharmaceutical compositions of the present invention, comprise e.g. calcium carbonate, dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose including silicified microcrystalline cellulose, powdered cellulose, dextrates, dextrin, dextrose excipient, fructose, kaolin, lactitol, lactose anhydrous, lactose monohydrate, mannitol, sorbitol, starch, pregelatinized starch, sodium chloride, sucrose, compressible sugar, confectioner's sugar, a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25), commercially available as Microcelac[®], a co-processed spray-dried mixture of microcrystalline cellulose and colloidal silicon dioxide (98:2), commercially available as Prosolv[®], whereat lactose monohydrate, microcrystalline cellulose silicified microcrystalline cellulose, starch, modified starch, dibasic calcium phosphate and dibasic calcium phosphate dihydrate are preferred.

Paragraph [0076] of EP1632232 B1 discloses examples of glidants for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred glidants, which can also be used for the pharmaceutical compositions of the present invention comprise talc, colloidal silicon dioxide, starch and magnesium stearate, whereat magnesium stearate is preferred.

Paragraph [0078] of EP1632232 B1 discloses examples of disintegrants for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred disintegrants, which can also be used for the pharmaceutical compositions of the present invention, comprise starch, ion exchange resins, e.g. Amberlite, cross-linked polyvinylpyrrolidone, modified cellulose gum, e.g. croscarmellose sodium, sodium starch glycolate, sodium carboxymethylcellulose, sodium dodecyl sulphate, modified corn starch, microcrystalline cellulose, magnesium aluminium silicate, alginic acid, alginate and powdered cellulose, whereat croscarmellose sodium is preferred.

Paragraph [0079] of EP1632232 B1 discloses examples of lubricants for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The preferred lubricants, which can also be used for the pharmaceutical compositions of the present invention, are e.g. magnesium stearate, calcium stearate, stearic acid, talc, polyethylene glycol, sodium lauryl sulphate and magnesium lauryl sulphate, whereat magnesium stearate is preferred.

In addition the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F may comprise other optional excipients such as, for example, flavors, sweeteners and colors.

Paragraph [0083] of EP1632232 B1 discloses examples of film coatings for the pharmaceutical compositions of the present invention comprising rilpivirine hydrochloride form F. The film coatings, which can also be used for the pharmaceutical compositions of the present invention, are preferably immediate release film coatings comprising a film-forming polymer, optionally a plasticizer, optionally a pigment or an opacifier and/or optionally a filler of the coating layer. An example for a suitable film-forming polymer is hydroxypropyl methylcellulose e.g. hypromellose 2910 mPa.s, an example for a suitable plasticizer is polyethyleneglycol e.g. macrogol 3000 or 6000 and/or triacetin, an example for a suitable pigment respectively opacifier is titanium dioxide and an example for a suitable filler is lactose monohydrate. A suitable commercially available ready to use film coating powder which can be applied for the preparation of the pharmaceutical composition of the present invention is e.g. Opadry® II White.

Examples of suitable processes for the preparation of the pharmaceutical compositions of the present invention, which are preferably film coated tablets, are given e.g. in EP1632232 B1, which is herein incorporated by reference in paragraphs [0084] to [0086], wherein it is to be understood that whenever the term compound of formula (I), (Ia) or (I-b) or active ingredient is used in EP1632232 B1 an equivalent amount of rilpivirine hydrochloride form F of the present invention is to be used.

Concrete examples for the production of formulations of the present invention are given e.g. in EP1632232 B1, paragraphs [0120] to [0137]. These examples can be repeated by substituting the compound of formula (1-a) against rilpivirine hydrochloride form F of the present invention.

The pharmaceutical composition of the present invention comprising rilpivirine hydrochloride form F preferably is an oral dosage form, in particular a capsule or tablet.

A preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, lactose monohydrate, silicified microcrystalline cellulose, croscarmellose sodium, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30) and magnesium stearate and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

Another preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30), dibasic calcium phosphate (dihydrate or anhydrate e.g. Emcompress® or anhydrous Emcompress®), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

In addition a preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, lactose monohydrate, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

A further preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, modified starch, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30) and magnesium stearate and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

In one embodiment a tablet of the present invention may be prepared by wet granulation comprising the steps of:

- a) dry blending rilpivirine hydrochloride form F of the present invention and a part of the diluent,
- b) preparing a binder solution by dissolving a binder and a wetting agent in a suitable solvent,
- c) spraying the binder solution of step b) on the mixture obtained in step a),
- d) drying the obtained granulate and sieving the same,
- e) mixing the obtained granulate with the remaining part of diluent and a disintegrant,
- f) adding an optional glidant and/or an optional lubricant to the mixture,
- g) compressing the obtained mixture into a tablet and
- h) optionally film-coating the obtained tablet.

Suitable solvents in step b) of the herein disclosed wet granulation process are e.g. water, acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl

ketone, methylisobutyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate and tetrahydrofuran.

A particular tablet of the present invention may be prepared by wet granulation comprising the steps of:

- a) dry blending rilpivirine hydrochloride form F of the present invention and lactose monohydrate,
- b) preparing a binder solution by dissolving polyvinylpyrrolidone K30 (PVP K30) and polysorbate 20 (Tween 20) in a suitable solvent,
- c) spraying the binder solution of step b) on the mixture obtained in step a),
- d) drying the obtained granulate and sieving the same,
- e) mixing the obtained granulate with silicified microcrystalline cellulose and croscarmellose sodium,
- f) adding magnesium stearate to the mixture,
- g) compressing the obtained mixture into a tablet and
- h) optionally film-coating the obtained tablet.

Suitable solvents in step b) of the herein disclosed wet granulation process are e.g. water, acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate and tetrahydrofuran.

A further preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, lactose monohydrate, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

Another preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, dibasic calcium phosphate (dihydrate or anhydrate e.g. Emcompress[®] or anhydrous Emcompress[®]), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

Moreover, a preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, lactose monohydrate, magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

In addition a preferred tablet of the present invention comprises a tablet core comprising rilpivirine hydrochloride form F of the present invention, microcrystalline cellulose, modified starch and magnesium stearate and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

In another embodiment a tablet of the present invention may be prepared by direct compression comprising the steps of:

- a) dry blending rilpivirine hydrochloride form F of the present invention, a disintegrant, an optional glidant and an optional lubricant with at least one diluent,
- b) compressing the obtained mixture in the dry state into a tablet and
- c) optionally film-coating the obtained tablet.

A particular tablet of the present invention may be prepared by direct compression comprising the steps of:

- a) dry blending rilpivirine hydrochloride form F of the present invention, croscarmellose sodium and magnesium stearate with lactose monohydrate and silicified microcrystalline cellulose,
- b) compressing the obtained mixture in the dry state into a tablet and
- c) optionally film-coating the obtained tablet.

Formulations of the present invention typically comprise about 100 mg, preferably about 75 mg, more preferably about 50 mg and most preferably about 25 mg rilpivirine hydrochloride form F (calculated as rilpivirine free base).

The pharmaceutical compositions of the present invention comprising crystalline form F of rilpivirine hydrochloride are preferably packaged or filled into containers. Containers are typically used for stable storage of the pharmaceutical compositions of the present invention for example at a temperature of about 20 °C to 30 °C e.g. at about 25 °C for a prolonged time e.g. for at least 6 months, preferably at least about 24 months, for up to at least 24 months e.g. for up to at least about 30 months, such as for up to about 60 months.

The container used for the stable storage of the pharmaceutical compositions of the present invention comprising crystalline form F of rilpivirine hydrochloride ensures an environment having a relative humidity of about 0 to 70 %, more preferably of about 0 to 50 % and most preferably of about 0 to 30 %.

A preferred container is a bottle, in particular a polyethylene bottle e.g. a HDPE bottle or a glass bottle, having e.g. a screw closure with an aluminum induction seal liner, or is a blister, e.g. an aluminum blister or strip, e.g. a blister consisting of two aluminum foils or strips, or may be any other suitable container. More preferably said container is a gas-tight container, such as an air-tight container.

In a further embodiment the present invention relates to a pharmaceutical combination comprising an effective amount of rilpivirine hydrochloride form F and one or more additional therapeutic agents such as e.g. anti-virals, antibiotics, immunomodulators or vaccines for the treatment of viral infections. Preferably the additional therapeutic agents are chosen from e.g. emtricitabine, tenofovir, abacavir, lamivudine, efavirenz, ritonavir, atazanavir, raltegravir, darunavir, fosamprenavir, lopinavir, telaprevir, boceprevir and/or zidovudine, most preferably emtricitabine, tenofovir, abacavir and/or lamivudine are used for the pharmaceutical combinations.

The anti-viral agent for the pharmaceutical combination with rilpivirine hydrochloride form F of the present invention is preferably chosen from the class of nucleoside analog HIV-1 reverse transcriptase inhibitors, whereat emtricitabine and tenofovir are most preferred.

A preferred pharmaceutical combination of the present invention comprises 25 mg rilpivirine hydrochloride form F (calculated as free base), 200 mg emtricitabine and 245 mg tenofovir disoproxil fumarate (calculated as free base) and one or more pharmaceutically acceptable excipients.

In a second aspect the present invention relates to novel crystalline solvates of rilpivirine hydrochloride.

Some of the solvates of rilpivirine hydrochloride produce very similar X-ray powder diffractograms indicating that these solvates are isomorphic. Isomorphic solvates means that even though the solvates contain different solvents, they exhibit essentially the same molecular packing resulting in very similar corresponding unit cell parameters. Thus these solvates can be identified by some common characteristic reflections as described below.

Hence in one embodiment the present invention relates to crystalline isomorphic solvates of rilpivirine hydrochloride, which are characterized by an X-ray powder diffraction pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.8 \pm 0.2^\circ$. Representative diffractograms are displayed in figure 3.

The isomorphic solvates of rilpivirine hydrochloride are characterized by a solvent content of about 0.3 to 0.7 mol, more preferably about 0.4 to 0.6 mol solvent per mol rilpivirine hydrochloride, wherein the solvent incorporated into the crystal lattice is selected from 1-propanol, 2-propanol, acetone, tetrahydrofuran or chloroform.

In addition the isomorphic solvates of rilpivirine hydrochloride are surprisingly stable as the desolvation occurs only at about $> 150^\circ\text{C}$, more preferably at about $> 200^\circ\text{C}$ as indicated by thermogravimetric analysis.

In another embodiment the present invention relates to additional crystalline isomorphic solvates of rilpivirine hydrochloride, which are characterized by an X-ray powder diffraction pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $16.1 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$. Representative diffractograms are displayed in figure 4.

The isomorphic solvates of rilpivirine hydrochloride are characterized by a solvent content of about 0.3 to 0.7 mol, more preferably about 0.4 to 0.6 mol solvent per mol rilpivirine hydrochloride, wherein the solvent incorporated into the crystal lattice is selected from 1,4-dioxane or 2-butanone.

In addition the isomorphic solvates of rilpivirine hydrochloride are surprisingly stable as the desolvation occurs only at about $> 150^\circ\text{C}$, more preferably at about $> 200^\circ\text{C}$ as indicated by thermogravimetric analysis.

In still another embodiment the present invention relates to a dichloromethane solvate which is characterized by an X-ray powder diffraction pattern comprising peaks at 2- theta angles of $8.2 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$ and $24.1 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 5.

The dichloromethane solvate of rilpivirine hydrochloride is characterized by a solvent content of about 0.3 to 0.7 mol, more preferably about 0.4 to 0.6 mol dichloromethane per mol rilpivirine hydrochloride.

In addition the dichloromethane solvate of rilpivirine hydrochloride is surprisingly stable as the desolvation occurs only at about $> 150\text{ }^{\circ}\text{C}$ indicated by thermogravimetric analysis.

In a further embodiment the present invention relates to a cyclohexanone solvate characterized by an X-ray powder diffraction pattern showing peaks at 2-theta angles of $8.1 \pm 0.2^{\circ}$, $17.3 \pm 0.2^{\circ}$, $18.8 \pm 0.2^{\circ}$, $20.8 \pm 0.2^{\circ}$ and $23.3 \pm 0.2^{\circ}$. A representative diffractogram is displayed in figure 6.

The cyclohexanone solvate of rilpivirine hydrochloride is characterized by a solvent content of about 0.3 to 0.7 mol, more preferably about 0.4 to 0.6 mol cyclohexanone per mol rilpivirine hydrochloride.

In addition the cyclohexanone solvate of rilpivirine hydrochloride is surprisingly stable as the desolvation occurs only at about $> 200\text{ }^{\circ}\text{C}$ as indicated by thermogravimetric analysis.

The novel crystalline solvates of the present invention cannot be distinguished unambiguously by means of FTIR-spectroscopy as they all show very similar FTIR-spectra. Differences are only detectable at some peak positions, which can directly be related to the incorporated solvent. Acetone, 2-butanone and cyclohexanone e.g. display a peak between $1710 - 1717\text{ cm}^{-1}$ which can directly be related to the C=O stretching vibration of these solvents. But apart from these differences no significant differences are detectable, thus again indicating that the solvates crystallize in similar crystal structures. However, the FTIR-spectra of the novel solvates of rilpivirine hydrochloride of the present invention can be distinguished from these of non-solvated crystalline forms of rilpivirine hydrochloride such as e.g. forms A, B and C of EP1632232 B1 or form F of the present invention and from hydrated forms of rilpivirine hydrochloride such as form D of EP1632232 B1.

Hence, the present invention relates to novel crystalline solvates of rilpivirine hydrochloride characterized by an infrared spectrum displaying peaks at wavenumbers of $3057 \pm 2\text{ cm}^{-1}$, $2228 \pm 2\text{ cm}^{-1}$, $2218 \pm 2\text{ cm}^{-1}$, $1656 \pm 2\text{ cm}^{-1}$ and $1542 \pm 2\text{ cm}^{-1}$. Representative infrared spectra are displayed in figures 7 and 8.

In a further embodiment the present invention relates to a process for the preparation of the novel solvates comprising the steps of:

- a) providing a suspension or solution of rilpivirine free base in a solvent selected from alcohols, ketones, ethers or chlorinated hydrocarbons,
- b) adding hydrochloric acid to the suspension or solution and

c) recovering the novel solvate of rilpivirine hydrochloride.

Suitable alcohols, which can be used for the present process are e.g. 1-propanol or 2-propanol, suitable ketones are e.g. acetone, 2-butanone or cyclohexanone, suitable chlorinated hydrocarbons are e.g. dichloromethane or chloroform and suitable ethers are e.g. tetrahydrofuran or 1,4-dioxane.

The initial rilpivirine concentration applied in the process may range from about 1 to 200 g/L, preferably from about 1 to 200 g/L, more preferably from about 1 to 150 g/L and most preferably from about 1 to 100 g/L.

Rilpivirine free base may either be suspended or dissolved in the applied solvent prior to the hydrochloric acid addition. A possible dissolution step may be performed at elevated temperatures ranging from about room temperature to about the reflux temperature of the applied solvent.

Hydrochloric acid may be applied in the process in any suitable concentration e.g. gaseous hydrochloric acid or aqueous hydrochloric acid, whereat the applied aqueous hydrochloric acid preferably has a concentration between about 9 % and about 37 %, more preferably between about 18 % and about 37 % and most preferably concentrated hydrochloric acid is used having a concentration of about 37 %.

The amount of hydrochloric acid used in the process of the present invention preferably ranges from about 1.0 to 10.0 mol equivalents, more preferably from about 1.0 to 8.0 mol equivalents and most preferably from about 1.0 to 5.0 mol equivalents.

After the hydrochloric acid addition the mixture is stirred at a temperature preferably ranging from about 0 to 40 °C, more preferably from about 10 to 30 °C and most preferably at about room temperature, for a time ranging from about 1 to 72 hours, preferably from about 1 to 48 hours, more preferably from about 1 to 24 hours and most preferably from about 1 to 18 hours.

The obtained crystals are collected by any conventional methods such as filtration, centrifugation or evaporation of the solvent, most preferably by filtration.

Thereafter the crystals are dried preferably under vacuum at a temperature preferably ranging from about 25 °C to 150 °C, more preferably from about 30 °C to 100 °C and most

preferably from about 40 °C to 80 °C for a time preferably ranging from about 2 to 72 hours, more preferably from about 12 to 48 hours and most preferably from about 24 to 36 hours.

