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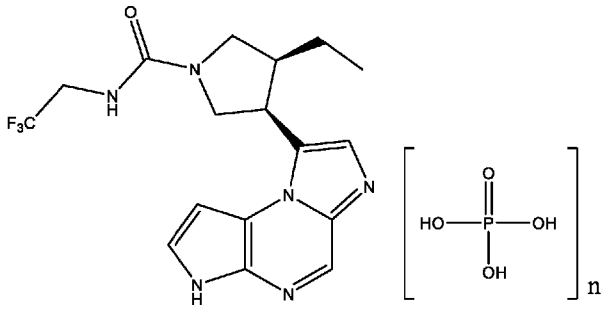

(II),

(57) **Abstract:** The invention relates to crystalline upadacitinib phosphate, especially of formula (II), and a process for preparing the same. The invention also relates to a pharmaceutical composition comprising crystalline upadacitinib phosphate, preferably in a predetermined and/or effective amount and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the invention can be used as a medicament, in particular for the treatment and/or prophylaxis of rheumatoid arthritis. (ll) n is in the range of from 1.8 to 2.2.

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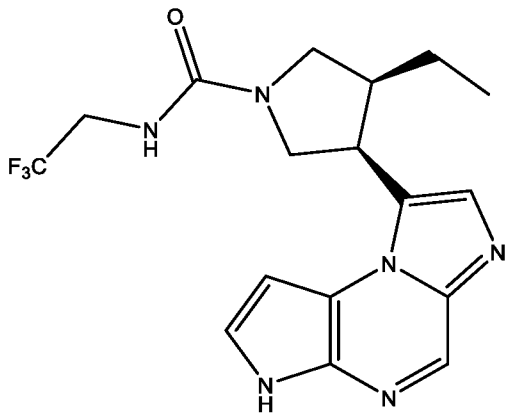
CRYSTALLINE PHOSPHATE SALT OF SELECTIVE JAK1 INHIBITOR UPADACITINIB

FIELD OF THE INVENTION

The present invention relates to crystalline upadacitinib phosphate and a process for preparing the same. The invention also relates to a pharmaceutical composition comprising crystalline upadacitinib phosphate, preferably in a predetermined and/or effective amount and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present invention can be used as a medicament, in particular for the treatment and/or prophylaxis of rheumatoid arthritis.

BACKGROUND OF THE INVENTION

Janus kinases (JAKs) belong to the superfamily of tyrosine kinase proteins and consist of four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Upadacitinib is an investigational oral agent engineered to selectively inhibit JAK1 and is currently tested in clinical studies to treat rheumatoid arthritis and various other chronic diseases. It can be chemically designated as (3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and is represented by the following chemical structure according to Formula (I)



Formula (I).

The compound upadacitinib is disclosed in WO 2011/068881 A1. Various solid-state forms of upadacitinib free base as well as different acid addition salts of upadacitinib are disclosed in WO 2017/066775 A1. The described upadacitinib salts include a tartrate hydrate, various hydrochloride solvates designated Form AA, Form BB and Form CC as well as crystalline forms of an *L*-maleate salt designated Form AAA and Form BBB, respectively.

Although salt formation is a common means for customizing the physicochemical properties of active pharmaceutical ingredients with a process or clinical need, the salt forms of WO 2017/066775 A1 all suffer from certain drawbacks, which to a certain degree compromize their utility for formulation into a pharmaceutical dosage form. For example, according to the teaching of WO 2017/066775 A1, the hydrochloride solvates are highly unstable and already convert to amorphous material upon drying at ambient conditions (page 104, paragraph [00522]). The L-maleate salt forms also do not exhibit pharmaceutically acceptable stability for use as an active ingredient in a pharmaceutical dosage form (page 105, paragraph [00522]). Moreover, the tartarte hydrate salt tends to release its crystal water fairly quickly already at moderate temperature stress leading to amorphization (page 357, paragraph [001506] and corresponding Figure 4E, page 358 [001517] and corresponding Figure 5D). Dehydration followed by amorphization also occurs when the tartarate hydrate is exposed to dry conditions (page 359, paragraph 001528]. In addition, the needle-shaped morphology of the tartarte hydrate (page 342, Table 15-A) is not preferred since such material often shows poor powder properties.

Hence, there remains a need for improved solid-state forms of upadacitinib possessing physicochemical properties which allow for the stable formulation of upadacitinib into a pharmaceutical dosage form such that reliable quality and efficacy are achieved throughout shelf-life.

SUMMARY OF THE INVENTION

The present invention relates to crystalline upadacitinib phosphate. Crystalline upadacitinib phosphate of the present invention possesses favorable physicochemical properties for a drug substance intended for use in an oral solid dosage form with regards to chemical stability, physical stability, melting point, hygroscopicity, solubility, dissolution, morphology, crystallinity, flowability, compactibility and wettability.

In particular, the crystalline upadacitinib phosphate salt of the present invention is physically and chemically stable against temperature stress and can thus be reliably formulated into a pharmaceutical dosage form and safely stored. For example, unlike known upadacitinib salts, the crystalline upadacitinib phosphate salt forms of the present invention do not show a tendency towards amorphization upon temperature stress and/or when subjected to an atmosphere of low relative humidity but rather one crystalline form reversibly transforms into another crystalline form, thus preserving overall crystallinity of upadacitinib phosphate.

Abbreviations

PXRD	powder X-ray diffractogram
FTIR	Fourier transform infrared
ATR	attenuated total reflection
DSC	differential scanning calorimetry
TGA	thermogravimetric analysis
GMS	gravimetric moisture sorption
RH	relative humidity
w-%	weight percent
v-%	volume percent

Definitions

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

As used herein the term "room temperature" refers to a temperature in the range of from 20 to 30 °C.

As used herein, the term "measured at a temperature in the range of from 20 to 30 °C" refers to a measurement under standard conditions. Typically, standard conditions mean a temperature in the range of from 20 to 30 °C, i.e. at room temperature. Standard conditions can mean a temperature of about 22 °C. Typically, standard conditions can additionally mean a measurement under 20-80% relative humidity, preferably 30-70% relative humidity, more preferably 40-60% relative humidity and most preferably 50% relative humidity.

The term "reflection" with regards to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material which lacks long-range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately 100 to 1000 atoms, whereas short-range order is over a few atoms only (see *"Fundamentals of Powder Diffraction and Structural Characterization of Materials" by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003*, page 3).

The term “essentially the same” with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably in the range of ± 0.1° 2-Theta. Thus, a reflection that usually appears at 7.4° 2-Theta for example can appear between 7.2° and 7.6° 2-Theta, preferably between 7.3 and 7.5° 2-Theta on most X-ray diffractometers under standard conditions. Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

The term “essentially the same” with reference to Fourier transform infrared spectroscopy means that variabilities in peak positions and relative intensities of the peaks are to be taken into account. For example, a typical precision of the wavenumber values is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}. Thus, a peak at 3143 cm^{-1} for example can appear in the range of from 3139 to 3147 cm^{-1}, preferably of from 3141 to 3145 on most infrared spectrometers under standard conditions. Differences in relative intensities are typically smaller compared to X-ray diffraction. However, one skilled in the art will appreciate that small differences in peak intensities due to degree of crystallinity, sample preparation and other factors can also occur in infrared spectroscopy. Relative peak intensities should therefore be taken as qualitative measure only.

Crystalline upadacitinib phosphate of the present invention may be referred to herein as being characterized by a powder X-ray diffractogram or an FTIR spectrum "as shown in" a figure. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample concentration, sample purity, sample history and sample preparation may lead to variations, for example relating to the exact reflection and peak positions and their intensities. However, a comparison of the graphical data in the figures herein with the graphical data generated for an unknown physical form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

The term “solid-state form” as used herein refers to any crystalline and/or amorphous phase of a compound.

The term “anhydrous ” or “anhydrate” as used herein refers to a compound where no water is cooperated in or accommodated by the crystal structure. An anhydrous compound may still contain residual water, which is not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal.

The term “hydrate” as used herein, refers to a crystalline solid where either water is cooperated in or accommodated by the crystal structure e.g. is part of the crystal structure or entrapped into the crystal (water inclusions). When water is present in stoichiometric amount, the hydrate may be referred to by adding greek numeral prefixes. For example, a hydrate may be referred to as a *mono*hydrate or as a *di*hydrate depending on the water/compound stoichiometry. The water content can be measured, for example, by Karl-Fischer-Coulometry.