Depending on the solvent applied in the above described process different crystalline solvates such as a 1-propanol solvate, a 2-propanol solvate, an acetone solvate, a 2-butanone solvate, a tetrahydrofuran solvate, a 1,4-dioxane solvate, a dichloromethane solvate, a chloroform solvate or a cyclohexanone solvate of rilpivirine hydrochloride are obtained.

Therefore the present invention also relates to a novel 1-propanol solvate of rilpivirine hydrochloride.

The novel crystalline 1-propanol solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.1 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.9 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline 1-propanol solvate comprises additional characteristic peaks at 2-theta angles of $10.6 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.6 \pm 0.2^\circ$, $16.4 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $18.5 \pm 0.2^\circ$, $19.0 \pm 0.2^\circ$, $19.7 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.6 \pm 0.2^\circ$, $21.9 \pm 0.2^\circ$, $22.7 \pm 0.2^\circ$, $24.2 \pm 0.2^\circ$, $25.1 \pm 0.2^\circ$, $26.4 \pm 0.2^\circ$, $26.6 \pm 0.2^\circ$, $27.8 \pm 0.2^\circ$, $29.4 \pm 0.2^\circ$ and $32.4 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 3.

In addition the novel crystalline 1-propanol solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3059 \pm 2 \text{ cm}^{-1}$, $2230 \pm 2 \text{ cm}^{-1}$, $2220 \pm 2 \text{ cm}^{-1}$, $1657 \pm 2 \text{ cm}^{-1}$ and $1543 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline 1-propanol solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3277 \pm 2 \text{ cm}^{-1}$, $3242 \pm 2 \text{ cm}^{-1}$, $3182 \pm 2 \text{ cm}^{-1}$, $2968 \pm 2 \text{ cm}^{-1}$, $2875 \pm 2 \text{ cm}^{-1}$, $1637 \pm 2 \text{ cm}^{-1}$, $1603 \pm 2 \text{ cm}^{-1}$, $1567 \pm 2 \text{ cm}^{-1}$, $1506 \pm 2 \text{ cm}^{-1}$, $1450 \pm 2 \text{ cm}^{-1}$, $1419 \pm 2 \text{ cm}^{-1}$, $1387 \pm 2 \text{ cm}^{-1}$, $1345 \pm 2 \text{ cm}^{-1}$, $1273 \pm 2 \text{ cm}^{-1}$, $1245 \pm 2 \text{ cm}^{-1}$, $1217 \pm 2 \text{ cm}^{-1}$, $1181 \pm 2 \text{ cm}^{-1}$, $1156 \pm 2 \text{ cm}^{-1}$, $1074 \pm 2 \text{ cm}^{-1}$, $1055 \pm 2 \text{ cm}^{-1}$, $970 \pm 2 \text{ cm}^{-1}$, $872 \pm 2 \text{ cm}^{-1}$, $825 \pm 2 \text{ cm}^{-1}$ and $797 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 7.

Furthermore the 1-propanol solvate of rilpivirine hydrochloride of the present invention preferably contains from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol 1-propanol per mol rilpivirine hydrochloride. E.g. the 1-propanol solvate contains about 0.5 mol 1-propanol per mol rilpivirine hydrochloride as detected by single X-ray diffraction and can thus be characterized as being a hemisolvate.

In addition the present invention relates to a novel crystalline 2-propanol solvate of rilpivirine hydrochloride.

The novel crystalline 2-propanol solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.1 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.9 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline 2-propanol solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $10.6 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.6 \pm 0.2^\circ$, $16.4 \pm 0.2^\circ$, $18.2 \pm 0.2^\circ$, $18.5 \pm 0.2^\circ$, $19.0 \pm 0.2^\circ$, $19.7 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.5 \pm 0.2^\circ$, $21.9 \pm 0.2^\circ$, $22.7 \pm 0.2^\circ$, $24.1 \pm 0.2^\circ$, $24.5 \pm 0.2^\circ$, $25.1 \pm 0.2^\circ$, $26.3 \pm 0.2^\circ$, $26.6 \pm 0.2^\circ$, $27.5 \pm 0.2^\circ$, $27.8 \pm 0.2^\circ$, $28.8 \pm 0.2^\circ$, $29.1 \pm 0.2^\circ$, $29.4 \pm 0.2^\circ$, $32.4 \pm 0.2^\circ$ and $33.4 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 3.

In addition the novel crystalline 2-propanol solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3057 \pm 2 \text{ cm}^{-1}$, $2228 \pm 2 \text{ cm}^{-1}$, $2218 \pm 2 \text{ cm}^{-1}$, $1656 \pm 2 \text{ cm}^{-1}$ and $1541 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline 2-propanol solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3277 \pm 2 \text{ cm}^{-1}$, $3230 \pm 2 \text{ cm}^{-1}$, $3178 \pm 2 \text{ cm}^{-1}$, $2968 \pm 2 \text{ cm}^{-1}$, $2872 \pm 2 \text{ cm}^{-1}$, $1634 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1563 \pm 2 \text{ cm}^{-1}$, $1499 \pm 2 \text{ cm}^{-1}$, $1448 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1384 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1315 \pm 2 \text{ cm}^{-1}$, $1271 \pm 2 \text{ cm}^{-1}$, $1244 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1155 \pm 2 \text{ cm}^{-1}$, $1129 \pm 2 \text{ cm}^{-1}$, $1098 \pm 2 \text{ cm}^{-1}$, $1073 \pm 2 \text{ cm}^{-1}$, $1033 \pm 2 \text{ cm}^{-1}$, $969 \pm 2 \text{ cm}^{-1}$, $951 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $844 \pm 2 \text{ cm}^{-1}$, $822 \pm 2 \text{ cm}^{-1}$ and $795 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 7.

Furthermore the 2-propanol solvate of rilpivirine hydrochloride of the present invention preferably contains from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol 2-propanol per mol rilpivirine hydrochloride. E.g. the 2-propanol solvate contains about 0.5 mol 2-propanol per mol rilpivirine hydrochloride as detected by single X-ray diffraction and can thus be characterized as being a hemisolvate.

Moreover the present invention relates to a novel crystalline acetone solvate of rilpivirine hydrochloride.

The novel crystalline acetone solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.1 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.8 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline acetone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $9.4 \pm$

0.2° , $9.9 \pm 0.2^\circ$, $10.6 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.6 \pm 0.2^\circ$, $16.4 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $18.5 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.6 \pm 0.2^\circ$, $21.9 \pm 0.2^\circ$, $22.7 \pm 0.2^\circ$, $24.1 \pm 0.2^\circ$, $24.6 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $26.3 \pm 0.2^\circ$, $26.5 \pm 0.2^\circ$, $27.7 \pm 0.2^\circ$, $29.2 \pm 0.2^\circ$, $29.6 \pm 0.2^\circ$ and $32.5 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 3.

In addition the novel crystalline acetone solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3056 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2218 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1542 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline acetone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3276 \pm 2 \text{ cm}^{-1}$, $3239 \pm 2 \text{ cm}^{-1}$, $3178 \pm 2 \text{ cm}^{-1}$, $2963 \pm 2 \text{ cm}^{-1}$, $2873 \pm 2 \text{ cm}^{-1}$, $1716 \pm 2 \text{ cm}^{-1}$, $1635 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1564 \pm 2 \text{ cm}^{-1}$, $1503 \pm 2 \text{ cm}^{-1}$, $1448 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1383 \pm 2 \text{ cm}^{-1}$, $1343 \pm 2 \text{ cm}^{-1}$, $1314 \pm 2 \text{ cm}^{-1}$, $1270 \pm 2 \text{ cm}^{-1}$, $1242 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1100 \pm 2 \text{ cm}^{-1}$, $1072 \pm 2 \text{ cm}^{-1}$, $1030 \pm 2 \text{ cm}^{-1}$, $969 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $850 \pm 2 \text{ cm}^{-1}$, $823 \pm 2 \text{ cm}^{-1}$, $794 \pm 2 \text{ cm}^{-1}$ and $717 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 7.

Furthermore the acetone solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol acetone per mol rilpivirine hydrochloride. E.g. the acetone solvate comprises about 0.4 mol acetone per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

The present invention also relates to a novel crystalline 2-butanone solvate of rilpivirine hydrochloride.

The novel crystalline 2-butanone solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $16.1 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.4 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline 2-butanone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $10.6 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.1 \pm 0.2^\circ$, $15.3 \pm 0.2^\circ$, $17.4 \pm 0.2^\circ$, $17.7 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $18.7 \pm 0.2^\circ$, $19.9 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.4 \pm 0.2^\circ$, $21.9 \pm 0.2^\circ$, $22.5 \pm 0.2^\circ$, $24.0 \pm 0.2^\circ$, $24.4 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $25.9 \pm 0.2^\circ$, $26.2 \pm 0.2^\circ$, $27.5 \pm 0.2^\circ$, $27.8 \pm 0.2^\circ$, $29.2 \pm 0.2^\circ$ and $29.6 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 4.

In addition the novel crystalline 2-butanone solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3056 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2219 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1542 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of

the novel crystalline 2-butanone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3277 \pm 2 \text{ cm}^{-1}$, $3241 \pm 2 \text{ cm}^{-1}$, $3173 \pm 2 \text{ cm}^{-1}$, $2968 \pm 2 \text{ cm}^{-1}$, $2873 \pm 2 \text{ cm}^{-1}$, $1711 \pm 2 \text{ cm}^{-1}$, $1636 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1563 \pm 2 \text{ cm}^{-1}$, $1520 \pm 2 \text{ cm}^{-1}$, $1498 \pm 2 \text{ cm}^{-1}$, $1447 \pm 2 \text{ cm}^{-1}$, $1418 \pm 2 \text{ cm}^{-1}$, $1382 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1314 \pm 2 \text{ cm}^{-1}$, $1270 \pm 2 \text{ cm}^{-1}$, $1243 \pm 2 \text{ cm}^{-1}$, $1214 \pm 2 \text{ cm}^{-1}$, $1180 \pm 2 \text{ cm}^{-1}$, $1155 \pm 2 \text{ cm}^{-1}$, $1099 \pm 2 \text{ cm}^{-1}$, $1073 \pm 2 \text{ cm}^{-1}$, $1037 \pm 2 \text{ cm}^{-1}$, $988 \pm 2 \text{ cm}^{-1}$, $970 \pm 2 \text{ cm}^{-1}$, $884 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $849 \pm 2 \text{ cm}^{-1}$, $823 \pm 2 \text{ cm}^{-1}$ and $794 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 8.

Furthermore the 2-butanone solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol 2-butanone per mol rilpivirine hydrochloride. E.g. the 2-butanone solvate comprises about 0.5 mol 2-butanone per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

In addition the present invention relates to a novel crystalline tetrahydrofuran solvate of rilpivirine hydrochloride.

The novel crystalline tetrahydrofuran solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $17.5 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.7 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline tetrahydrofuran solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $10.6 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.5 \pm 0.2^\circ$, $16.3 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$, $21.5 \pm 0.2^\circ$, $22.0 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$, $24.0 \pm 0.2^\circ$, $24.5 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $26.2 \pm 0.2^\circ$, $26.4 \pm 0.2^\circ$, $27.6 \pm 0.2^\circ$, $29.2 \pm 0.2^\circ$ and $29.5 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 3.

In addition the novel crystalline tetrahydrofuran solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3056 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2219 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1542 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline 2-butanone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3278 \pm 2 \text{ cm}^{-1}$, $3240 \pm 2 \text{ cm}^{-1}$, $3174 \pm 2 \text{ cm}^{-1}$, $2969 \pm 2 \text{ cm}^{-1}$, $2872 \pm 2 \text{ cm}^{-1}$, $1635 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1563 \pm 2 \text{ cm}^{-1}$, $1521 \pm 2 \text{ cm}^{-1}$, $1499 \pm 2 \text{ cm}^{-1}$, $1448 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1384 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1311 \pm 2 \text{ cm}^{-1}$, $1271 \pm 2 \text{ cm}^{-1}$, $1243 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1099 \pm 2 \text{ cm}^{-1}$, $1071 \pm 2 \text{ cm}^{-1}$, $1038 \pm 2 \text{ cm}^{-1}$, $988 \pm 2 \text{ cm}^{-1}$, $969 \pm 2 \text{ cm}^{-1}$, $884 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $850 \pm 2 \text{ cm}^{-1}$, 824

$\pm 2 \text{ cm}^{-1}$, $793 \pm 2 \text{ cm}^{-1}$ and $716 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 7.

Furthermore the tetrahydrofuran solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol tetrahydrofuran per mol rilpivirine hydrochloride. E.g. the tetrahydrofuran solvate comprises about 0.5 mol tetrahydrofuran per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

Moreover the present invention relates to a novel crystalline 1,4-dioxane solvate of rilpivirine hydrochloride.

The novel crystalline 1,4-dioxane solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $16.2 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline 1,4-dioxane solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $14.0 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.1 \pm 0.2^\circ$, $15.4 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.4 \pm 0.2^\circ$, $17.7 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$, $21.1 \pm 0.2^\circ$, $21.4 \pm 0.2^\circ$, $21.9 \pm 0.2^\circ$, $22.5 \pm 0.2^\circ$, $23.8 \pm 0.2^\circ$, $24.4 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $26.0 \pm 0.2^\circ$, $26.3 \pm 0.2^\circ$, $27.6 \pm 0.2^\circ$, $29.2 \pm 0.2^\circ$, $29.5 \pm 0.2^\circ$, 32.2 ± 0.2 and $32.4 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 4.

In addition the novel crystalline 1,4-dioxane solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3056 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2220 \pm 2 \text{ cm}^{-1}$, $1654 \pm 2 \text{ cm}^{-1}$ and $1541 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline 1,4-dioxane solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3274 \pm 2 \text{ cm}^{-1}$, $3237 \pm 2 \text{ cm}^{-1}$, $3179 \pm 2 \text{ cm}^{-1}$, $2962 \pm 2 \text{ cm}^{-1}$, $2874 \pm 2 \text{ cm}^{-1}$, $2852 \pm 2 \text{ cm}^{-1}$, $1635 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1563 \pm 2 \text{ cm}^{-1}$, $1520 \pm 2 \text{ cm}^{-1}$, $1498 \pm 2 \text{ cm}^{-1}$, $1447 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1384 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1314 \pm 2 \text{ cm}^{-1}$, $1271 \pm 2 \text{ cm}^{-1}$, $1244 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1122 \pm 2 \text{ cm}^{-1}$, $1073 \pm 2 \text{ cm}^{-1}$, $1031 \pm 2 \text{ cm}^{-1}$, $987 \pm 2 \text{ cm}^{-1}$, $968 \pm 2 \text{ cm}^{-1}$, $873 \pm 2 \text{ cm}^{-1}$, $849 \pm 2 \text{ cm}^{-1}$, $825 \pm 2 \text{ cm}^{-1}$, $792 \pm 2 \text{ cm}^{-1}$, $727 \pm \text{cm}^{-1}$ and $716 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 8.

Furthermore the 1,4-dioxane solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol 1,4-dioxane per mol rilpivirine hydrochloride. E.g. the 1,4-dioxane solvate comprises about

0.6 mol 1,4-dioxane per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

The present invention also relates to a novel crystalline dichloromethane solvate of rilpivirine hydrochloride.

The novel crystalline dichloromethane solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$ and $24.1 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline dichloromethane solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $8.9 \pm 0.2^\circ$, $14.6 \pm 0.2^\circ$, $15.3 \pm 0.2^\circ$, $15.8 \pm 0.2^\circ$, $16.2 \pm 0.2^\circ$, $18.4 \pm 0.2^\circ$, $18.6 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$, $19.1 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$, $21.5 \pm 0.2^\circ$, $21.7 \pm 0.2^\circ$, $22.0 \pm 0.2^\circ$, $22.8 \pm 0.2^\circ$, $23.7 \pm 0.2^\circ$, $24.4 \pm 0.2^\circ$, $24.6 \pm 0.2^\circ$, $24.9 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $26.6 \pm 0.2^\circ$, $26.8 \pm 0.2^\circ$, $27.6 \pm 0.2^\circ$, $28.0 \pm 0.2^\circ$, $29.1 \pm 0.2^\circ$, $29.5 \pm 0.2^\circ$, $32.5 \pm 0.2^\circ$, $32.9 \pm 0.2^\circ$ and $33.7 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 5.