The term “non-solvated” as used herein refer to a compound where no organic solvent is cooperated in or accommodated by the crystal structure. A non-solvated compound may still contain residual organic solvent, which is not part of the crystal structure but may be adsorbed on the surface or absorbed in disordered regions of the crystal.

As used herein, the term “mother liquor” refers to the solution remaining after crystallization of a solid from said solution.

A “predetermined amount” as used herein with regards to crystalline upadacitinib phosphate of the present invention refers to the initial amount of the crystalline upadacitinib phosphate used for the preparation of a pharmaceutical composition having a desired dosage strength of upadacitinib.

The term “effective amount” as used herein with regards to crystalline upadacitinib phosphate of the present invention encompasses an amount of crystalline upadacitinib phosphate, which causes the desired therapeutic and/or prophylactic effect.

As used herein, the term “about” means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: illustrates a representative PXRD of the crystalline upadacitinib phosphate of the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 2: illustrates a representative FTIR spectrum of the crystalline upadacitinib phosphate of the present invention. The x-axis shows the wavenumbers in cm^{-1}, the y-axis shows the relative intensity in percent transmittance.

Figure 3: illustrates a representative DSC curve of the crystalline upadacitinib phosphate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 4: illustrates a representative TGA curve of the crystalline upadacitinib phosphate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the mass (loss) of the sample in weight percent (weight%).

Figure 5: illustrates a representative PXRD of the crystalline upadacitinib phosphate hydrate of the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

Figure 6: illustrates a representative FTIR spectrum of the crystalline upadacitinib phosphate hydrate of the present invention. The x-axis shows the wavenumbers in cm^{-1}, the y-axis shows the relative intensity in percent transmittance.

Figure 7: illustrates a representative DSC curve of the crystalline upadacitinib phosphate hydrate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the heat flow rate in Watt per gram (W/g) with endothermic peaks going up.

Figure 8: illustrates a representative TGA curve of the crystalline upadacitinib phosphate hydrate of the present invention. The x-axis shows the temperature in degree Celsius (°C), the y-axis shows the mass (loss) of the sample in weight percent (weight%).

Figure 9: illustrates an overlay of the PXRDs of crystalline upadacitinib phosphate anhydrate (top diffractogram) and crystalline upadacitinib phosphate hydrate (bottom diffractogram). The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons. The PXRD of crystalline upadacitinib phosphate was shifted along the y-axis.

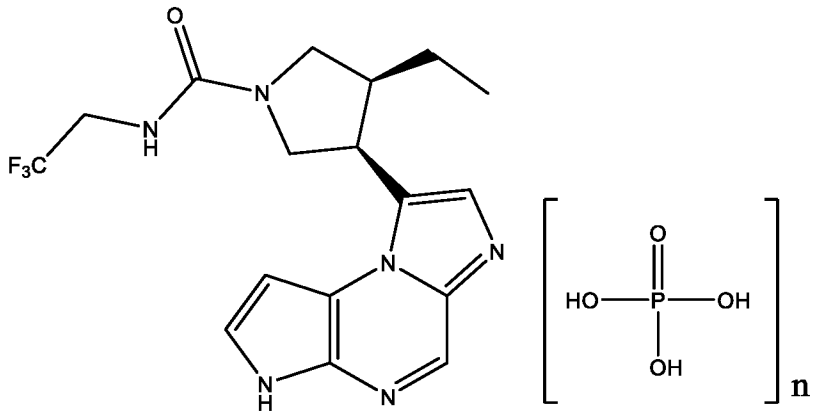
Figure 10: illustrates the GMS curve of crystalline upadacitinib phosphate of the present invention between 0 and 90% RH. The displayed equilibrium curve shows the sorption cycle (marked by triangles) and the desorption cycle (marked by squares). The x-axis displays the

relative humidity in percent (%) measured at (25.0 ± 0.1) °C, the y-axis the mass changes in percent (%).

Figure 11: illlustrates the GMS curve of upadacitinib tartrate between 0 and 90% RH. The displayed equlibirum curve shows the sorption cycle (marked by triangles) and the desorption cycle (marked by squares). The x-axis displays the relative humidity in percent (%) measured at (25.0 ± 0.1) °C, the y-axis the mass changes in percent (%). In contrary to upadacitinib phosphate, where the starting form was the crystalline anhydrate, the starting form of upadacitinib tartrate was the hydrated form. Therefore in Figure 11 the sample mass at 0% RH was set as reference weight (for the anhydrate), and all other points were adapted to this weight accordingly, in order to be directly comparable with the GMS curve of upadacitinib phosphate from Figure 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a crystalline salt comprising upadacitinib and phosphoric acid. In particular, the present invention relates to crystalline upadacitinib phosphate. More precisely, the present invention relates to crystalline upadacitinib phosphate characterized by the chemical structure according to Formula (II)



Formula (II),

wherein n is in the range of from 1.8 to 2.2, preferably in the range of from 1.9 to 2.1, more preferably in the range of from 1.95 to 2.05 and most preferably n is about 2.0. For example, n is selected from the group consisting of about 1.8, 1.9, 1.95, 2.0, 2.05, 2.1 and 2.2. The crystalline upadacitinib phosphate salt of the present invention is a *di*-phosphate salt e.g. a salt having a molar ratio of upadacitinib and phosphoric acid in the range of from 1.0: 1.8 to 2.2, preferably of from 1.0: 1.9 to 2.1, more preferably of from 1.0: 1.95 to 2.05 and most preferably

the molar ratio is about 1.0 to 2.0. The skilled person will appreciate that in the crystalline upadacitinib phosphate of the present invention upadacitinib may be in protonated form while phosphoric acid may be in a deprotonated form.

The crystalline upadacitinib phosphate salt of the present invention as defined in any one of the above described embodiments may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise but are not limited to powder X-ray diffraction, Fourier transform infrared spectroscopy, differential scanning calorimetry and thermogravimetric analysis as well as gravimetric moisture sorption. It may be characterized by one of the aforementioned analytical methods or by combining two or more of them. In particular, the crystalline upadacitinib phosphate of the present invention may be characterized by any one of the following embodiments or by combining two or more of the following embodiments.

Anhydrous crystalline upadacitinib phosphate (anhydrate)

The present invention relates to crystalline upadacitinib phosphate characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.4 ± 0.2)°, (17.6 ± 0.2)° and (19.3 ± 0.2)°; or

(7.4 ± 0.2)°, (13.1 ± 0.2)°, (17.6 ± 0.2)° and (19.3 ± 0.2)°; or

(7.4 ± 0.2)°, (13.1 ± 0.2)°, (17.6 ± 0.2)°, (19.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (17.6 ± 0.2)°, (19.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.6 ± 0.2)°, (19.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (19.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (20.3 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (20.3 ± 0.2)°, (23.5 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (20.3 ± 0.2)°, (23.1 ± 0.2)°, (23.5 ± 0.2)° and (24.7 ± 0.2)°; or

(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (20.3 ± 0.2)°, (22.7 ± 0.2)°, (23.1 ± 0.2)°, (23.5 ± 0.2)° and (24.7 ± 0.2)°; or
(7.4 ± 0.2)°, (12.6 ± 0.2)°, (13.1 ± 0.2)°, (13.8 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (20.3 ± 0.2)°, (22.3 ± 0.2)°, (22.7 ± 0.2)°, (23.1 ± 0.2)°, (23.5 ± 0.2)° and (24.7 ± 0.2)°,

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline upadacitinib phosphate characterized by having a PXRD comprising reflections at 2-Theta angles of:

(7.4 ± 0.1)°, (17.6 ± 0.1)° and (19.3 ± 0.1)°; or
(7.4 ± 0.1)°, (13.1 ± 0.1)°, (17.6 ± 0.1)° and (19.3 ± 0.1)°; or
(7.4 ± 0.1)°, (13.1 ± 0.1)°, (17.6 ± 0.1)°, (19.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (17.6 ± 0.1)°, (19.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.6 ± 0.1)°, (19.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (19.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (20.3 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (20.3 ± 0.1)°, (23.5 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (20.3 ± 0.1)°, (23.1 ± 0.1)°, (23.5 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (20.3 ± 0.1)°, (22.7 ± 0.1)°, (23.1 ± 0.1)°, (23.5 ± 0.1)° and (24.7 ± 0.1)°; or
(7.4 ± 0.1)°, (12.6 ± 0.1)°, (13.1 ± 0.1)°, (13.8 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (20.3 ± 0.1)°, (22.3 ± 0.1)°, (22.7 ± 0.1)°, (23.1 ± 0.1)°, (23.5 ± 0.1)° and (24.7 ± 0.1)°,