In addition the novel crystalline dichloromethane solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3058 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2218 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1541 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline dichloromethane solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3280 \pm 2 \text{ cm}^{-1}$, $3242 \pm 2 \text{ cm}^{-1}$, $3177 \pm 2 \text{ cm}^{-1}$, $2968 \pm 2 \text{ cm}^{-1}$, $2873 \pm 2 \text{ cm}^{-1}$, $1635 \pm 2 \text{ cm}^{-1}$, $1601 \pm 2 \text{ cm}^{-1}$, $1563 \pm 2 \text{ cm}^{-1}$, $1521 \pm 2 \text{ cm}^{-1}$, $1504 \pm 2 \text{ cm}^{-1}$, $1448 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1385 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1315 \pm 2 \text{ cm}^{-1}$, $1270 \pm 2 \text{ cm}^{-1}$, $1243 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1122 \pm 2 \text{ cm}^{-1}$, $1099 \pm 2 \text{ cm}^{-1}$, $1073 \pm 2 \text{ cm}^{-1}$, $1031 \pm 2 \text{ cm}^{-1}$, $987 \pm 2 \text{ cm}^{-1}$, $969 \pm 2 \text{ cm}^{-1}$, $871 \pm 2 \text{ cm}^{-1}$, $849 \pm 2 \text{ cm}^{-1}$, $823 \pm 2 \text{ cm}^{-1}$, $795 \pm 2 \text{ cm}^{-1}$, $761 \pm \text{cm}^{-1}$ and $740 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 8.

Furthermore the dichloromethane solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol dichloromethane per mol rilpivirine hydrochloride. E.g. the dichloromethane solvate comprises about 0.5 mol dichloromethane per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

In addition the present invention relates to a novel crystalline chloroform solvate of rilpivirine hydrochloride.

The novel crystalline chloroform solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $17.5 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.7 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline chloroform solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $9.4 \pm 0.2^\circ$, $9.8 \pm 0.2^\circ$, $10.6 \pm 0.2^\circ$, $14.0 \pm 0.2^\circ$, $14.5 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.5 \pm 0.2^\circ$, $16.3 \pm 0.2^\circ$, $16.6 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $19.8 \pm 0.2^\circ$, $21.1 \pm 0.2^\circ$, $21.5 \pm 0.2^\circ$, $22.0 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$, $24.5 \pm 0.2^\circ$, $25.2 \pm 0.2^\circ$, $26.2 \pm 0.2^\circ$, $26.4 \pm 0.2^\circ$, $27.6 \pm 0.2^\circ$, $29.2 \pm 0.2^\circ$, $29.5 \pm 0.2^\circ$, $31.3 \pm 0.2^\circ$, $32.4 \pm 0.2^\circ$, $33.2 \pm 0.2^\circ$ and $33.6 \pm 0.2^\circ$. A representative diffractogram is displayed in figure 3.

In addition the novel crystalline chloroform solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3057 \pm 2 \text{ cm}^{-1}$, $2229 \pm 2 \text{ cm}^{-1}$, $2219 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1541 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline chloroform solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3278 \pm 2 \text{ cm}^{-1}$, $3236 \pm 2 \text{ cm}^{-1}$, $3179 \pm 2 \text{ cm}^{-1}$, $2966 \pm 2 \text{ cm}^{-1}$, $2872 \pm 2 \text{ cm}^{-1}$, $1634 \pm 2 \text{ cm}^{-1}$, $1600 \pm 2 \text{ cm}^{-1}$, $1562 \pm 2 \text{ cm}^{-1}$, $1520 \pm 2 \text{ cm}^{-1}$, $1499 \pm 2 \text{ cm}^{-1}$, $1447 \pm 2 \text{ cm}^{-1}$, $1417 \pm 2 \text{ cm}^{-1}$, $1384 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1271 \pm 2 \text{ cm}^{-1}$, $1243 \pm 2 \text{ cm}^{-1}$, $1215 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1154 \pm 2 \text{ cm}^{-1}$, $1072 \pm 2 \text{ cm}^{-1}$, $1035 \pm 2 \text{ cm}^{-1}$, $969 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $942 \pm 2 \text{ cm}^{-1}$, $823 \pm 2 \text{ cm}^{-1}$, $795 \pm 2 \text{ cm}^{-1}$, $758 \pm 2 \text{ cm}^{-1}$ and $729 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 7.

Furthermore the chloroform solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol chloroform per mol rilpivirine hydrochloride. E.g. the chloroform solvate comprises about 0.4 mol chloroform per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

Moreover the present invention relates to a novel crystalline cyclohexanone solvate of rilpivirine hydrochloride.

The novel crystalline cyclohexanone solvate of rilpivirine hydrochloride can be characterized by an XRPD pattern comprising peaks at 2-theta angles of $8.1 \pm 0.2^\circ$, $17.3 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$, $20.8 \pm 0.2^\circ$ and $23.3 \pm 0.2^\circ$. The X-ray powder diffractogram of the novel crystalline cyclohexanone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at 2-theta angles of $8.6 \pm 0.2^\circ$, $14.4 \pm 0.2^\circ$, $14.8 \pm 0.2^\circ$, $15.2 \pm 0.2^\circ$, $15.9 \pm 0.2^\circ$, $16.1 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.7 \pm 0.2^\circ$, $18.0 \pm 0.2^\circ$, $18.2 \pm 0.2^\circ$, $18.6 \pm 0.2^\circ$, $20.0 \pm 0.2^\circ$, $21.1 \pm 0.2^\circ$, $21.3 \pm$

0.2° , $21.8 \pm 0.2^{\circ}$, $22.4 \pm 0.2^{\circ}$, $24.0 \pm 0.2^{\circ}$, $24.8 \pm 0.2^{\circ}$, $25.6 \pm 0.2^{\circ}$, $26.0 \pm 0.2^{\circ}$, $28.1 \pm 0.2^{\circ}$, 29.0 ± 0.2 and $31.9 \pm 0.2^{\circ}$. A representative diffractogram is displayed in figure 6.

In addition the novel crystalline cyclohexanone solvate of rilpivirine hydrochloride can be characterized by showing an FTIR-spectrum comprising peaks at wavenumbers of $3056 \pm 2 \text{ cm}^{-1}$, $2228 \pm 2 \text{ cm}^{-1}$, $2219 \pm 2 \text{ cm}^{-1}$, $1655 \pm 2 \text{ cm}^{-1}$ and $1541 \pm 2 \text{ cm}^{-1}$. The FTIR-spectrum of the novel crystalline cyclohexanone solvate of rilpivirine hydrochloride comprises additional characteristic peaks at wavenumbers of $3278 \pm 2 \text{ cm}^{-1}$, $3240 \pm 2 \text{ cm}^{-1}$, $3173 \pm 2 \text{ cm}^{-1}$, $2961 \pm 2 \text{ cm}^{-1}$, $2869 \pm 2 \text{ cm}^{-1}$, $1709 \pm 2 \text{ cm}^{-1}$, $1634 \pm 2 \text{ cm}^{-1}$, $1600 \pm 2 \text{ cm}^{-1}$, $1562 \pm 2 \text{ cm}^{-1}$, $1520 \pm 2 \text{ cm}^{-1}$, $1498 \pm 2 \text{ cm}^{-1}$, $1447 \pm 2 \text{ cm}^{-1}$, $1418 \pm 2 \text{ cm}^{-1}$, $1384 \pm 2 \text{ cm}^{-1}$, $1344 \pm 2 \text{ cm}^{-1}$, $1312 \pm 2 \text{ cm}^{-1}$, $1271 \pm 2 \text{ cm}^{-1}$, $1243 \pm 2 \text{ cm}^{-1}$, $1214 \pm 2 \text{ cm}^{-1}$, $1179 \pm 2 \text{ cm}^{-1}$, $1155 \pm 2 \text{ cm}^{-1}$, $1117 \pm 2 \text{ cm}^{-1}$, $1097 \pm 2 \text{ cm}^{-1}$, $1072 \pm 2 \text{ cm}^{-1}$, $1032 \pm 2 \text{ cm}^{-1}$, $1018 \pm 2 \text{ cm}^{-1}$, $987 \pm 2 \text{ cm}^{-1}$, $970 \pm 2 \text{ cm}^{-1}$, $886 \pm 2 \text{ cm}^{-1}$, $870 \pm 2 \text{ cm}^{-1}$, $848 \pm \text{cm}^{-1}$, $824 \pm 2 \text{ cm}^{-1}$, $793 \pm 2 \text{ cm}^{-1}$, $728 \pm \text{cm}^{-1}$ and $694 \pm 2 \text{ cm}^{-1}$. A representative FTIR spectrum is displayed in figure 8.

Furthermore the cyclohexanone solvate of rilpivirine hydrochloride of the present invention preferably comprises from about 0.3 to 0.7 mol, more preferably from about 0.4 to 0.6 mol cyclohexanone per mol rilpivirine hydrochloride. E.g. the cyclohexanone solvate comprises about 0.5 mol cyclohexanone per mol rilpivirine hydrochloride as detected by NMR and can be characterized as being a hemisolvate.

The novel solvates of rilpivirine hydrochloride of the present invention are valuable intermediates for the preparation of rilpivirine hydrochloride form F of the present invention. The solvates of the present invention may be transformed to form F according to the process disclosed for form F production. The solvates of rilpivirine hydrochloride of the present invention are applied as starting materials and slurried in water, followed by drying the isolated crystals at increased temperatures ranging from about 80°C to 180°C , more preferably from about 90°C to 140°C and most preferably from about 100°C to 120°C and/or at decreased relative humidities such as $< 5\%$ relative humidity.

In addition the present invention relates to the use of the crystalline 1-propanol solvate, the crystalline 2-propanol solvate, the crystalline acetone solvate, the crystalline 2-butanone solvate and/or the crystalline tetrahydrofuran solvate of rilpivirine hydrochloride of the present invention for the preparation of a medicament.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood,

however, that the description and the following specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the description and the other parts of the present disclosure.

EXAMPLES

The X-ray powder diffractograms (XRPD) were obtained with an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a theta/theta coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-K α 1,2 radiation source (wavelength 0.15419 nm) and a solid state PIX'cel detector. The diffractograms were recorded at a tube voltage of 40 kV, tube current of 40 mA. A typical precision of the 2-theta values is in the range of about $\pm 0.2^\circ$ 2-theta. Thus a diffraction peak that appears at 5.0° 2-theta can appear between 4.8 and 5.2° 2-theta on most X-ray diffractometers under standard conditions.

The Fourier transform infrared (FTIR) spectra were recorded with a Bruker IFS 25 spectrometer (Bruker GmbH, Karlsruhe, D) in the spectral range from 4000 to 600 cm^{-1} . The samples were prepared on a ZnSe disk using the Bruker IR microscope I, with 15x-Cassegrain-objectives. A typical precision of the wavenumber values is in the range of about $\pm 2 \text{ cm}^{-1}$. Thus, an infrared peak that appears at 1716 cm^{-1} can appear between 1714 and 1718 cm^{-1} .

Intensity data for the crystal structures were collected with Mo ($\lambda = 0.71073 \text{ \AA}$) radiation on an Oxford Diffraction Gemini-R Ultra diffractometer at 173 K. The structures were solved using the direct methods procedure in SHELXS97 and refined by full-matrix least squares on F^2 using SHELXL97.

Thermogravimetric analysis (TGA) were performed with a TGA 7 thermogravimetric system (Perkin-Elmer). The samples were placed into a 50 μL platinum pan and heated at a heating rate of 10 $^\circ\text{C}/\text{min}$. The determinations were performed under nitrogen purge (balance purge: 40 mL/min, sample purge: 20 mL/min).

^1H NMR spectra were measured on a Bruker Avance DPX 300 at a frequency of 300 MHz. DMSO- d_6 was used as solvent.

Example 1: Preparation of polymorph F of rilpivirine hydrochloride

A novel solvate of rilpivirine hydrochloride of the present invention (see table 1) was suspended in water at a concentration of 20 mg/mL and stirred for 40 hours at room temperature. The obtained crystals were collected by filtration and dried at 105 °C under vacuum for 16 hours to obtain polymorph F of rilpivirine hydrochloride.

Table 1: Applied starting materials

example	rilpivirine HCl
a	1-propanol solvate e.g. prepared according to example 2
b	2-propanol solvate e.g. prepared according to example 3
c	acetone solvate e.g. prepared according to examples 4 or 5
d	2-butanone solvate e.g. prepared according to example 6
e	THF solvate e.g. prepared according to examples 7 or 8
f	1,4-dioxane solvate e.g. prepared according to examples 9 or 10

Table 2: XRPD angles 2-theta and relative intensities of polymorph F of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
5.6	40	21.2	16
6.1	45	21.8	14
6.9	11	22.0	12
12.5	100	22.8	52
13.8	93	23.5	19
15.9	20	23.8	23
16.6	62	24.2	39
17.6	28	24.6	58
17.9	15	24.9	31
18.5	14	25.5	21
19.6	39	26.6	63
20.9	33	27.4	20

Table 3: FTIR peaks of polymorph F of rilpivirine hydrochloride

wavenumber [cm⁻¹]		
3223	1444	1031
3176	1416	1018

3055	1386	985
2961	1357	966
2862	1338	869
2222	1308	851
1652	1273	811
1635	1241	794
1598	1213	713
1566	1178	680
1541	1154	666
1522	1097	623
1503	1072	

Example 2: Preparation of the 1-propanol solvate of rilpivirine hydrochloride

100 mg rilpivirine base were dissolved in 16 mL 1-propanol upon heating to reflux temperature. To the hot solution 100 μ L (4.4 mol equivalents) concentrated hydrochloric acid were added and the mixture was cooled to room temperature. The obtained suspension was further stirred at room temperature for 15 hours before the crystals were collected by filtration and dried at 80 °C under vacuum for 5 hours.

Yield: 100 mg

Table 4: XRPD angles 2-theta and relative intensities of the 1-propanol solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.1	39	21.2	33
8.8	31	21.6	36
10.6	6	21.9	21
14.5	16	22.7	27
15.2	12	23.9	100
15.6	14	24.2	12
16.4	67	25.1	47
17.6	39	26.4	11
18.3	16	26.6	10
18.5	10	27.8	11
18.8	25	29.4	21
19.0	18	32.4	18

19.7	21		
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Table 5: FTIR peaks of the 1-propanol solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3277	1603	1217
3242	1567	1181
3182	1543	1156
3059	1506	1074
2968	1450	1055
2875	1419	970
2230	1387	872
2220	1345	825
1657	1273	797
1637	1245	

Example 3: Preparation of the 2-propanol solvate of rilpivirine hydrochloride

100 mg rilpivirine base were dissolved in 18 mL 2-propanol upon heating to reflux temperature. To the hot solution 100 μ L (4.4 mol equivalents) concentrated hydrochloric acid were added and the mixture was cooled to room temperature. The obtained suspension was further stirred at room temperature for 15 hours before the crystals were collected by filtration and dried at 80 °C under vacuum for 5 hours.

Yield: 100 mg

Table 6: XRPD angles 2-theta and relative intensities of the 2-propanol solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.1	92	21.9	55
8.8	51	22.7	41
10.6	10	23.9	100
14.5	21	24.1	28
15.2	25	24.5	18
15.6	35	25.1	54
16.4	47	26.3	12
17.6	70	26.6	25

18.2	26	27.5	22
18.5	18	27.8	11
18.8	68	28.8	12
19.0	33	29.1	14
19.7	38	29.4	14
21.2	69	32.4	16
21.5	51	33.4	31

Table 7: FTIR peaks of the 2-propanol solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3277	1541	1129
3230	1499	1098
3178	1448	1073
3057	1417	1033
2968	1384	969
2872	1344	951
2228	1315	870
2218	1271	844
1656	1244	822
1634	1215	795
1601	1179	
1563	1155	

Example 4: Preparation of the acetone solvate of rilpivirine hydrochloride

To a suspension of 270 mg rilpivirine base in 7 mL acetone 200 μ L (3.3 mol equivalents) concentrated hydrochloric acid were added at room temperature. The suspension was stirred for additional 10 minutes at room temperature before the crystals were isolated by filtration and dried at 60 °C under vacuum for 5 hours.