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In addition, the present invention relates to crystalline upadacitinib phosphate characterized by having a PXRD comprising reflections at 2-Theta angles of (7.4 ± 0.2)°, (13.1 ± 0.2)°, (17.2 ± 0.2)°, (17.6 ± 0.2)°, (18.9 ± 0.2)°, (19.3 ± 0.2)°, (22.7 ± 0.2)°, (23.1 ± 0.2)°, (23.5 ± 0.2)° and (24.7 ± 0.2), when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline upadacitinib phosphate characterized by having a PXRD comprising reflections at 2-Theta angles of (7.4 ± 0.1)°, (13.1 ± 0.1)°, (17.2 ± 0.1)°, (17.6 ± 0.1)°, (18.9 ± 0.1)°, (19.3 ± 0.1)°, (22.7 ± 0.1)°, (23.1 ± 0.1)°, (23.5 ± 0.1)° and (24.7 ± 0.1), when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

The present invention also relates to crystalline upadacitinib phosphate characterized by having a PXRD essentially the same as shown in Figure 1 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Moreover, the present invention relates to crystalline upadacitinib phosphate characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1} and (1150 ± 4) cm^{-1} or;

(3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1428 ± 4) cm^{-1} and (1150 ± 4) cm^{-1}; or

(3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1428 ± 4) cm^{-1}, (1150 ± 4) cm^{-1} and (985 ± 4) cm^{-1}; or

(3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1428 ± 4) cm^{-1}, (1335 ± 4) cm^{-1}, (1150 ± 4) cm^{-1} and (985 ± 4) cm^{-1}; or

(3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1428 ± 4) cm^{-1}, (1335 ± 4) cm^{-1}, (1269 ± 4) cm^{-1}, (1150 ± 4) cm^{-1} and (985 ± 4) cm^{-1}; or

(3143 ± 4) cm^{-1}, (1578 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1428 ± 4) cm^{-1}, (1335 ± 4) cm^{-1}, (1269 ± 4) cm^{-1}, (1150 ± 4) cm^{-1} and (985 ± 4) cm^{-1}; or

(3143 ± 4) cm^{-1}, (1578 ± 4) cm^{-1}, (1549 ± 4) cm^{-1}, (1462 ± 4) cm^{-1}, (1428 ± 4) cm^{-1}, (1335 ± 4) cm^{-1}, (1269 ± 4) cm^{-1}, (1150 ± 4) cm^{-1} and (985 ± 4) cm^{-1},

when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

Alternatively, the present invention relates to crystalline upadacitinib phosphate characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(3143 ± 2) cm^{-1}, (1549 ± 2) cm^{-1} and (1150 ± 2) cm^{-1} or;

(3143 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1428 ± 2) cm^{-1} and (1150 ± 2) cm^{-1}; or
(3143 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1428 ± 2) cm^{-1}, (1150 ± 2) cm^{-1} and (985 ± 2) cm^{-1}; or
(3143 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1428 ± 2) cm^{-1}, (1335 ± 2) cm^{-1}, (1150 ± 2) cm^{-1} and (985 ± 2) cm^{-1}; or
(3143 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1428 ± 2) cm^{-1}, (1335 ± 2) cm^{-1}, (1269 ± 2) cm^{-1}, (1150 ± 2) cm^{-1} and (985 ± 2) cm^{-1}; or
(3143 ± 2) cm^{-1}, (1578 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1428 ± 2) cm^{-1}, (1335 ± 2) cm^{-1}, (1269 ± 2) cm^{-1}, (1150 ± 2) cm^{-1} and (985 ± 2) cm^{-1}; or
(3143 ± 2) cm^{-1}, (1578 ± 2) cm^{-1}, (1549 ± 2) cm^{-1}, (1462 ± 2) cm^{-1}, (1428 ± 2) cm^{-1}, (1335 ± 2) cm^{-1}, (1269 ± 2) cm^{-1}, (1150 ± 2) cm^{-1} and (985 ± 2) cm^{-1},

when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

In addition, the present invention relates to crystalline upadacitinib phosphate characterized by having an FTIR spectrum essentially the same as shown in Figure 2 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

Furthermore, the present invention relates to crystalline upadacitinib phosphate characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of (175 ± 5)°C, preferably of (175 ± 3)°C, even more preferably of (175 ± 2)°C and most preferably of (175 ± 1)°C, when measured at a heating rate of 10 K/min.

The present invention also relates to crystalline upadacitinib phosphate characterized by having a DSC curve comprising an endothermic peak having a peak maximum at a temperature of (178 ± 5)°C, preferably of (178 ± 3)°C, even more preferably of (178 ± 2)°C and most preferably of (178 ± 1)°C, when measured a heating rate of 10 K/min.

Moreover, the invention relates to crystalline upadacitinib phosphate characterized by having a DSC curve comprising an endothermic peak with an enthalpy of (60 ± 5) J/g, preferably of (60 ± 3) J/g, even more preferably of (60 ± 2) J/g and most preferably of (60 ± 1) J/g, when measured at a heating rate of 10 K/min.

In still another embodiment, the invention relates to crystalline upadacitinib phosphate, characterized by having a melting point onset at a temperature in the range of from (175 ± 5) °C, preferably of from (175 ± 3) °C, more preferably of from (175 ± 2)°C, even more preferably

of from (175 ± 1)°C, for example having a melting point onset at a temperature of about 175 °C, when measured with DSC at a heating rate of 10 K/min.

In another embodiment, the present invention relates to crystalline updadacitinib phosphate, characterized by having a TGA curve showing a mass loss of not more than 0.5 weight%, based on the weight of the crystalline upadacitinib phosphate, when heated from 25 to 175 °C at a rate of 10 K/min.

In one embodiment, the present invention relates to crystalline updadacitinib phosphate characterized by showing a mass change of not more than 0.5 w-%, preferably of not more than 0.4 w-%, more preferably of not more than 0.3 w-% based on the weight of the crystalline form, when measured with GMS at a relative humidity in the range of from 0 to 75% and a temperature of (25.0 ± 0.1)°C.

Preferably, the crystalline upadacitinib phosphate of the present invention as defined in any one of the embodiments described above is anhydrous. More preferably, the invention relates to crystalline updadacitinib phosphate characterized by having a water content of not more than 0.5 w-%, preferably of not more than 0.4 w-%, more preferably of not more than 0.3 w-% based on the weight of the crystalline form, when measured with Karl-Fischer titration.

Even more preferably, the crystalline upadacitinib phosphate of the present invention as defined in any one of the embodiments described above is non-solvated.

In another aspect, the invention relates to a process for the preparation of the crystalline upadacitinib phosphate as defined in any one of the above described embodiments comprising:

(a) reacting upadacitinib and phosphoric acid in the presence of a suitable solvent;
(b) adding one or more antisolvent(s) to the solution obtained in step (a)
(c) adding upadacitinib phosphate seed crystals to the mixture obtained in step (b);
(d) allowing for the crystallization of upadacitinib phosphate;
(e) separating at least a part of the crystals obtained in step (c);
(f) optionally washing the crystals obtained in step (d); and
(g) drying the crystals obtained in any one of sstep (c) to (e).

Upadacitinib may be prepared according to the teachings of WO 2011/068881 A1 or WO 2017/066775 A1, in particular it may be prepared according to Example 3 or Example 4

of WO 2017/066775 A1. Phosphoric acid is commercially available (e.g. ortho-phosphoric acid 85% solution from Merck®).

In the first step (a) of the above described process upadacitinib is reacted with phosphoric acid in the presence of a suitable solvent, wherein the suitable solvent is selected from one or more alcohols, preferably selected from C_1-C_3 alcohols e.g. selected from the group consisting of methanol, ethanol, 1-propanol and 2-propanol, wherein methanol is most preferred. In a particularly preferred embodiment the suitable solvent comprises methanol. Most preferably, the solvent used is methanol.

The molar ratio of upadacitinib and phosphoric acid applied in step (a) is in the range of from 1.0: 1.0-3.0, preferably of from 1.0: 1.5-2.5 and most preferably of from 1.0: 1.7-2.3.

The upadacitinib (free compound) concentration in relation to the applied solvent in step (a) is in the range of from 80 – 120 g/L, preferably of from 90 – 110 g/L and most preferably of from 95 – 105 g/L such as 100 g/L.

The reaction may be carried out at room temperature or at elevated temperature e.g. between room temperature and reflux temperature. Preferably, the reaction is accomplished at room temperature.

Once the reaction is complete, one or more antisolvent(s) are added to the solution. Suitable antisolvents, which may be used are selected from one or more ethers. The one or more ethers may be selected from the group consisting of diethyl ether, diisopropyl ether and methyl *tert*-butyl ether. In one embodiment, the antisolvent used in step (b) is diisopropyl ether. Thereby, the solvent antisolvent ratio is in the range of from 1.0: 1.0 – 2.0, preferably of from 1.0: 1.0 – 1.5. The antisolvent is usually added until the solution turns slightly turbid.

In a subsequent step, upadacitinib phosphate seed crystals are added to the mixture obtained in step (b). The seed crystals may be prepared according to the procedure disclosed in example 3 of the present invention. Upadacitinib phosphate seed crystals obtained from any previous batch may be used as seed crystals of subsequent batches. The amount of seed crystals employed may range from about 1 to 20 weight%, preferably from about 1 to 10 weight% and most preferably from about 1 to 5 weight%, based on the weight of applied upadacitinib starting material.

Upadacitinib phosphate is then allowed to crystallize from the mother liquor. Usually, the material crystallizes gradually upon keeping the mixture at room temperature, preferably under stirring. The obrained suspension may be further stirred until plentiful crystallization has occurred e.g. for a period in the range of from 0.5 to 24 hours, preferably of from 0.5 to 12 hours and most preferably of from 0.5 to 3 hours. In order to increase the yield, the suspension may be further cooled e.g. to a temperature in the range of from 0 to 10 °C, e.g. of from 2 to 8 °C.

In the next step (e), at least a part of the crystals are separated from their mother liquor. Preferably, the crystals are separated from their mother liquor by any conventional method such as filtration, centrifugation, solvent evaporation or decantation, more preferably by filtration or centrifugation and most preferably by filtration.

In an optional step (f), the isolated crystals may be washed with one or more antisolvent(s). Suitable antisolvents, which may be used are selected from one or more ethers. The one or more ethers may be selected from the group consisting of diethyl ether, diisopropyl ether and methyl *tert*-butyl ether. In one embodiment, the antisolvent used in step (f) is diisopropyl ether.

Finally, the obtained crystals are dried, wherein drying may be performed at a temperature in the range of from about 20 to 120 °C, preferably of from about 20 to 100 °C , even more preferably of from about 40 to 80 °C. Drying may be performed at ambient pressure and/or under reduced pressure. Preferably, drying is performed at a pressure of about 100 mbar or less, more preferably of about 50 mbar or less for example a vacuum of about 30 mbar or less. Drying may be performed for a period in the range of from about 1 to 24 hours, preferably from about 1 to 12 hours and most preferably from about 2 to 6 hours.

Crystalline upadacitinib phosphate hydrate

The present invention also relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD comprising reflections at 2-Theta angles of:

(12.7 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (18.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (14.8 ± 0.2)°, (18.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (14.8 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (14.8 ± 0.2)°, (16.8 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (13.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (13.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (17.2 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (13.2 ± 0.2)°, (13.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (17.2 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)° and (24.1 ± 0.2)°; or

(12.7 ± 0.2)°, (13.2 ± 0.2)°, (13.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (17.2 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)°, (24.1 ± 0.2)° and (26.6 ± 0.2)°; or

(12.7 ± 0.2)°, (13.2 ± 0.2)°, (13.7 ± 0.2)°, (14.1 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (16.8 ± 0.2)°, (17.2 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)°, (24.1 ± 0.2)°, (26.6 ± 0.2)° and (28.1 ± 0.2)°,

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD comprising reflections at 2-Theta angles of:

(12.7 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (18.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (14.8 ± 0.1)°, (18.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (14.8 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (14.8 ± 0.1)°, (16.8 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (13.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (13.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (17.2 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (13.2 ± 0.1)°, (13.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (17.2 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)° and (24.1 ± 0.1)°; or

(12.7 ± 0.1)°, (13.2 ± 0.1)°, (13.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (17.2 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)°, (24.1 ± 0.1)° and (26.6 ± 0.1)°; or

(12.7 ± 0.1)°, (13.2 ± 0.1)°, (13.7 ± 0.1)°, (14.1 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (16.8 ± 0.1)°, (17.2 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)°, (24.1 ± 0.1)°, (26.6 ± 0.1)° and (28.1 ± 0.1)°,

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

In addition, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD comprising reflections at 2-Theta angles of (12.7 ± 0.2)°, (14.8 ± 0.2)°, (15.5 ± 0.2)°, (18.3 ± 0.2)°, (19.3 ± 0.2)°, (20.4 ± 0.2)°, (24.1 ± 0.2)°, (24.4 ± 0.2)°, (25.1 ± 0.2)° and (28.1 ± 0.2), when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Alternatively, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD comprising reflections at 2-Theta angles of (12.7 ± 0.1)°, (14.8 ± 0.1)°, (15.5 ± 0.1)°, (18.3 ± 0.1)°, (19.3 ± 0.1)°, (20.4 ± 0.1)°, (24.1 ± 0.1)°, (24.4 ± 0.1)°, (25.1 ± 0.1)° and (28.1 ± 0.1), when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Moreover, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD comprising no reflection at 2-Theta angles in the range of from 2.0 to 12.4° 2-Theta, preferably in the range of from 2.0 to 12.2° 2-Theta, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

The present invention also relates to crystalline upadacitinib phosphate hydrate characterized by having a PXRD essentially the same as shown in Figure 5 of the present invention, when

measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.

Moreover, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(2969 ± 4) cm^{-1}, (1540 ± 4) cm^{-1} and (1149 ± 4) cm^{-1} or;

(2969 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1} and (1149 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1334 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1334 ± 4) cm^{-1}, (1272 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1600 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1334 ± 4) cm^{-1}, (1272 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1600 ± 4) cm^{-1}, (1581 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1334 ± 4) cm^{-1}, (1272 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1}; or

(2969 ± 4) cm^{-1}, (1600 ± 4) cm^{-1}, (1581 ± 4) cm^{-1}, (1540 ± 4) cm^{-1}, (1461 ± 4) cm^{-1}, (1426 ± 4) cm^{-1}, (1334 ± 4) cm^{-1}, (1272 ± 4) cm^{-1}, (1149 ± 4) cm^{-1} and (942 ± 4) cm^{-1},

when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

Alternatively, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having an FTIR spectrum comprising peaks at wavenumbers of:

(2969 ± 2) cm^{-1}, (1540 ± 2) cm^{-1} and (1149 ± 2) cm^{-1} or;

(2969 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1} and (1149 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1334 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1334 ± 2) cm^{-1}, (1272 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1600 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1334 ± 2) cm^{-1}, (1272 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1600 ± 2) cm^{-1}, (1581 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1334 ± 2) cm^{-1}, (1272 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1}; or

(2969 ± 2) cm^{-1}, (1600 ± 2) cm^{-1}, (1581 ± 2) cm^{-1}, (1540 ± 2) cm^{-1}, (1461 ± 2) cm^{-1}, (1426 ± 2) cm^{-1}, (1334 ± 2) cm^{-1}, (1272 ± 2) cm^{-1}, (1149 ± 2) cm^{-1} and (942 ± 2) cm^{-1},

when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

In addition, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having an FTIR spectrum essentially the same as shown in Figure 6 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.

Furthermore, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a first endothermic peak in the range of from 40 to 90 °C, when measured at a heating rate of 10 K/min.

The present invention also relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a first endothermic peak having an onset at a temperature of (51 ± 10)°C, preferably of (51 ± 5)°C, even more preferably of (51 ± 3)°C and most preferably of (51 ± 1)°C, when measured at a heating rate of 10 K/min.

The present invention also relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a first endothermic peak having a peak maximum at a temperature of (80 ± 10)°C, preferably of (80 ± 5)°C, even more preferably of (80 ± 3)°C and most preferably of (80 ± 1)°C, when measured a heating rate of 10 K/min.

Moreover, the invention relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a first endothermic peak with an enthalpy of (143 ± 10) J/g, preferably of (143 ± 5) J/g, even more preferably of (143 ± 3) J/g and most preferably of (143 ± 1) J/g, when measured at a heating rate of 10 K/min.