Yield: 255 mg

Example 5: Preparation of the acetone solvate of rilpivirine hydrochloride

250 mg rilpivirine base were dissolved in 6 mL acetone upon heating to reflux temperature. To the hot solution 200 μ L (3.3 mol equivalents) concentrated hydrochloric acid were added, whereat crystallization occurred within about 5 minutes. The suspension was cooled to room temperature before the crystals were collected by filtration and dried at 60 °C under vacuum for 5 hours.

Yield: 270 mg

Table 8: XRPD angles 2-theta and relative intensities of the acetone solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.1	92	21.2	93
8.8	34	21.6	52
9.4	6	21.9	24
9.9	6	22.7	42
10.6	11	23.8	100
14.5	24	24.1	12
15.2	31	24.6	15
15.6	40	25.2	46
16.4	53	26.3	16
17.6	50	26.5	25
17.8	25	27.7	25
18.5	21	29.2	12
18.9	77	29.6	10
19.8	38	32.5	19

Table 9: FTIR peaks of the acetone solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3276	1564	1154
3239	1542	1100
3178	1503	1072
3056	1448	1030
2963	1417	969
2873	1383	870
2229	1343	850
2218	1314	823
1716	1270	794
1655	1242	717
1635	1215	
1601	1179	

Example 6: Preparation of the 2-butanone solvate of rilpivirine hydrochloride

To a suspension of 100 mg rilpivirine base in 3 mL 2-butanone 100 μ L (4.4 mol equivalents) concentrated hydrochloric acid were added at room temperature, whereat a clear solution was obtained. Within about 5 minutes crystallization was observed and the obtained suspension was further stirred for 15 hours before the crystals were isolated and dried at 80 $^{\circ}$ C under vacuum for 5 hours.

Yield: 92 mg

Table 10: XRPD angles 2-theta and relative intensities of the 2-butanone solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.2	61	21.4	47
8.7	31	21.9	28
10.6	10	22.5	30
14.5	27	23.4	100
15.1	25	24.0	11
15.3	39	24.4	14
16.1	59	25.2	37
17.4	58	25.9	16
17.7	17	26.2	30
18.3	27	27.5	13
18.7	27	27.8	16
18.9	73	29.2	13
19.9	36	29.6	16
21.2	92		

Table 11: FTIR peaks of the 2-butanone solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3277	1563	1180
3241	1542	1155
3173	1520	1099
3056	1498	1073
2968	1447	1037
2873	1418	988

2229	1382	970
2219	1344	884
1711	1314	870
1655	1270	849
1636	1243	823
1601	1214	794

Example 7: Preparation of the tetrahydrofuran solvate of rilpivirine hydrochloride

To a solution of 250 mg rilpivirine base in 3 mL tetrahydrofuran 200 μ L (3.5 mol equivalents) concentrated hydrochloric acid were added at room temperature, whereat a suspension was obtained. The mixture was further stirred for about 10 minutes before the crystals were isolated by filtration and dried at 80 °C under vacuum for 5 hours.

Yield: 271 mg

Example 8: Preparation of the tetrahydrofuran solvate of rilpivirine hydrochloride

A solution of 250 mg rilpivirine base in 3 mL tetrahydrofuran was heated to reflux temperature. To the hot solution 200 μ L (3.5 mol equivalents) concentrated hydrochloric acid were added and the resulting suspension was cooled to room temperature. Thereafter the crystals were isolated by filtration and dried at 80 °C under vacuum for 5 hours.

Yield: 268 mg

Table 12: XRPD angles 2-theta and relative intensities of the tetrahydrofuran solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.2	83	21.5	39
8.7	32	22.0	41
10.6	6	22.6	41
14.5	32	23.7	100
15.2	31	24.0	13
15.5	29	24.5	15
16.3	54	25.2	37
17.5	70	26.2	13
17.8	14	26.4	25
18.3	28	27.6	25
18.9	85	29.2	14
19.8	33	29.5	13

21.2	89		
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Table 13: FTIR peaks of the tetrahydrofuran solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3278	1542	1154
3240	1521	1099
3174	1499	1071
3056	1448	1038
2969	1417	988
2872	1384	969
2229	1344	884
2219	1311	870
1655	1271	850
1635	1243	824
1601	1215	793
1563	1179	716

Example 9: Preparation of the 1,4-dioxane solvate of rilpivirine hydrochloride

To a solution of 100 mg rilpivirine base in 4 mL 1,4-dioxane 100 μ L (4.4 mol equivalents) concentrated hydrochloric acid were added at room temperature. The solution was cooled to about 4 °C and stored at the same for 15 hours, whereat crystallization was observed. The crystals were filtered off and dried at 80 °C under vacuum.

Yield: 150 mg

Example 10: Preparation of the 1,4-dioxane solvate of rilpivirine hydrochloride

25 mg rilpivirine base were dissolved in 2 mL 1,4-dioxane upon heating to reflux temperature. To the hot solution 50 μ L (8.8 mol equivalents) concentrated hydrochloric acid were added and the solution was cooled to room temperature, whereat crystallization was observed. The crystals were isolated by filtration and dried at 80 °C under vacuum.

Table 14: XRPD angles 2-theta and relative intensities of the 1,4-dioxane solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.2	43	21.4	42
8.7	25	21.9	40
14.0	7	22.5	41

14.5	32	23.5	93
15.1	33	23.8	13
15.4	20	24.4	13
16.2	50	25.2	43
16.5	10	26.0	12
17.4	70	26.3	24
17.7	10	27.6	17
18.3	38	29.2	17
18.8	97	29.5	14
19.8	32	32.2	10
21.1	100	32.4	19

Table 15: FTIR peaks of the 1,4-dioxane solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3274	1541	1122
3237	1520	1073
3179	1498	1031
3056	1447	987
2962	1417	968
2874	1384	873
2852	1344	849
2229	1314	825
2220	1271	792
1654	1244	727
1635	1215	716
1601	1179	
1563	1154	

Example 11: Preparation of the dichloromethane solvate of rilpivirine hydrochloride

A mixture of 108 mg rilpivirine base in 45 mL dichloromethane was dissolved upon heating to 45 °C. To the hot solution 100 µl (4.1 mol equivalents) concentrated hydrochloric acid were added and the solution was cooled to about 4 °C and stored at the same temperature for 65 hours. The obtained crystals were isolated by filtration and dried at 80 °C under vacuum.

Yield: 110 mg

Example 12: Preparation of the dichloromethane solvate of rilpivirine hydrochloride

To a suspension of 25 mg rilpivirine base in 2 mL dichloromethane 50 μ L (8.8 mol equivalents) concentrated hydrochloric acid were added at room temperature. The suspension was stirred for 4 hours at room temperature before the crystals were isolated by filtration and dried at 80 °C under vacuum for 5 hours.

Table 16: XRPD angles 2-theta and relative intensities of the dichloromethane solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.2	50	22.8	44
8.9	32	23.7	12
14.6	28	24.1	100
15.3	27	24.4	19
15.8	35	24.6	14
16.2	13	24.9	10
16.5	59	25.2	44
17.8	80	26.6	19
18.4	21	26.8	20
18.6	13	27.6	15
18.8	46	28.0	10
19.1	33	29.1	14
19.8	31	29.5	14
21.2	67	32.5	14
21.5	34	32.9	10
21.7	38	33.7	11
22.0	31		

Table 17: FTIR peaks of the dichloromethane solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3280	1521	1099
3242	1504	1073
3177	1448	1031
3058	1417	987
2968	1385	969
2873	1344	871

2229	1315	849
2218	1270	823
1655	1243	795
1635	1215	761
1601	1179	740
1563	1154	
1541	1122	

Example 13: Preparation of the chloroform solvate of rilpivirine hydrochloride

To a suspension of 120 mg rilpivirine base in 3 mL chloroform 100 μ L (3.7 mol equivalents) concentrated hydrochloric acid were added at room temperature and the suspension was stirred for 65 hours. Thereafter the obtained crystals were isolated by filtration and dried at 100 °C under vacuum for 5 hours.

Yield: 130 mg

Example 14: Preparation of the chloroform solvate of rilpivirine hydrochloride

32 mg of rilpivirine base were dissolved in 15 mL chloroform upon heating to 40 °C. To the hot solution 50 μ L (6.9 mol equivalents) concentrated hydrochloric acid were added, whereat crystallization occurred. The obtained suspension was cooled to room temperature before the crystals were collected by filtration and dried at 80 °C under vacuum for 5 hours.

Table 18: XRPD angles 2-theta and relative intensities of the chloroform solvate of rilpivirine hydrochloride

angle [2-theta]	relative intensity [%]	angle [2-theta]	relative intensity [%]
8.2	45	21.5	45
8.7	21	22.0	36
9.4	5	22.6	44
9.8	5	23.7	100
10.6	9	24.5	21
14.0	8	25.2	40
14.5	34	26.2	17
15.2	27	26.4	32
15.5	28	27.6	24
16.3	40	29.2	20
16.6	16	29.5	18
17.5	77	31.3	10

18.3	34	32.4	22
18.8	95	33.2	11
19.8	38	33.6	11
21.1	75		

Table 19: FTIR peaks of the chloroform solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3278	1562	1179
3236	1541	1154
3179	1520	1072
3057	1499	1035
2966	1447	969
2872	1417	870
2229	1384	842
2219	1344	823
1655	1271	795
1634	1243	758
1600	1215	729

Example 15: Preparation of the cyclohexanone solvate of rilpivirine hydrochloride

To a solution of 34 mg rilpivirine base in 1 mL cyclohexanone 50 μ L (6.5 mol equivalents) concentrated hydrochloric acid were added at room temperature, whereat crystallization occurred within about 5 minutes. The obtained suspension was further stirred at room temperature for 4 hours before the crystals were isolated by filtration and dried at 80 °C for 5 hours.

Example 16: Preparation of the cyclohexanone solvate of rilpivirine hydrochloride

A solution of 34 mg rilpivirine base in 2 mL cyclohexanone was heated to reflux temperature. To the hot solution 50 μ L (6.5 mol equivalents) concentrated hydrochloric acid were added, whereat crystallization occurred within about 10 minutes. The obtained suspension was cooled to room temperature before the crystals were isolated by filtration and dried at 80 °C under vacuum for 5 hours.

Table 20: XRPD angles 2-theta and relative intensities of the cyclohexanone solvate of rilpivirine hydrochloride

angle	relative intensity	angle	relative intensity
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[2-theta]	[%]	[2-theta]	[%]
8.1	44	20.0	36
8.6	18	20.8	36
14.4	39	21.1	28
14.8	14	21.3	23
15.2	44	21.8	39
15.9	18	22.4	44
16.1	16	23.3	98
16.5	10	24.0	12
17.3	75	24.8	13
17.7	15	25.6	11
18.0	14	26.0	28
18.2	22	28.1	10
18.6	36	29.0	23
18.8	100	31.9	11

Table 21: FTIR peaks of the cyclohexanone solvate of rilpivirine hydrochloride

wavenumber [cm ⁻¹]		
3278	1520	1072
3240	1498	1032
3173	1447	1018
3056	1418	987
2961	1384	970
2869	1344	886
2228	1312	870
2219	1271	848
1709	1243	824
1655	1214	793
1634	1179	728
1600	1155	694
1562	1117	
1541	1097	

Example 17: Tablet formulation comprising rilpivirine hydrochloride form F

tablet core

rilpivirine hydrochloride form F	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 18: Tablet formulation comprising rilpivirine hydrochloride form F

tablet core	
rilpivirine hydrochloride form F	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 19: Tablet formulation comprising rilpivirine hydrochloride 1-propanol solvate

tablet core	
rilpivirine hydrochloride 1-propanol solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 20: Tablet formulation comprising rilpivirine hydrochloride 1-propanol solvate

tablet core	
rilpivirine hydrochloride 1-propanol solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 21: Tablet formulation comprising rilpivirine hydrochloride 2-propanol solvate

tablet core	
rilpivirine hydrochloride 2-propanol solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 22: Tablet formulation comprising rilpivirine hydrochloride 2-propanol solvate

tablet core	
rilpivirine hydrochloride 2-propanol solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 23: Tablet formulation comprising rilpivirine hydrochloride acetone solvate

tablet core	
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rilpivirine hydrochloride acetone solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 24: Tablet formulation comprising rilpivirine hydrochloride acetone solvate

tablet core	
rilpivirine hydrochloride acetone solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 25: Tablet formulation comprising rilpivirine hydrochloride 2-butanone solvate

tablet core	
rilpivirine hydrochloride 2-butanone solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 26: Tablet formulation comprising rilpivirine hydrochloride 2-butanone solvate

tablet core	
rilpivirine hydrochloride 2-butanone solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 27: Tablet formulation comprising rilpivirine hydrochloride tetrahydrofuran solvate

tablet core	
rilpivirine hydrochloride THF solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
polyvinylpyrrolidone K30 (PVP K30)	3.25 mg
polysorbate 20 (Tween 20)	0.35 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Example 28: Tablet formulation comprising rilpivirine hydrochloride tetrahydrofuran solvate

tablet core	
rilpivirine hydrochloride THF solvate	25.0 mg (calculated as free base)
lactose monohydrate	55.145 mg
silicified microcrystalline cellulose	16.605 mg
croscarmellose sodium	6.05 mg
magnesium stearate	1.10 mg
tablet film coat	
coating powder Opadry® II White	4.4 mg
purified water (not present in final tablet)	q.s.

Claims

- 1) Crystalline form of rilpivirine hydrochloride having an X-ray powder diffraction pattern comprising peaks at 2- theta angles of $5.6 \pm 0.2^\circ$, $6.1 \pm 0.2^\circ$, $6.9 \pm 0.2^\circ$, $12.5 \pm 0.2^\circ$ and $13.8 \pm 0.2^\circ$, preferably characterized by an X-ray powder diffraction pattern essentially in accordance with figure 1.
- 2) The crystalline form of rilpivirine hydrochloride according to claim 1 characterized by an infrared spectrum comprising peaks at wavenumbers of $3223 \pm 2 \text{ cm}^{-1}$, $2222 \pm 2 \text{ cm}^{-1}$, $1652 \pm 2 \text{ cm}^{-1}$, $965 \pm 2 \text{ cm}^{-1}$ and $811 \pm 2 \text{ cm}^{-1}$, preferably characterized by an infrared spectrum essentially in accordance with figure 2.
- 3) The crystalline form of rilpivirine hydrochloride according to any of claims 1 to 2 having a water content of $< 1.5 \%$.
- 4) A pharmaceutical composition comprising the crystalline form of rilpivirine hydrochloride according to any one of claims 1 to 3, further comprising at least one pharmaceutically acceptable excipient.
- 5) The pharmaceutical composition according to claim 4, which is an oral dosage form, in particular a capsule or tablet.
- 6) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet, comprising a tablet core comprising the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3, croscarmellose sodium, magnesium stearate, lactose monohydrate, polyvinylpyrrolidone K30, polysorbate 20 and silicified microcrystalline cellulose and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, polyethylene glycol 3000, titanium dioxide and triacetin.
- 7) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30), dibasic calcium phosphate (dihydrate or anhydrate), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

- 8) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, lactose monohydrate, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.
- 9) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, modified starch, polysorbate 20 (Tween 20), polyvinylpyrrolidone K30 (PVP K30) and magnesium stearate and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.
- 10) A pharmaceutical composition according to any of claims 4 to 5, which is a tablet, comprising a tablet core comprising the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3, croscarmellose sodium, magnesium stearate, lactose monohydrate and silicified microcrystalline cellulose and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, polyethylene glycol 3000, titanium dioxide and triacetin.
- 11) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, dibasic calcium phosphate (dihydrate or anhydrate), magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.
- 12) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, lactose monohydrate, magnesium stearate and starch and a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.
- 13) A pharmaceutical composition according to any of the claims 4 to 5, which is a tablet comprising a tablet core comprising rilpivirine hydrochloride according to any of the claims 1 to 3, microcrystalline cellulose, modified starch and magnesium stearate and

a tablet coating comprising hypromellose 2910 mPa.s, lactose monohydrate, macrogol 3000, triacetin and titanium dioxide.