Furthermore, the present invention relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a second endothermic peak having an onset at a temperature of (175 ± 5)°C, preferably of (175 ± 3)°C, even more preferably of (175 ± 2)°C and most preferably of (175 ± 1)°C, when measured at a heating rate of 10 K/min.

The present invention also relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a second endothermic peak having a peak maximum at a temperature of (178 ± 5)°C, preferably of (178 ± 3)°C, even more preferably of (178 ± 2)°C and most preferably of (178 ± 1)°C, when measured a heating rate of 10 K/min.

Moreover, the invention relates to crystalline upadacitinib phosphate hydrate characterized by having a DSC curve comprising an endothermic peak, preferably a second endothermic peak with an enthalpy of (60 ± 5) J/g, preferably of (60 ± 3) J/g, even more preferably of (60 ± 2) J/g and most preferably of (60 ± 1) J/g, when measured at a heating rate of 10 K/min.

In another embodiment, the present invention relates to crystalline updadacitinib phosphate hydrate, characterized by having a TGA curve showing a mass loss of about 5.6 w-% based on the weight of the crystalline upadacitinib phosphate, when heated from 25 to 90 °C at a rate of 10 K/min.

Preferably, the crystalline upadacitinib phosphate hydrate of the present invention as defined in any one of the embodiments described above is a *di*hydrate.

In one embodiment, the present invention relates to crystalline updadacitinib phosphate hydrate characterized by showing a mass change of not more than 0.5 w-%, preferably of not more than 0.4 w-%, more preferably of not more than 0.3 w-% based on the weight of the crystalline form, when measured with GMS at a relative humidity in the range of from 0 to 75% and a temperature of (25.0 ± 0.1)°C.

In one embodiment, the present invention relates to crystalline updadacitinib phosphate hydrate characterized by showing a mass change of not more than 1.5 w-%, preferably of not more than 1.2 w-%, more preferably of not more than 1.1 w-% based on the weight of the crystalline hydrate, when measured with GMS at a relative humidity in the range of from 20 to 90% and a temperature of (25.0 ± 0.1)°C.

In another aspect, the present invention relates to a process for the preparation of the crystalline upadacitinib phosphate hydrate as defined in any one of the above described embodiments comprising subjecting crystalline upadacitinib phosphate anhydrate of the present invention to an atmosphere having a relative humidity of at least 80%, preferably of at least 85%, when measured at a temperature of (25.0 ± 0.1)°C.In a further aspect the present invention relates to

the use of the crystalline upadacitinib phosphate of the present invention as defined in any one of the embodiments described above for the preparation of a pharmaceutical composition.

In a further aspect, the present invention relates to a pharmaceutical composition comprising the crystalline upadacitinib phosphate of the present invention as defined in any one of the embodiments described above, preferably in an effective and/or predetermined amount, and at least one pharmaceutically acceptable excipient. Preferably, the pharmaceutical composition of the present invention is an oral solid dosage form, such as a tablet or a capsule. More preferably, the pharmaceutical composition of the present invention is a tablet e.g. a film-coated tablet. Most preferably, the pharmaceutical composition of the present invention is an extended release film-coated tablet.

The at least one pharmaceutically acceptable excipient, which is comprised in the pharmaceutical composition of the present invention, is preferably selected from the group consisting of fillers, pH-modifiers, release control polymers, lubricants, glidants, coating materials and combinations thereof. In one embodiment all of these pharmaceutically acceptable excipients are comprised by the pharmaceutical composition of the present invention.

In a preferred embodiment, the at least one pharmaceutically acceptable excipient is selected from the group consisting of microcrystalline cellulose, mannitol, tartaric acid, hydroxyproyplmethyl cellulose, colloidal silicon dioxide, magnesium stearate and Opadry®. In a preferred embodiment, all of these pharmaceutically acceptable excipients are comprised by the pharmaceutical composition of the present invention.

Preferably, the present invention relates to a pharmaceutical composition as describe above, wherein the predetermined and/or effective amount of crystalline upadacitinib phosphate is selected from the group consisting of 7.5 mg, 15 mg, 24 mg, 30 mg and 45 mg calculated as upadacitinib. Most preferably, the invention relates to a pharmaceutical composition as describe above, wherein the predetermined and/or effective amount of crystalline upadacitinib phosphate is 15 mg or 30 mg calculated as upadacitinib.

Preferably, the present invention relates to a pharmaceutical composition as defined in any one of the above described embodiments, wherein the pharmaceutical composition is to be administered once-daily.

In a further aspect, the present invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use as a medicament.

In yet another aspect, the present invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment or prophylaxis of a condition selected from the group consisting of rheumatoid arthritis, psoriasis, hidrandenitis suppurativa, ulcerative colitis, psoriatic arthritis, atopic dermatitis, Crohn's disease, giant cell arteritis and ankylosing spondylitis. Most preferably, the invention relates to the pharmaceutical composition as defined in any one of the above described embodiments for use in the treatment or prophylaxis of rheumatoid arthritis.

In another embodiment, the present invention is directed to a method of treating or prophylactically preventing a condition selected from the group consisting of rheumatoid arthritis, psoriasis, hidrandenitis suppurativa, ulcerative colitis, psoriatic arthritis, atopic dermatitis, Crohn's disease, giant cell arteritis and ankylosing spondylitis by administering the pharmaceutical composition as defined in any one of the above described embodiments to a patient in need of such a treatment and/or prophylaxis. Preferably, the condition is rheumatoid arthritis.

EXAMPLES

The following non-limiting examples are illustrative for the disclosure and are not to be construed as to be in any way limiting for the scope of the invention.

Analytical Methods

Powder X-ray diffraction was performed with a PANalytical X'Pert PRO diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, Cu-Kalpha$_{1,2}$ radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. Diffractograms were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a stepsize of 0.013° 2-Theta with 40s per step (255 channels) in the angular range of 2° to 40° 2-Theta at ambient conditions. A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta.

FTIR spectrum was recorded (obtained) on a MKII Golden Gate™ Single Reflection Diamond ATR cell with a Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution at a temperature in the range of from 20 to 30 °C. To record a spectrum a spatula tip of the sample was applied

to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum. A typical precision of the wavenumber values is in the range of ± 4 cm^{-1} preferably of ± 2 cm^{-1}.

DSC was performed on a Mettler Polymer DSC R instrument. Upadacitinib phosphate (2.63 mg anhydrate for figure 3 and 3.87 mg hydrate for figure 7) was heated in a 40 microliter aluminium pan with a pierced aluminium lid from 25 to 250 °C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas.

TGA was performed on a Mettler TGA/DSC 1 instrument. Upadacitinib phosphate (8.28 mg anhydrate for figure 4 and 6.46 mg hydrate for figure 8) was heated in a 100 microliter aluminum pan closed with an aluminum lid. The lid was automatically pierced at the beginning of the measurement. The samples were heated from 25 to 250 °C at a rate of 10 K/min. Nitrogen (purge rate 50 mL/min) was used as purge gas. **Example 1:** Preparation of crystalline upadacitinib phosphate

Upadacitinib (500 mg, 1.31 mmol, e.g. prepared according to Example 3 of WO 2017/066775 A1) was dissolved in methanol (5 mL) at RT followed by addition of aqueous phosphoric acid (assay 85%, 100 microliter, 1.48 mmol). Thereafter, diisopropyl ether (6.5 mL) was added carefully until the solution became slightly turbid. Seed crystals (prepared according to example 3) were charged before another 2 drops of diisopropyl ether were added and the mixture was stirred for 3 hours at RT. Subsequently, the mixture was allowed to stand at a temperature ranging from 2-8 °C for about 48 hours, before the crystals were collected by filtration, washed with diisopropyl ether and dried at 80 °C under vacuum (25 mbar) for 1 hour.

Example 2: Solid-state characterization of upadacitinib phosphate

Powder X-ray diffraction

A representative diffractogram of upadacitinib phosphate is displayed in Figure 1 herein. The corresponding reflection list is provided in Table 1 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
7.4	17.2	22.7	27.0
12.6	17.6	23.1	27.9
13.1	18.9	23.5	29.0

13.8	19.3	24.7	29.7
14.8	20.3	25.2	
15.3	22.3	26.0	

Table 1: PXRD reflections of upadacitinib phosphate in the range of from 2 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta.

Fourier transform infrared spectroscopy

A representative FTIR spectrum of upadacitinib phosphate according to the present invention is displayed in Figure 2 and the corresponding peak list is provided in Table 2 below.