14) A wet granulation process for preparing a tablet according to any of the claims 6 to 9 comprising the steps of:

- a) dry blending the crystalline form of rilpivirine hydrochloride according to any of the claims 1 to 3 and a part of the diluent,
- b) preparing a binder solution by dissolving a binder and a wetting agent in a suitable solvent,
- c) spraying the binder solution of step b) on the mixture obtained in step a),
- d) drying the obtained granulate and sieving the same,
- e) mixing the obtained granulate with the remaining part of diluent and a disintegrant,
- f) adding an optional glidant and/or an optional lubricant to the mixture,
- g) compressing the obtained mixture into a tablet and
- h) optionally film-coating the obtained tablet.

15) The wet granulation process according to claim 14, wherein the solvent in step b) is selected from water, acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate and tetrahydrofuran.

16) A tablet according to any of the claims 6 to 9 prepared by the wet granulation process according to any of claims 14 to 15.

17) A wet granulation process for preparing a tablet according to claim 6 comprising the steps of:

- a) dry blending the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3 and lactose monohydrate,
- b) preparing a binder solution by dissolving polyvinylpyrrolidone K30 and polysorbate 20 in a solvent,
- c) spraying the binder solution of step b) on the mixture obtained in step a),
- d) drying the obtained granulate and sieving the same,

- e) mixing the obtained granulate with silicified microcrystalline cellulose and croscarmellose sodium,
 - f) adding magnesium stearate to the mixture,
 - g) compressing the obtained mixture into a tablet and
 - h) optionally film-coating the obtained tablet.
- 18) The wet granulation process according to claim 17, wherein the solvent in step b) is selected from water, acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate and tetrahydrofuran.
- 19) A tablet according to claim 6 prepared by the wet granulation process according to any of the claims 17 to 18.
- 20) A process for preparing a tablet according to any of the claims 10 to 13 comprising the steps of:
- a) dry blending the crystalline form of rilpivirine hydrochloride according to any of the claims 1 to 3, a disintegrant, an optional glidant and an optional lubricant with at least one diluent,
 - b) compressing the obtained mixture in the dry state into a tablet and
 - c) optionally film-coating the obtained tablet.
- 21) A tablet according to any of the claims 10 to 13 prepared by the direct compression process according to claim 20.
- 22) A process for preparing a tablet according to claim 10 comprising the steps of:
- a) dry blending the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3, croscarmellose sodium and magnesium stearate with lactose monohydrate and silicified microcrystalline cellulose,
 - b) compressing the obtained mixture in the dry state into a tablet and
 - c) optionally film-coating the obtained tablet.
- 23) A tablet according to claim 10 prepared by the direct compression process according to claim 22.

- 24) Use of the crystalline form of rilpivirine hydrochloride according to any one of claims 1 to 3 for the production of a pharmaceutical composition.
- 25) The pharmaceutical compositions as defined in any of the claims 4 to 13 or as obtained by the use according to claim 24 for use in the treatment of HIV-1 infections.
- 26) The tablet according to any of the claims 16, 19, 21 or 23 for use in the treatment of HIV-1 infections.
- 27) Crystalline isomorphic solvates of rilpivirine hydrochloride having an X-ray powder diffraction pattern with peaks at 2- theta angles of $8.2 \pm 0.2^\circ$, $8.8 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $18.9 \pm 0.2^\circ$ and $23.8 \pm 0.2^\circ$.
- 28) The crystalline isomorphic solvates of rilpivirine hydrochloride according to claim 27 with 0.3 to 0.7 mol, preferably 0.4 to 0.6 mol solvent per mol rilpivirine hydrochloride.
- 29) The crystalline isomorphic solvates of rilpivirine hydrochloride according to any of claims 27 to 28, wherein the solvent is selected from 1-propanol, 2-propanol, acetone, tetrahydrofuran or chloroform.
- 30) Crystalline isomorphic solvates of rilpivirine hydrochloride having an X-ray powder diffraction pattern with peaks at 2- theta angles of $8.2 \pm 0.2^\circ$, $8.7 \pm 0.2^\circ$, $16.1 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$ and $23.5 \pm 0.2^\circ$.
- 31) The crystalline isomorphic solvates of rilpivirine hydrochloride according to claim 30 with 0.3 to 0.7 mol, preferably 0.4 to 0.6 mol solvent per mol rilpivirine hydrochloride.
- 32) The crystalline isomorphic solvates of rilpivirine hydrochloride according to any of claims 30 to 31, wherein the solvent is selected from 1,4-dioxane or 2-butanone.
- 33) Crystalline dichloromethane solvate of rilpivirine hydrochloride having an X-ray powder diffraction pattern comprising peaks at 2- theta angles of $8.2 \pm 0.2^\circ$, $16.5 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$, $21.2 \pm 0.2^\circ$ and $24.1 \pm 0.2^\circ$.
- 34) The crystalline dichloromethane solvate of rilpivirine hydrochloride according to claim 33 comprising 0.3 to 0.7 mol, preferably 0.4 to 0.6 mol dichloromethane per mol rilpivirine hydrochloride.

- 35) Crystalline cyclohexanone solvate of rilpivirine hydrochloride having an X-ray powder diffraction pattern with peaks at 2- theta angles of $8.1 \pm 0.2^\circ$, $17.3 \pm 0.2^\circ$, $18.8 \pm 0.2^\circ$, $20.8 \pm 0.2^\circ$ and $23.3 \pm 0.2^\circ$.
- 36) The crystalline cyclohexanone solvate of rilpivirine hydrochloride according to claim 35 comprising 0.3 to 0.7 mol, preferably 0.4 to 0.6 mol cyclohexanone per mol rilpivirine hydrochloride.
- 37) A crystalline solvate of rilpivirine hydrochloride characterized by an infrared spectrum displaying peaks at wavenumbers of $3057 \pm 2 \text{ cm}^{-1}$, $2228 \pm 2 \text{ cm}^{-1}$, $2218 \pm 2 \text{ cm}^{-1}$, $1656 \pm 2 \text{ cm}^{-1}$ and $1542 \pm 2 \text{ cm}^{-1}$, preferably characterized by an infrared spectrum essentially in accordance with one of the infrared spectra of figure 7 or figure 8.
- 38) A method for the preparation of the crystalline solvates according to any of claims 27 to 37 comprising the steps of:
- a) providing a suspension or solution of rilpivirine free base in a solvent selected from alcohols, ketones, chlorinated hydrocarbons or ethers,
 - b) adding hydrochloric acid to the suspension or solution and
 - c) recovering the novel solvate of rilpivirine hydrochloride.
- 39) A method according to claim 38, wherein the alcohol is selected from 1-propanol or 2-propanol the ketone is selected from acetone, 2-butanone or cyclohexanone, the chlorinated hydrocarbon is selected from dichloromethane or chloroform and the ether is selected from tetrahydrofuran or 1,4-dioxane.
- 40) Use of the crystalline solvates of rilpivirine hydrochloride as defined in any of the claims 27 to 37 as intermediates in a process for the production of the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3.
- 41) A method for the preparation of the crystalline form of rilpivirine hydrochloride according to any one of claims 1 to 3 comprising the steps of slurrying the crystalline solvates of rilpivirine hydrochloride as defined in any of the claims 27 to 37 in water and drying the obtained crystals above 80°C and/or below 5 % relative humidity.
- 42) A pharmaceutical composition comprising a crystalline solvate of rilpivirine hydrochloride according to any one of claims 27 to 37, wherein the solvate is selected from a 1-propanol solvate, a 2-propanol solvate, an acetone solvate, a 2-butanone solvate or a tetrahydrofuran solvate.

- 43) The pharmaceutical composition according to claim 42, which is an oral dosage form, in particular a capsule or tablet.
- 44) A pharmaceutical combination comprising an effective amount of the crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3 and additional therapeutic agents selected from anti-viral agents, antibiotics, immunomodulators or vaccines for the treatment of viral infections.
- 45) A pharmaceutical combination according to claim 44, wherein the additional therapeutic agents are anti-viral agents.
- 46) The pharmaceutical combination according to claim 45, wherein the anti-viral agents are selected from nucleoside analog HIV-1 reverse transcriptase inhibitors.
- 47) The pharmaceutical combination according to claim 46, wherein the analog HIV-1 reverse transcriptase inhibitors are selected from emtricitabine and tenofovir.
- 48) The pharmaceutical composition according to any of the claims 5 to 13, having an equilibrium relative humidity ranging from 0 to 70 % determined according to the equilibrium relative humidity method.
- 49) The pharmaceutical composition of any of the claims 4 to 13, comprised in a container, preferably in a container containing means for keeping the equilibrium relative humidity of the pharmaceutical composition in a range from 0 to 70 % determined according to the equilibrium relative humidity method, preferably for an extended period of time, more preferably for at least 180 days, more preferably for at least 2 years.
- 50) A container comprising a pharmaceutical composition according to any of the claims 4 to 13, the container containing means for keeping the equilibrium relative humidity of the pharmaceutical composition in a range of from 0 to 70 % determined according to the equilibrium relative humidity method, preferably for an extended period of time, more preferably for at least 180 days, more preferably for at least 2 years.
- 51) The crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3 having a particle size of less than 50 μm .
- 52) The crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3 having a particle size of less than 25 μm .

- 53) The crystalline form of rilpivirine hydrochloride according to any of claims 1 to 3 having a particle size of less than 15 μm .

Figure 1

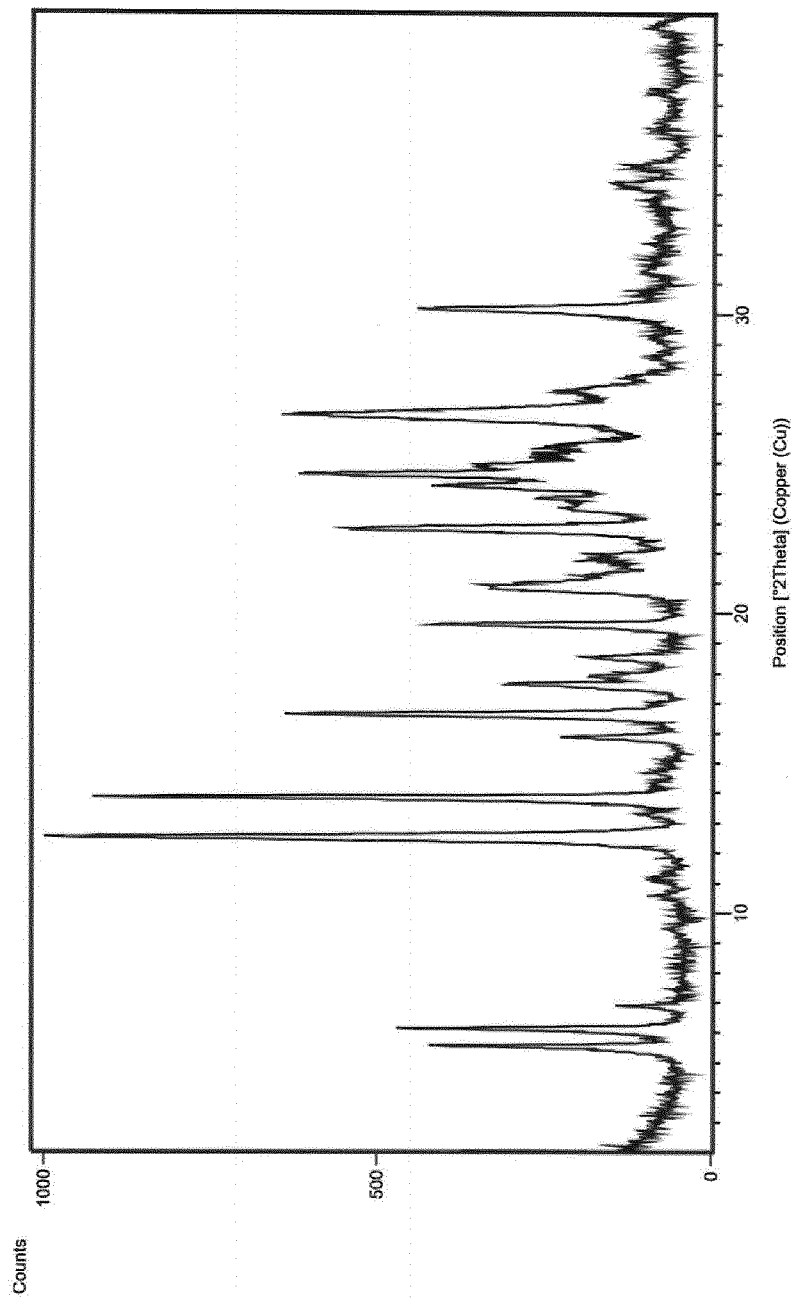


Figure 2

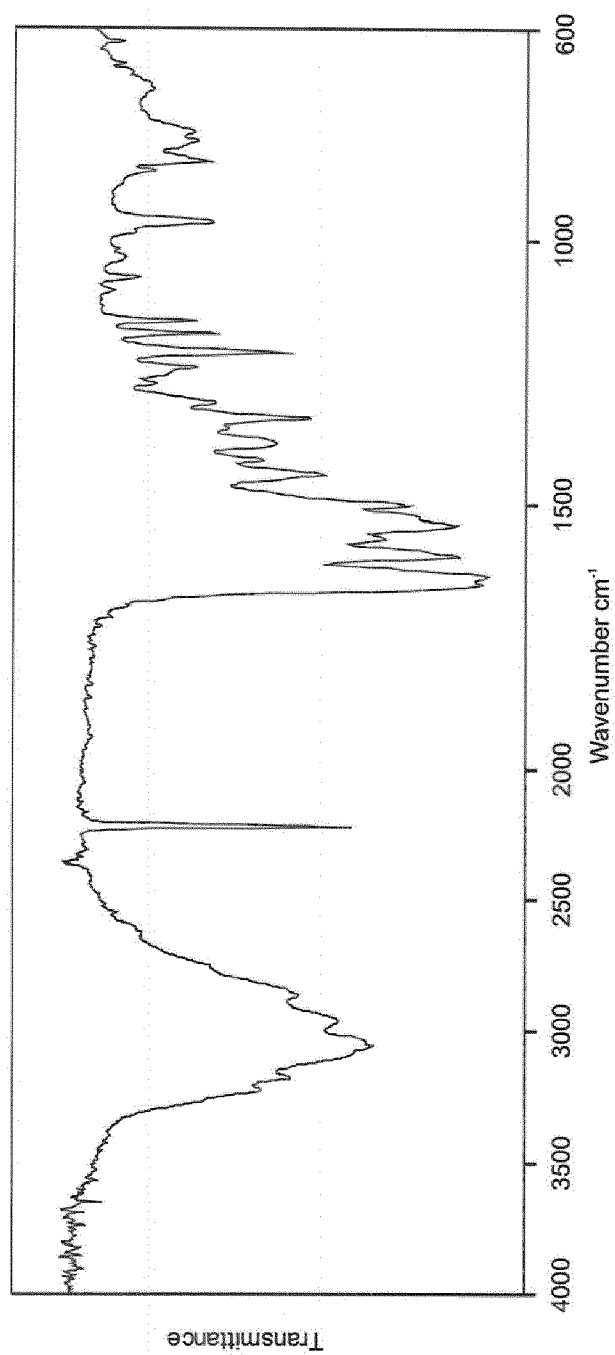


Figure 3

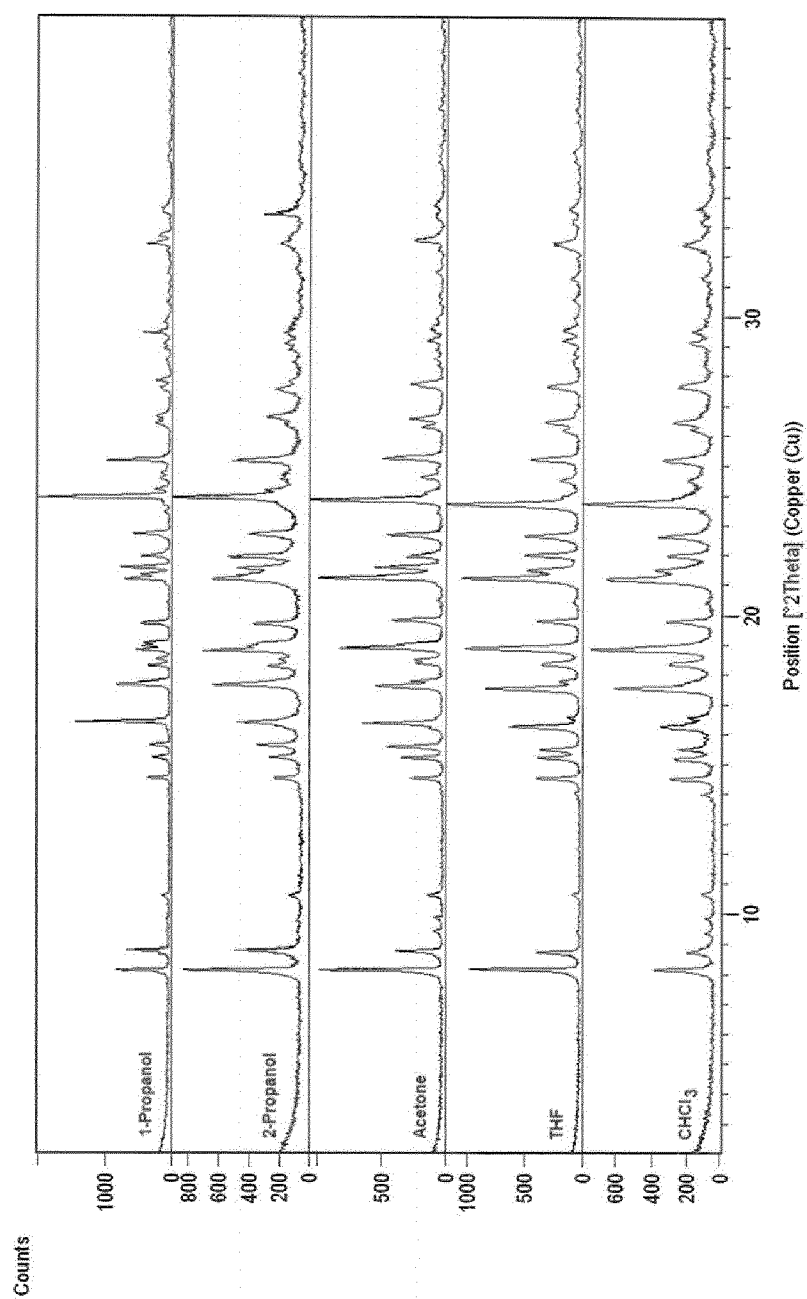


Figure 4

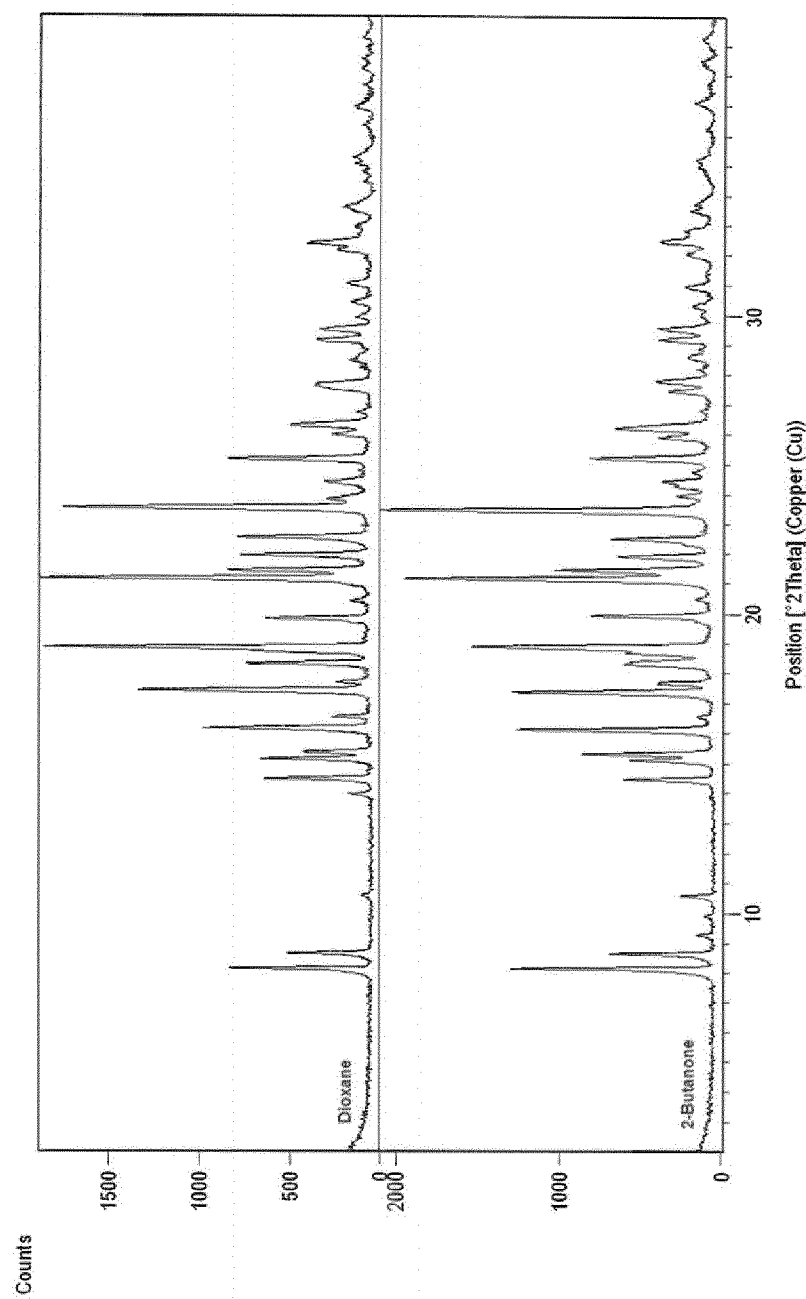


Figure 5

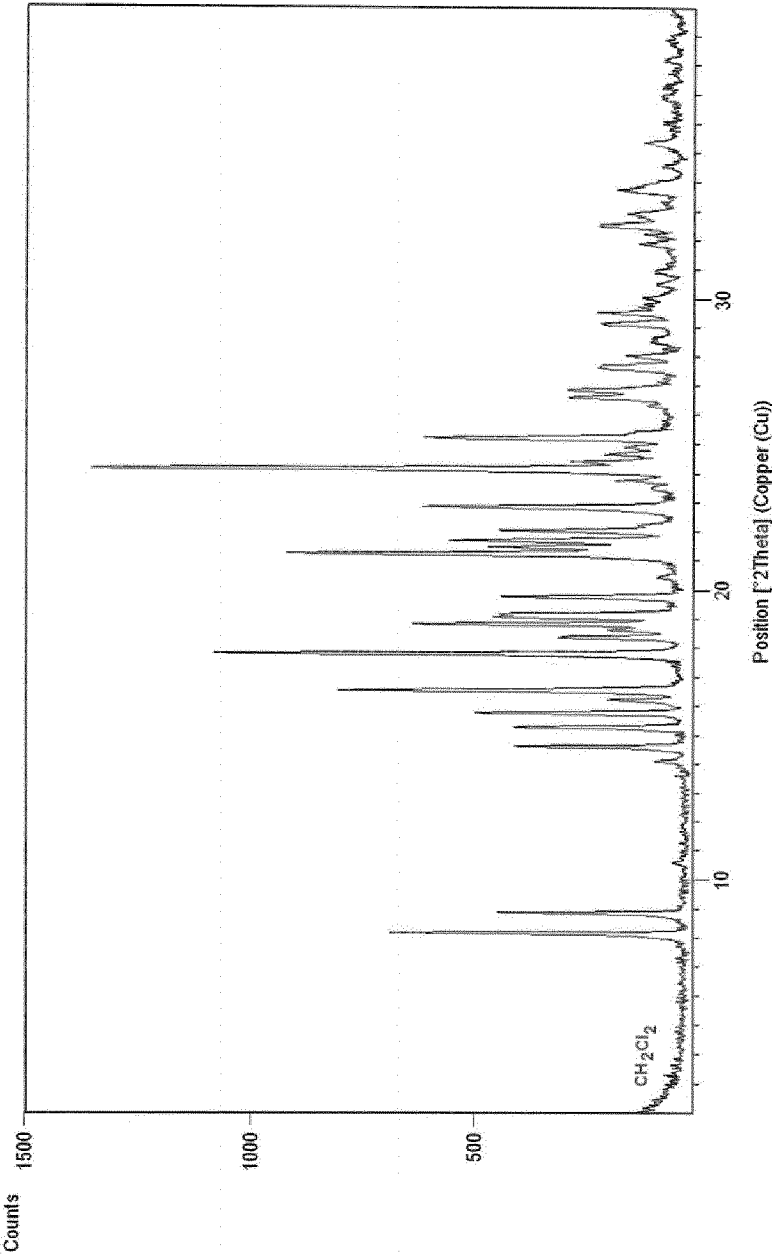


Figure 6