Wavenumber [cm^{-1}]	**Wavenumber [cm^{-1}]**
3143	1100
1578	985
1549	946
1462	910
1428	883
1335	759
1300	726
1269	695
1229	667
1150	

Table 2: FTIR peak list of upadacitinib phosphate according to the present invention; a typical precision of the wavenumbers is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}.

Differential scanning calorimetry

The DSC curve of upadacitinib phosphate shows an endothermic peak with an onset temperature of about 175 °C, a peak temperature of about 178 °C and an enthalpy of about 60 J/g, which is due to a concomitant melting and decomposition process (see also Figure 3 herein).

Thermogravimetric analysis

The TGA curve of upadacitinib phosphate shows a mass loss of only about 0.2 w-% in the temperature range of about 25 to 170 °C and a mass loss of only about 0.5 w-% from the start of the measurement at about 25 °C until melting/decomposition starts at about 175 °C. Hence, it can be concluded that neither water nor organic solvents are part of the crystal structure but the mass loss may rather be due to the release of residual solvent/water, which is loosely bound

on the surface. Only at temperatures above about 175 °C, where upadacitinib phosphate starts to melt a significant weight loss indicates concomitant decomposition (see also Figure 4 herein).

Example 3: Preparation of upadacitinib phosphate seed crystals

Upadacitinib (50 mg, 0.13 mmol, e.g. prepared according to Example 3 of WO 2017/066775 A1) was reacted with aqueous phosphoric acid (assay 85%, 9 microliter, 0.13 mmol) in aqueous methanol (90 v-%, 0.5 mL). The obtained solution was shaken at RT for 3 hours followed by storage at -20 °C. Since no crystallization occurred the solvent was allowed to evaporate naturally at RT. The residue was dissolved in isopropanol (0.8 mL) and the solution was allowed to evaporate naturally at RT. Since again no crystallization occurred the residue was dissolved in acetone (0.8 mL) and *n*-heptane was added carefully until the solution became slightly turbid. The mixture was stored at 2-8 °C but still no crystallization took place. The solvent was thus allowed to evaporate naturally and the residue was dispersed in diethyl ether for 4 hours leading to the receipt of crystalline upadacitinib phosphate.

Example 4: Preparation of crystalline upadacitinib phosphate

Upadacitinib (500 mg, 1.31 mmol, e.g. prepared according to Example 3 of WO 2017/066775 A1) was dissolved in methanol (5 mL) at RT followed by addition of aqueous phosphoric acid (assay 85%, 200 microliter, 2.97 mmol). Thereafter, diisopropyl ether (6.1 mL) was added carefully until the solution became slightly turbid. Seed crystals (prepared according to example 3) were charged and the mixture was stirred for 1 hour at RT. Subsequently, the mixture was allowed to stand at a temperature ranging from 2-8 °C for about 16 hours, before the crystals were collected by filtration and dried at 80 °C under vacuum (25 mbar) for 4 hour.

Example 5: Preparation of crystalline upadacitinib phosphate hydrate

Crystalline upadacitinib phosphate (500 mg, 1.31 mmol, e.g. prepared according to Example 1 or 3 herein) was stored open for 20 hours at an environment having a temperature of (25 ± 1)°C and a relative humidity of (85 ± 1)%. Crystalline upadacitinib phosphate hydrate was obtained quantitatively.

Example 6: Solid-state characterization of upadacitinib phosphate hydrate

Powder X-ray diffraction

A representative diffractogram of upadacitinib phosphate hydrate is displayed in Figure 5 herein. The corresponding reflection list is provided in Table 3 below.

Reflection position [° 2-Theta]	Reflection position [° 2-Theta]	Reflection position [° 2-Theta]
12.7	18.7	24.1
13.2	18.9	24.4
13.7	19.3	25.1
14.1	19.5	25.4
14.8	20.4	26.0
15.5	22.0	26.6
15.7	22.4	27.7
16.8	22.8	28.1
17.2	23.1	28.5
18.3	23.7	

Table 3: PXRD reflections of upadacitinib phosphate hydrate in the range of from 2 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta.

Fourier transform infrared spectroscopy

A representative FTIR spectrum of upadacitinib phosphate hydrate according to the present invention is displayed in Figure 6 and the corresponding peak list is provided in Table 4 below.

Wavenumber [cm^{-1}]	Wavenumber [cm^{-1}]	Wavenumber [cm^{-1}]
2969	1426	942
2738	1334	882
2324	1307	825
1600	1272	764
1581	1226	734
1540	1194	698
1489	1149	669
1461	1119	

Table 4: FTIR peak list of upadacitinib phosphate hydrate according to the present invention; a typical precision of the wavenumbers is in the range of ± 4 cm^{-1}, preferably of ± 2 cm^{-1}.

Differential scanning calorimetry

The DSC curve of upadacitinib phosphate hydrate shows a first broad endothermic peak in the range of about 40 to 90°C with an onset temperature of about 51 °C, a peak temperature of about 80 °C and an enthalpy of about 143 J/g, which is due to the release of water from the crystal structure. After dehydration the crystalline anhydrous upadacitinib phosphate according to the present invention is present, which then melts followed by decomposition as indicated by the second endothermic peak with an onset temperature of about 176 °C, a peak temperature of about 178 °C and an enthalpy of about 57 J/g (see also Figure 7 herein).

Thermogravimetric analysis

The TGA curve of upadacitinib phosphate hydrate shows a mass loss of about 5.6 w-% in the temperature range of about 25 to 90 °C, which corresponds well to the broad dehydration endotherm observed in the DSC curve and is due to the release of about 1.9 mol equivalents of water (see also Figure 8 herein). Hence, it can be concluded that the hydrate of the present invention is a *di*hydrate.

Gravimetric moisture sorption

Moisture sorption isotherms were recorded along with other samples with an SPSx-1µ moisture sorption analyzer (ProUmid, Ulm). The measurement cycle was started at ambient relative humidity (RH) of 25%. Relative humidity was then decreased to 5% RH in 5% steps, followed by a further decrease to 3% RH and to 0% RH. Afterwards RH was increased from 0% to 90% RH in a sorption cycle and decreased to 0 % in a desorption cycle in 5% steps. Finally the RH was increased to a relative humidity of 25% in 5% steps.

The time per step was set to a minimum of 2 hours and a maximum of 6 hours. If an equilibrium condition with a constant mass of ± 0.01% within 1 hour was reached before the maximum time for all examined samples the sequential humidity step was applied before the maximum time of 6 hours. If no equilibrium was achieved the consecutive humidity step was applied after the maximum time of 6 hours. The temperature was 25 ± 0.1 °C.

The displayed equilibrium curve shows the sorption (marked by triangles) and desorption curve (marked by squares) of crystalline upadacitinib phosphate between 0 and 90% RH. The experiment revealed that the crystalline anhydrous form of upadacitinib phosphate according to the present invention is stable at and below 75% RH and transforms to the crystalline dihydrate of the present invention above 75% RH. The crystalline dihydrate is stable at and

above 20% RH and transforms back to the crystalline anhydrate below 20% RH (see also Figure 9 herein).

Thus, crystalline upadacitinib phosphate of the present invention remains crystalline when subjected to an atmosphere of variable relative humidity, because one crystalline form reversibly transforms into another crystalline form. In particular, no amorphization is seen at low relative humidity, and no deliquescence is seen up to 90% relative humidity. Thus interconversion of crystalline forms into one another upon humidity stress preserves the overall crystallinity of upadacitinib phosphate.

Comparative Example 1: Gravimetric moisture sorption of upadacitinib tartrate

Moisture sorption isotherms were recorded along with other samples with an SPSx-1µ moisture sorption analyzer (ProUmid, Ulm). The measurement cycle was started at ambient relative humidity (RH) of 25%. Relative humidity was then decreased to 5% RH in 5% steps, followed by a further decrease to 3% RH and to 0% RH. Afterwards RH was increased from 0% to 90% RH in a sorption cycle.

The time per step was set to a minimum of 2 hours and a maximum of 6 hours. If an equilibrium condition with a constant mass of ± 0.01% within 1 hour was reached before the maximum time for all examined samples the sequential humidity step was applied before the maximum time of 6 hours. If no equilibrium was achieved the consecutive humidity step was applied after the maximum time of 6 hours. The temperature was 25 ± 0.1°C.