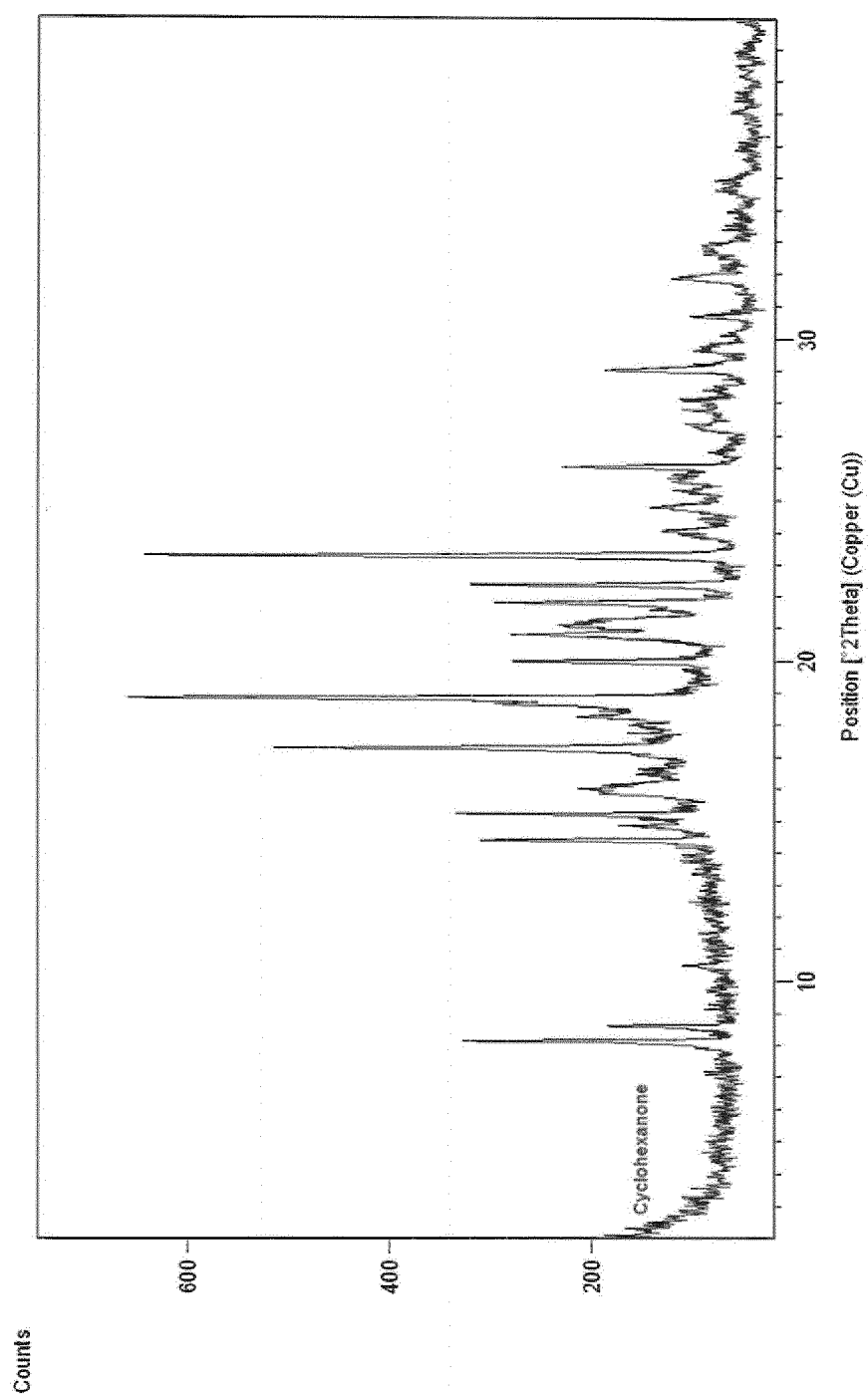


Figure 7

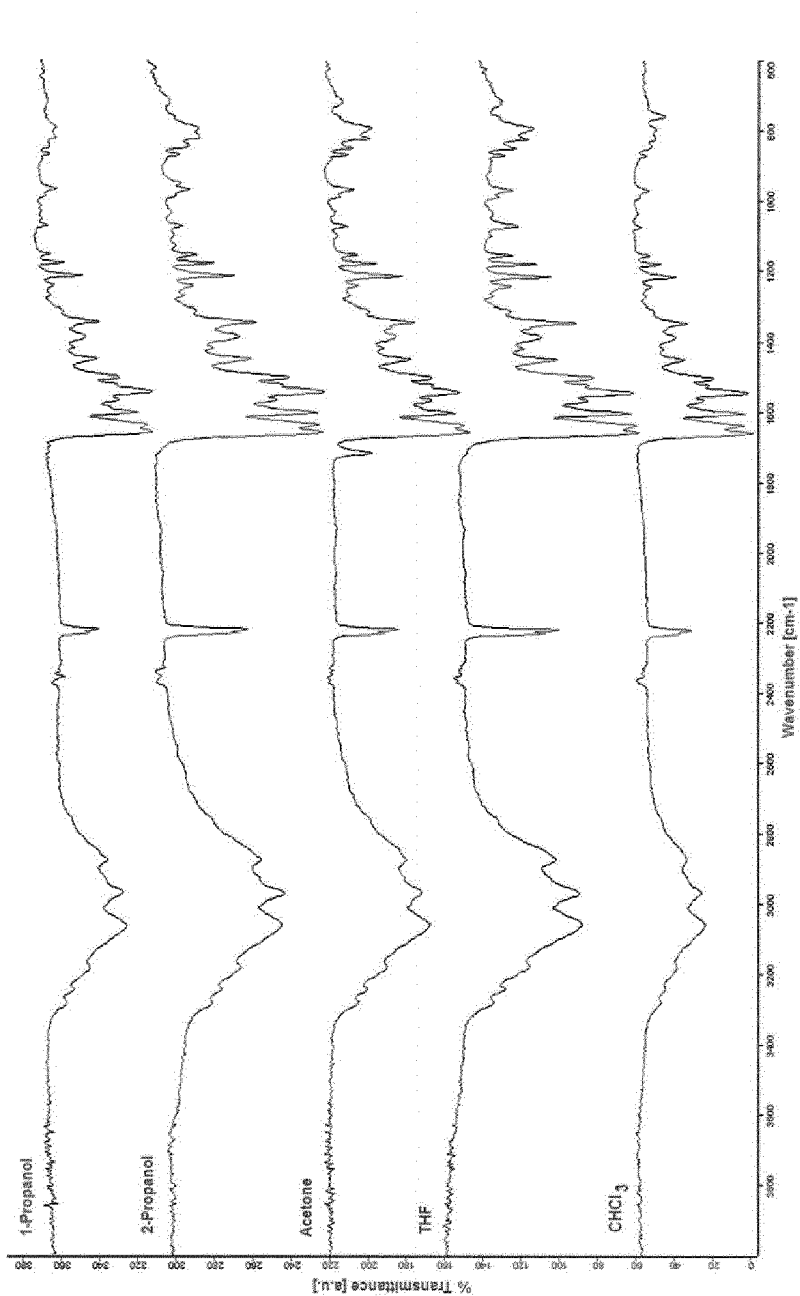


Figure 8

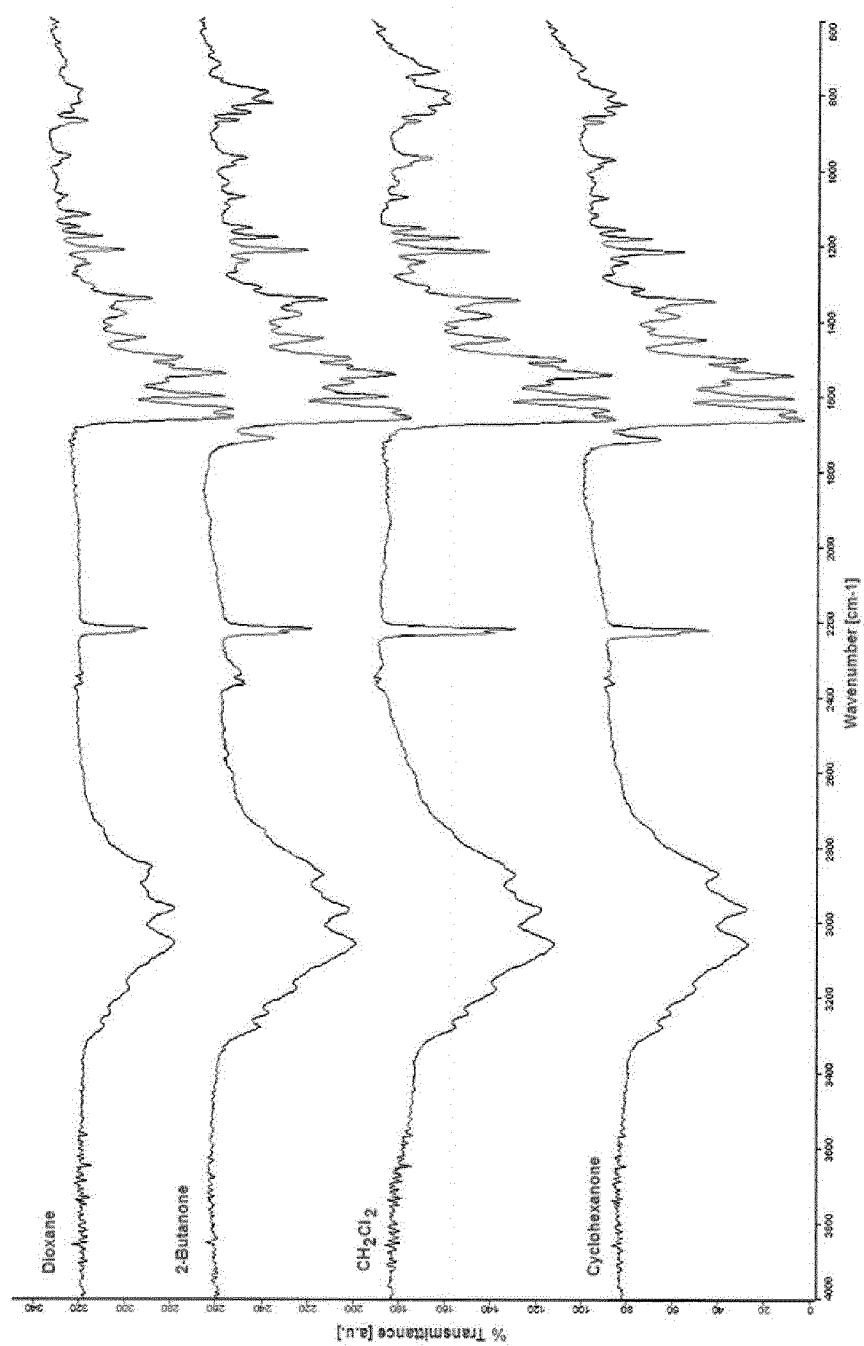


Figure 9

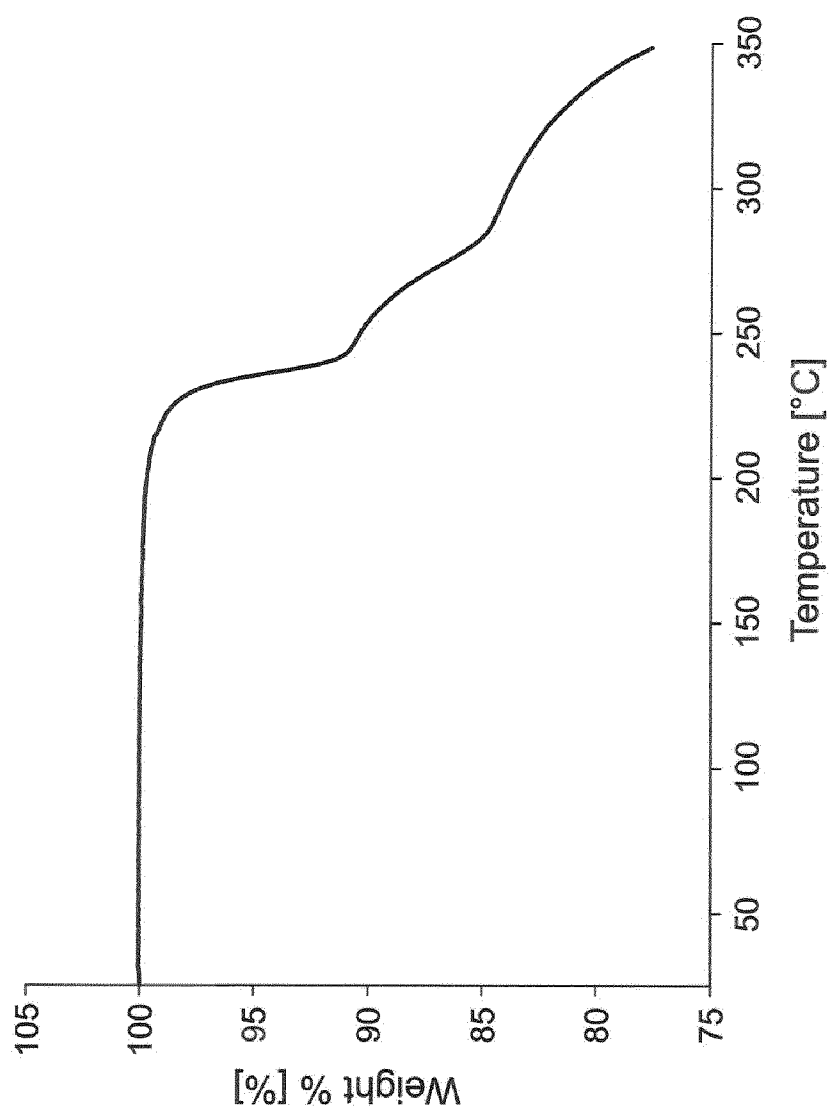


Figure 10

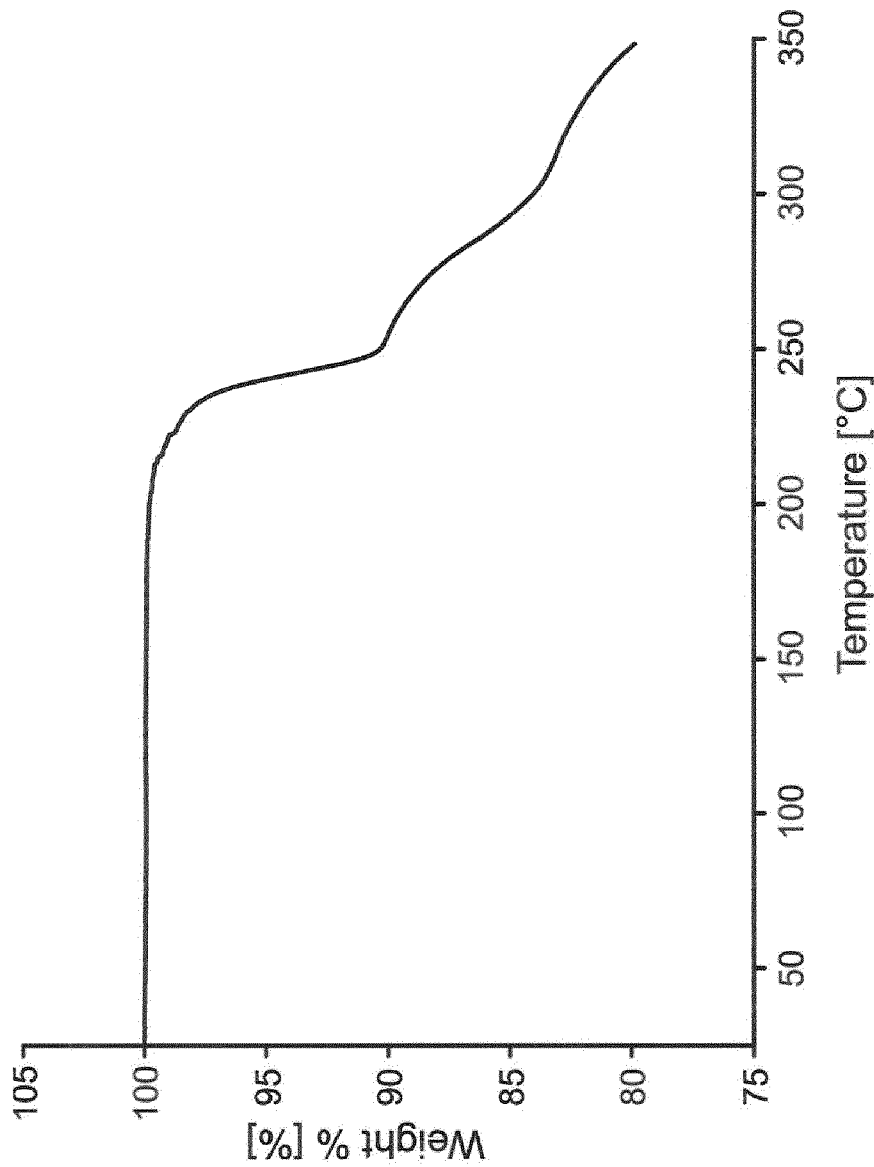


Figure 11

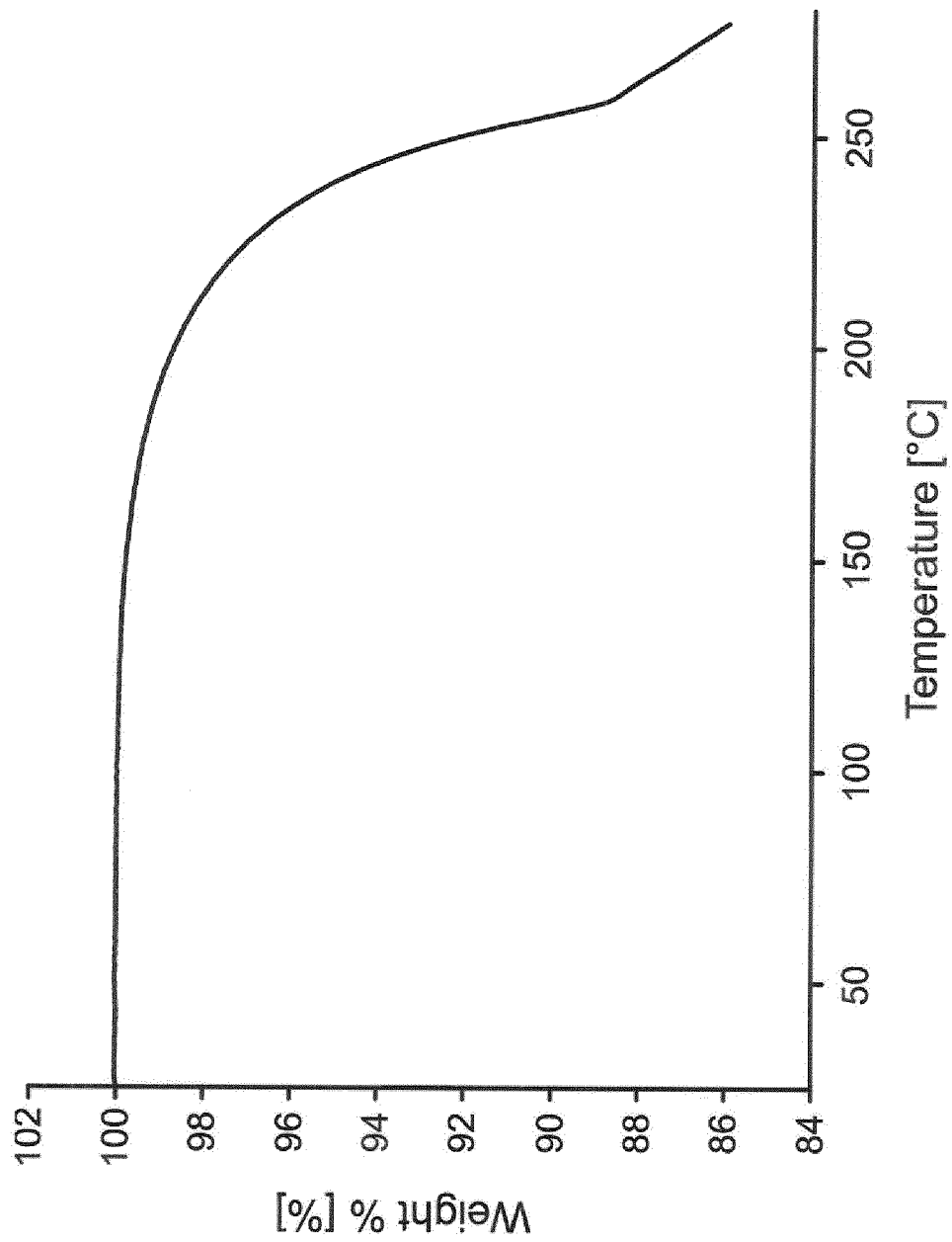


Figure 12

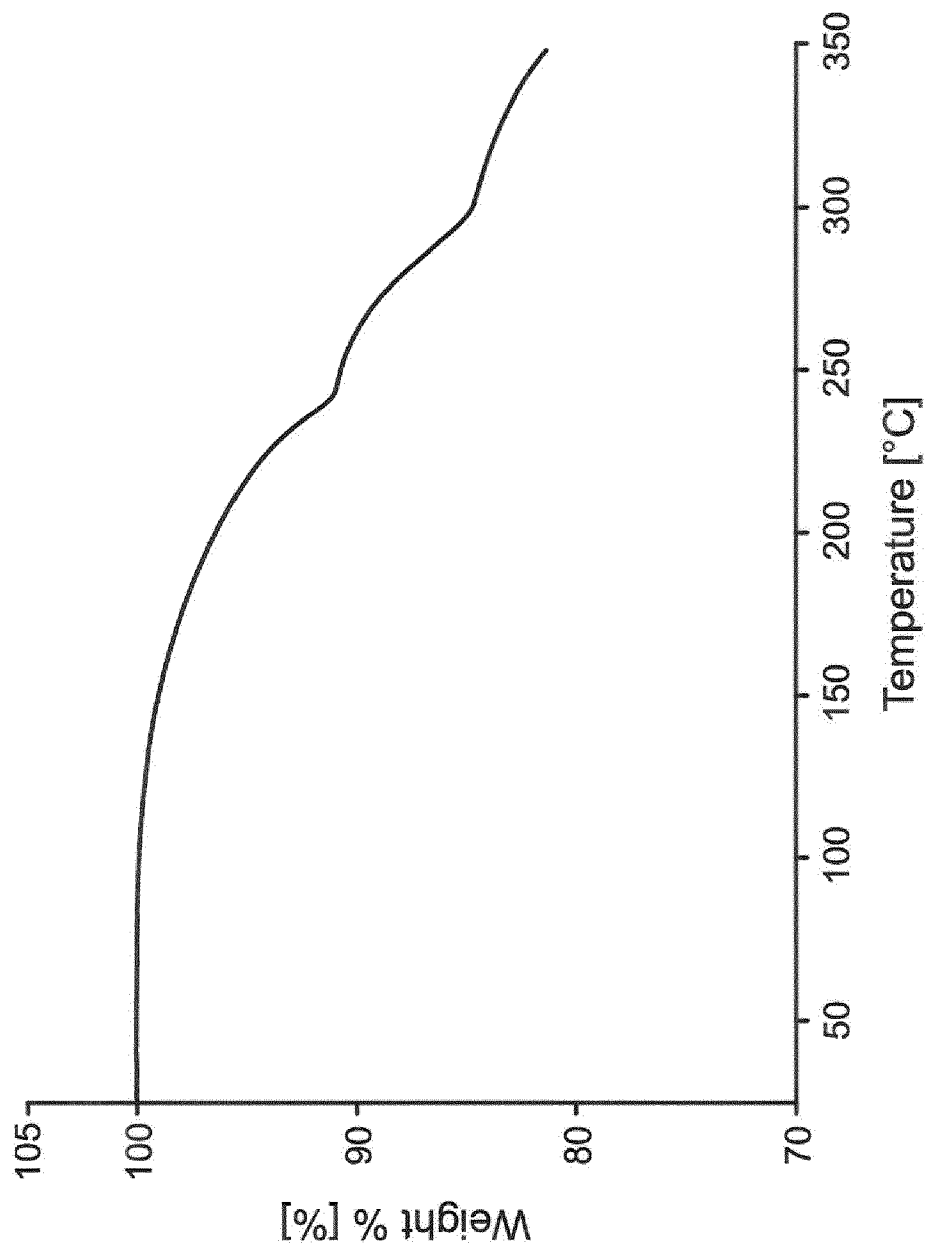


Figure 13

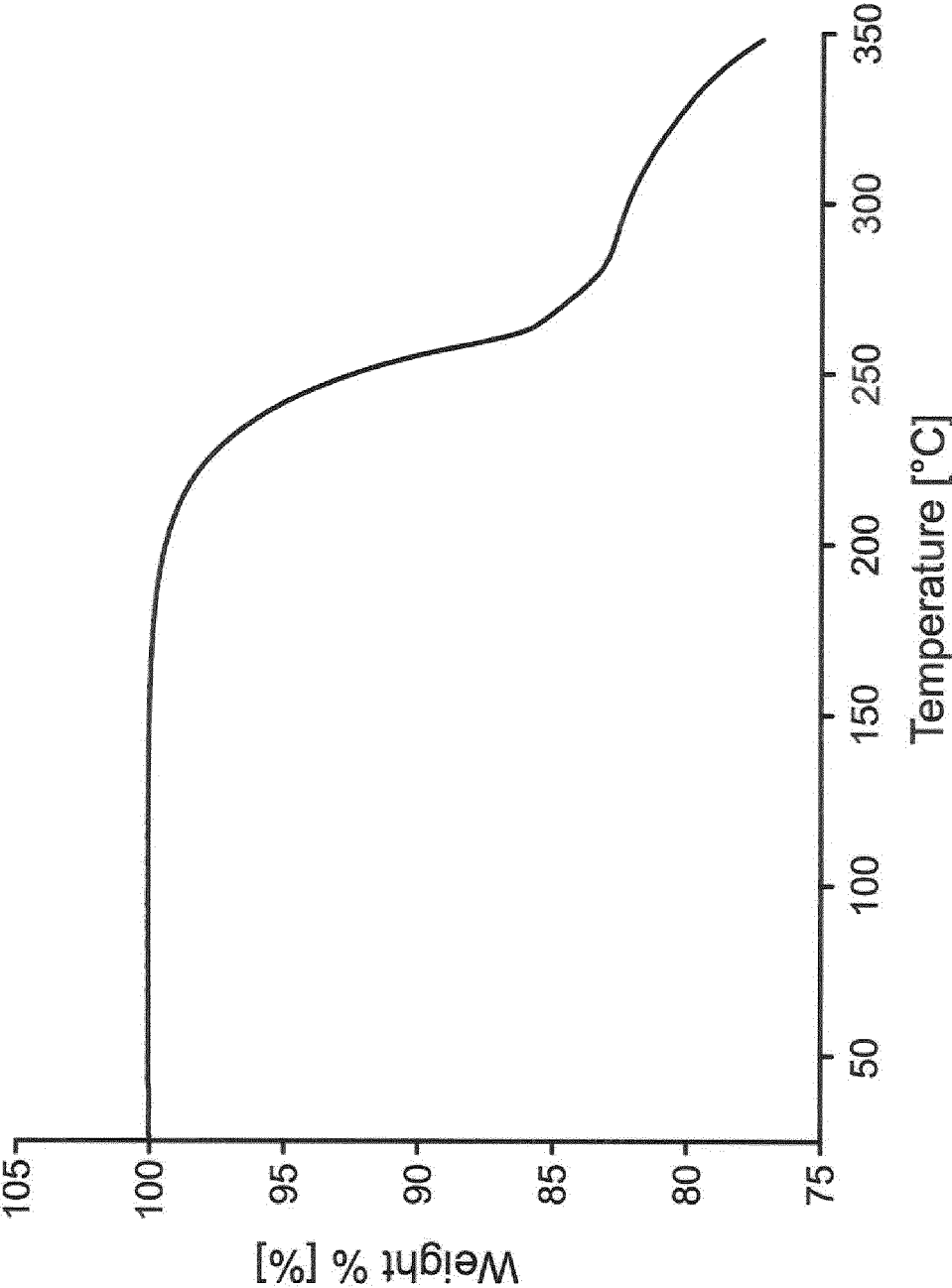


Figure 14

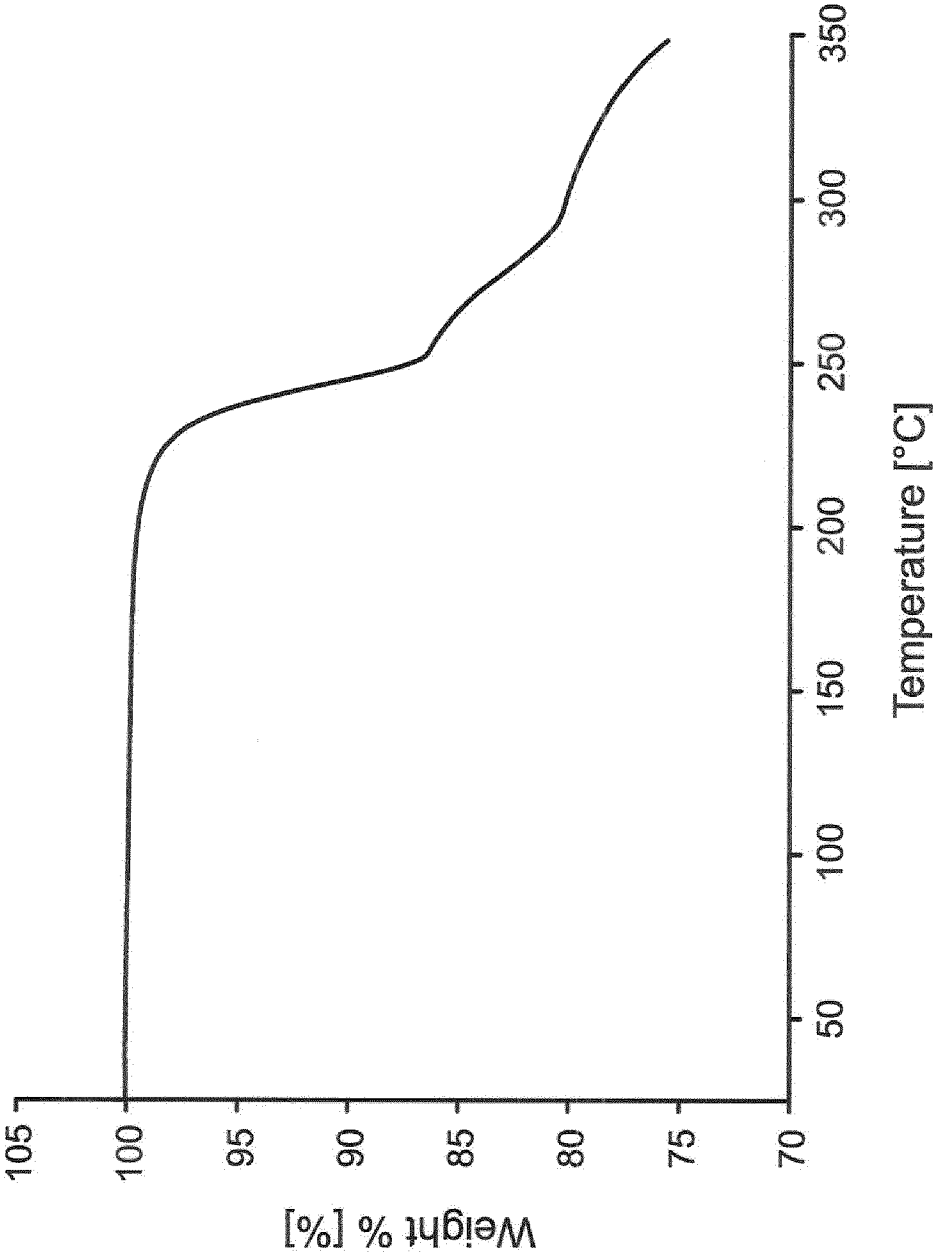


Figure 15

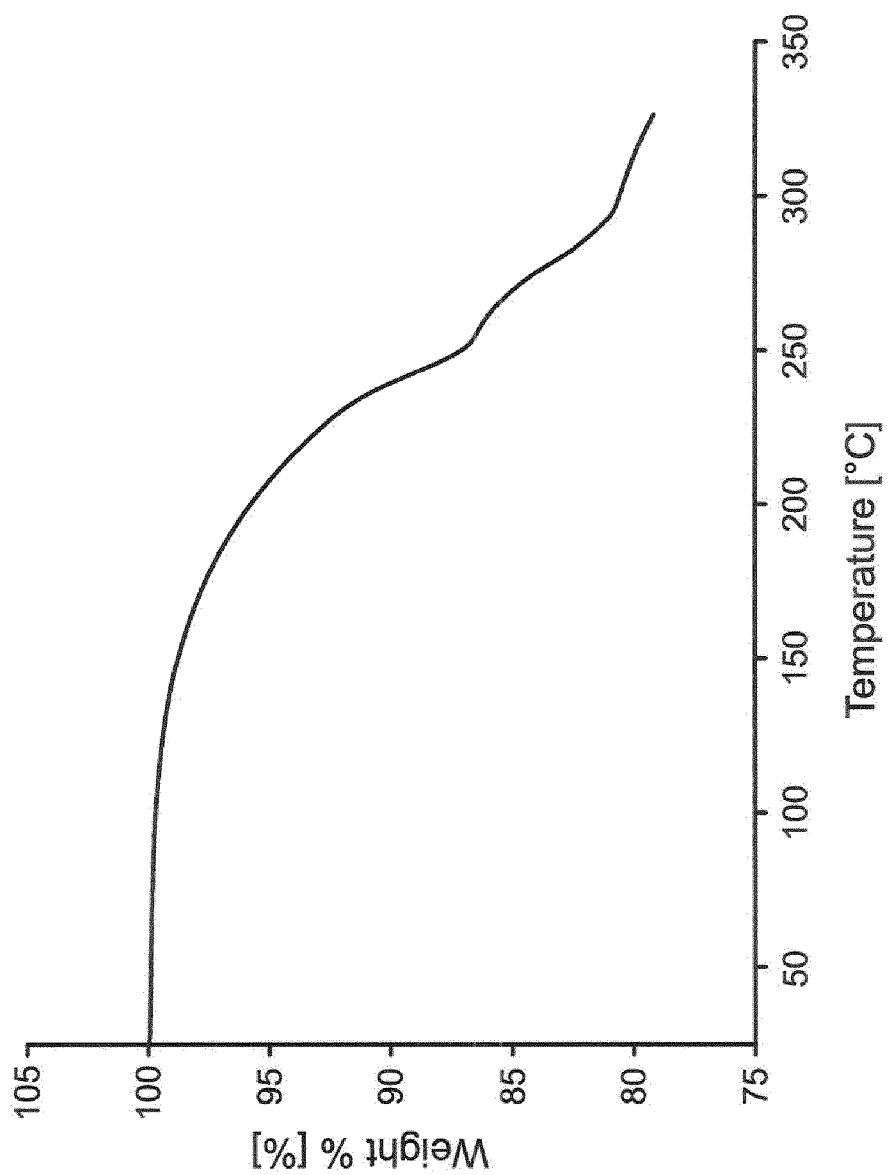


Figure 16

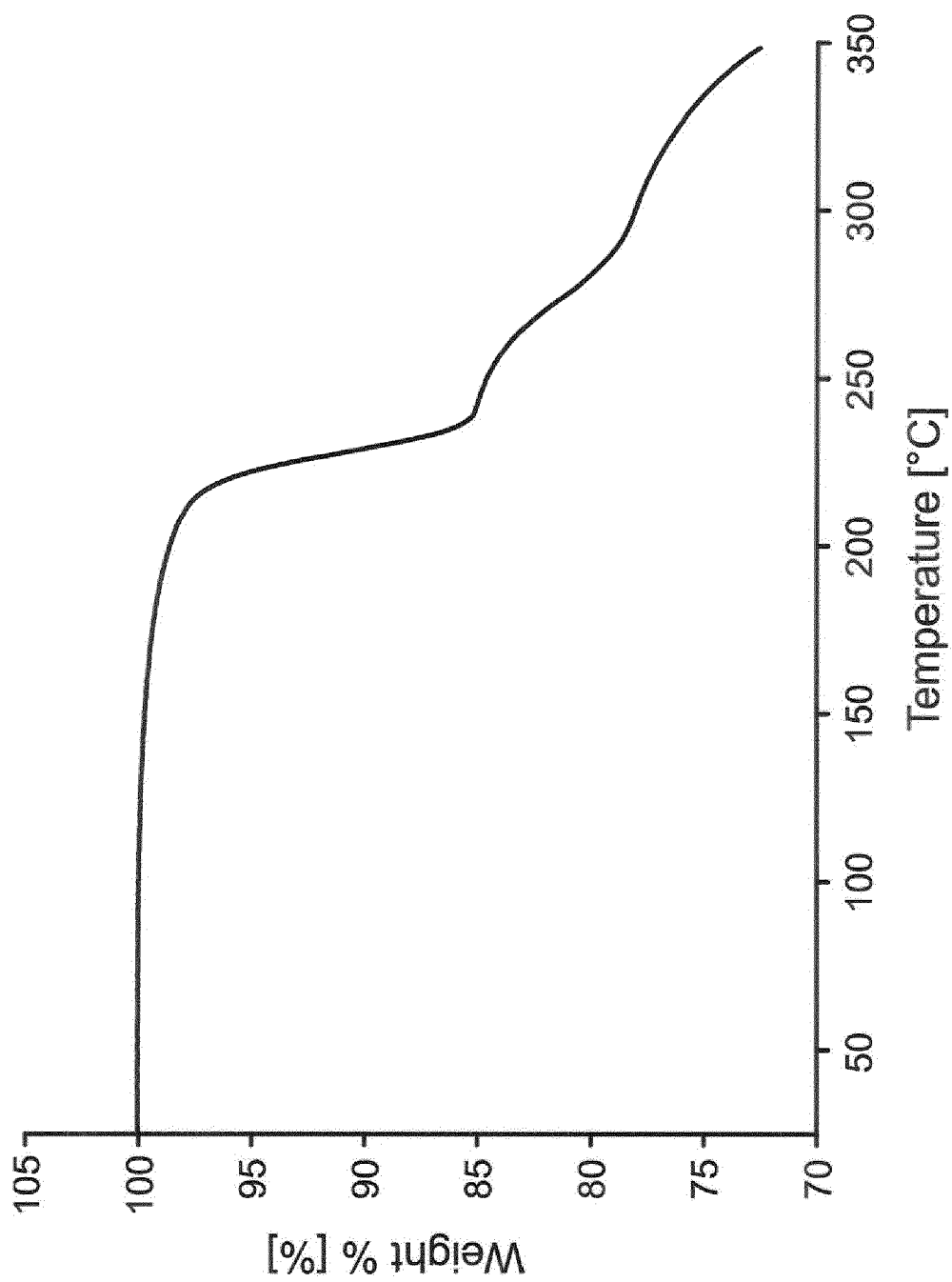


Figure 17