The displayed equilibrium curve shows the initial desorption (marked by squares) from 25 – 0% RH, as well as the consecutive sorption cycle (marked by triangles) from 0 – 90% RH of upadacitinib tartrate of WO 2017/066775 A1, Example 8, Method B. In contrary to upadacitinib phosphate, where the starting form was the crystalline anhydrate, the starting form of upadacitinib tartrate was the hydrated form. Therefore in Figure 11 the sample mass at 0% RH was set as reference weight (for the anhydrate), and all other points were adapted to this weight accordingly, in order to be directly comparable with the GMS curve of upadacitinib phosphate from Figure 10. As can be seen from Figure 11 herein during desorption the sample shows a high mass loss of about 12%, which is due to loss of water. In the course of this dehydration the tartrate becomes amorphous. During the following sorption cycle the sample takes up water again and liquefies.

Comparative Example 2:

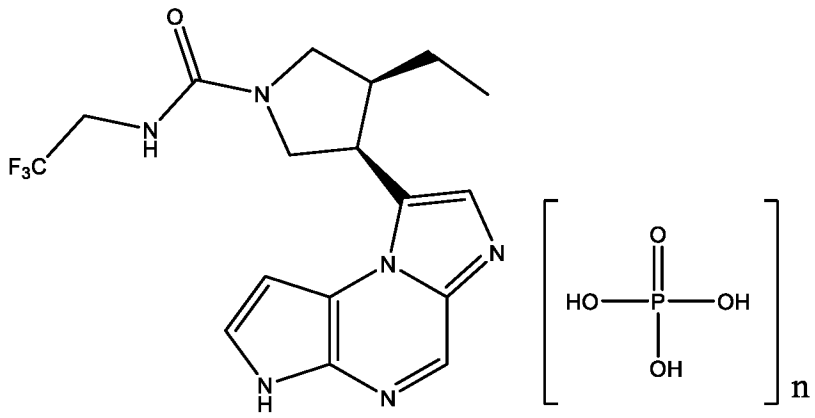
Chemical stability of upadacitinib phosphate and upadacitinib maleate was analyzed when exposed to 60°C/30% RH for 7 days or to 60°C/75% RH for 7 days. While upadacitinib phosphate was chemically stable, upadacitinib maleate showed major degradation at 60°C/75% RH (see Table 5).

Sample	Upadacitinib maleate	Upadacitinib phosphate
Initial sum of impurities	0.36%	< 0.05%
60°C/30% RH, 7 days	0.36%	< 0.05%
60°C/75% RH, 7 days	10.25%	< 0.05%

Table 5: Chemical stability of upadacitinib maleate and upadacitinib phosphate when exposed to a temperature of 60°C at different humidity.

CLAIMS

1) Crystalline upadacitinib phosphate.
2) The crystalline upadacitinib phosphate of claim 1, characterized by the chemical structure according to Formula (II)



(II),

wherein n is in the range of from 1.8 to 2.2.

3) The crystalline upadacitinib phosphate of claim 1 or 2, characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (7.4 ± 0.2)°, (17.6 ± 0.2)° and (19.3 ± 0.2)°, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.
4) The crystalline upadacitinib phosphate of claim 3 characterized by having a powder X-ray diffractogram comprising additional reflections at 2-Theta angles of (13.1 ± 0.2)° and (24.7 ± 0.2)°, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm.
5) The crystalline upadacitinib phosphate as defined in any one of the preceding claims, characterized by having an FTIR spectrum comprising peaks at wavenumbers of (3143 ± 4) cm^{-1}, (1549 ± 4) cm^{-1} and (1150 ± 4) cm^{-1}, when measured at a temperature in the range of from 20 to 30 °C with a diamond ATR cell.
6) The crystalline upadacitinib phosphate as defined in any one of the preceding claims, characterized by having a DSC curve comprising an endothermic peak having an onset at a temperature of (175 ± 5)°C, when measured at a heating rate of 10 K/min.
7) The crystalline upadacitinib phosphate as defined in any one of the preceding claims, characterized by having a TGA curve showing a mass loss of not more than 0.5

weight%, based on the weight of the crystalline upadacitinib phosphate, when heated from 25 to 175 °C at a rate of 10 K/min.

8) The crystalline upadacitinib phosphate as defined in any one of the preceding claims, characterized as bein anhydrous and non-solvated.

9) Use of the crystalline upadacitinib phosphate as defined in any one of the preceding claims for the preparation of a pharmaceutical composition.

10) A pharmaceutical composition comprising the crystalline upadacitinib phosphate as defined in any one of claims 1 to 8 and at least one pharmaceutically acceptable excipient.

11) The pharmaceutical composition of claim 10, wherein the pharmaceutical composition is an oral solid dosage form.

12) The pharmaceutical composition of claim 11, wherein the oral solid dosage form is an extended release film-coated tablet.

13) The pharmaceutical composition as defined in any one of claims 10 to 12, comprising 15 or 30 mg of the crystalline upadacitinib phosphate as defined in any one of claims 1 to 8, calculated as upadacitinib.

14) The pharmaceutical composition as defined in any one of claims 10 to 13 for use as a medicament.

15) The pharmaceutical composition as defined in any one of claims 10 to 13 for use in the treatment of rheumatoid arthritis.

Figure 1

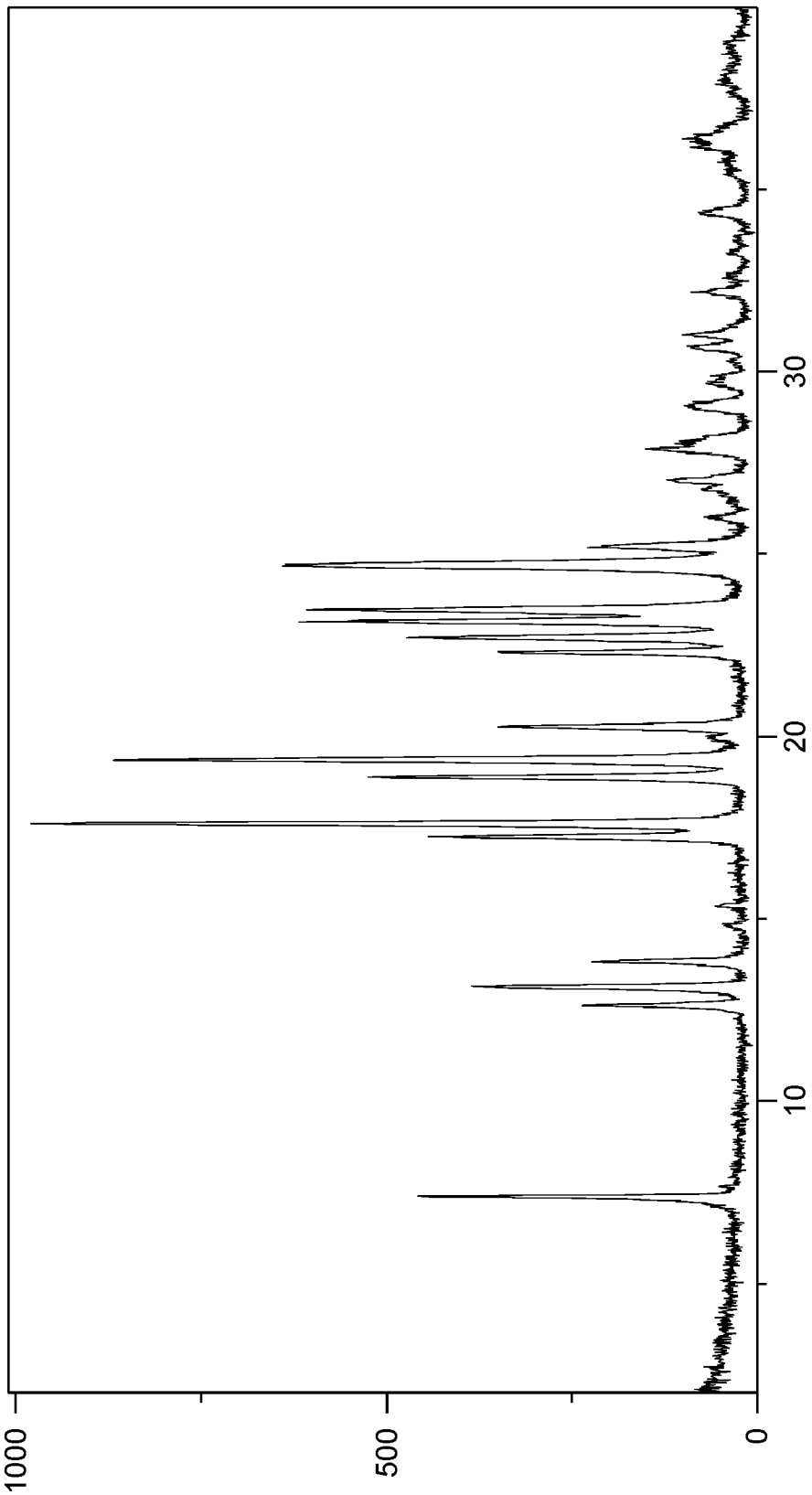


Figure 2

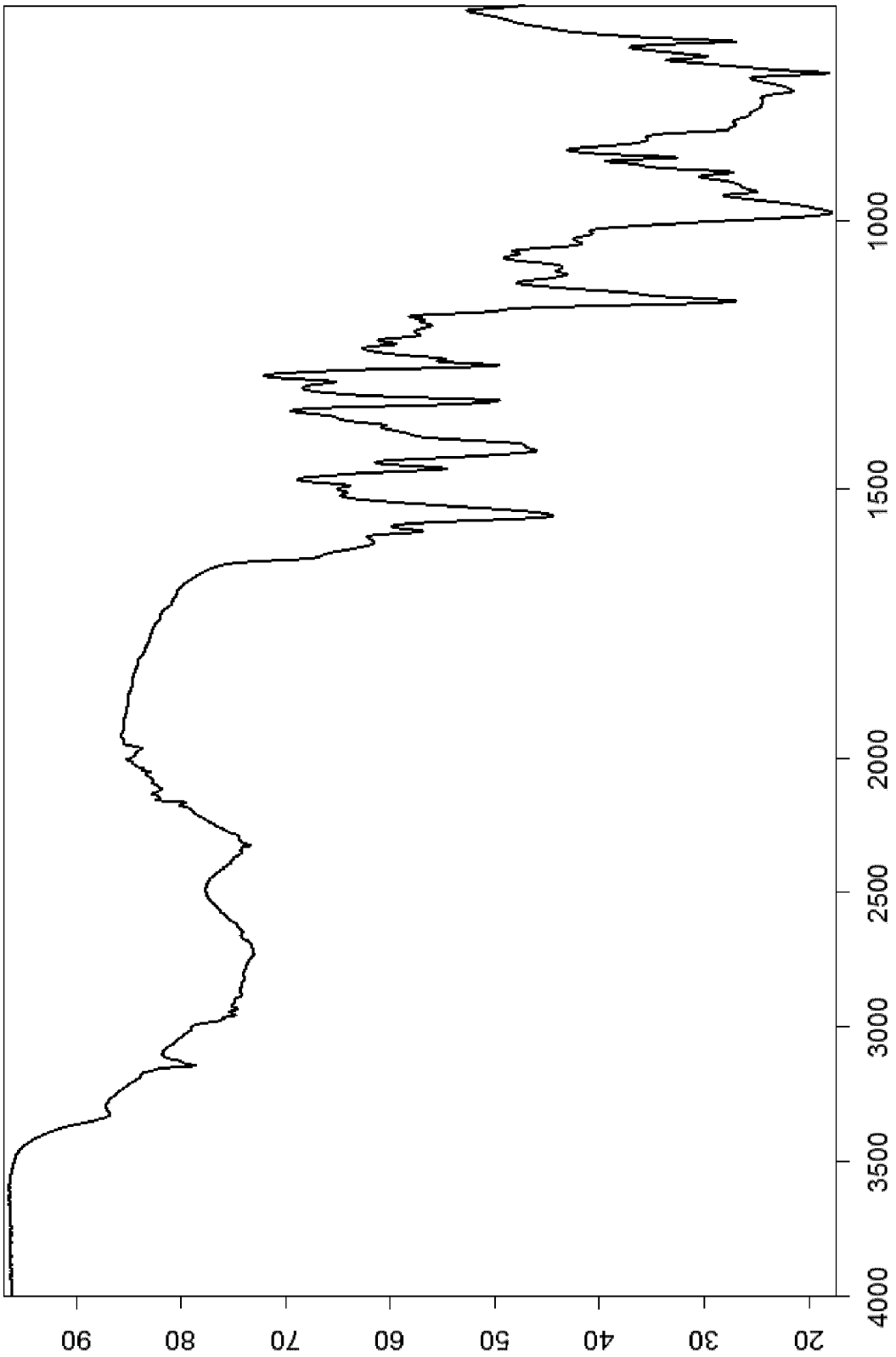


Figure 3

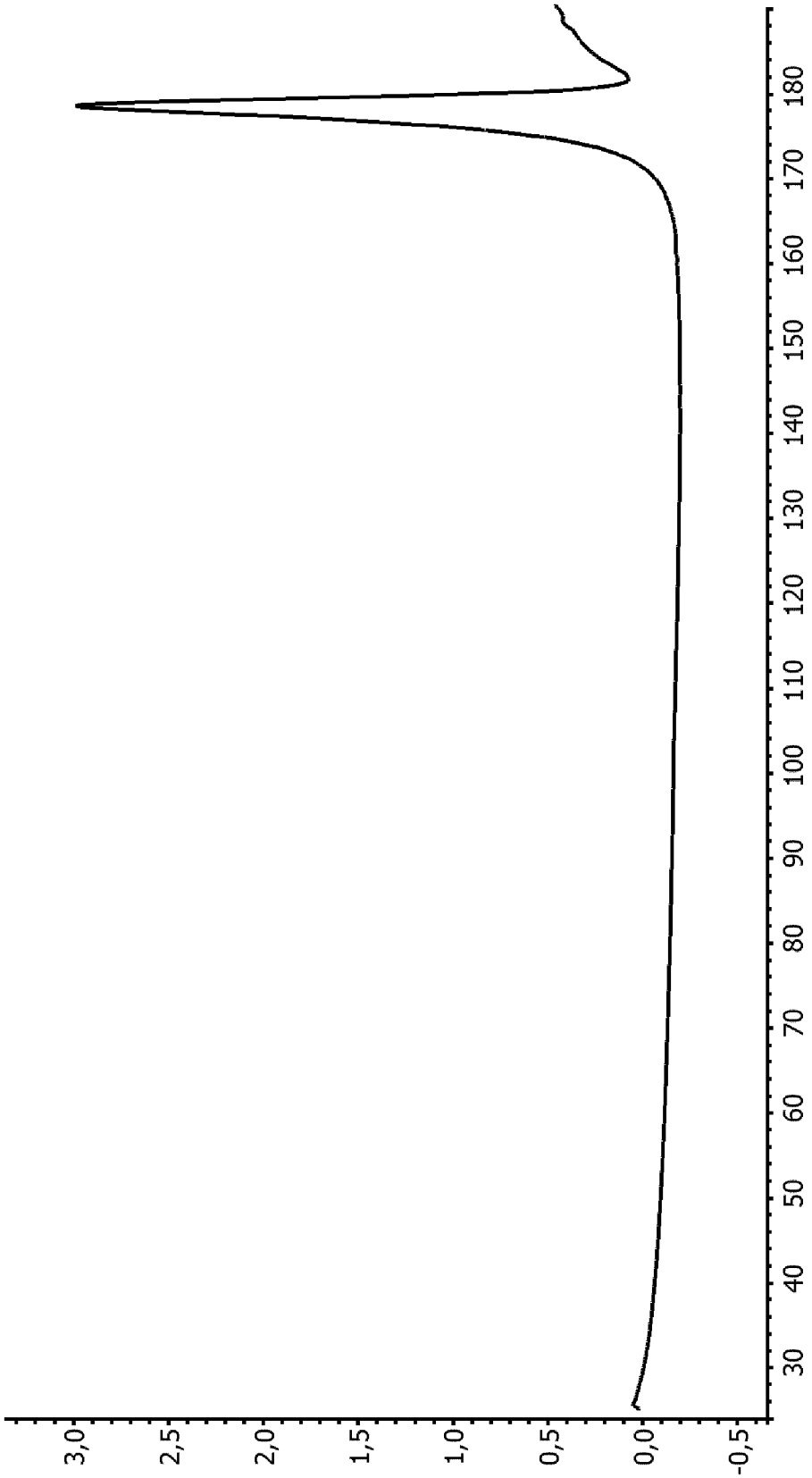

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Figure 4

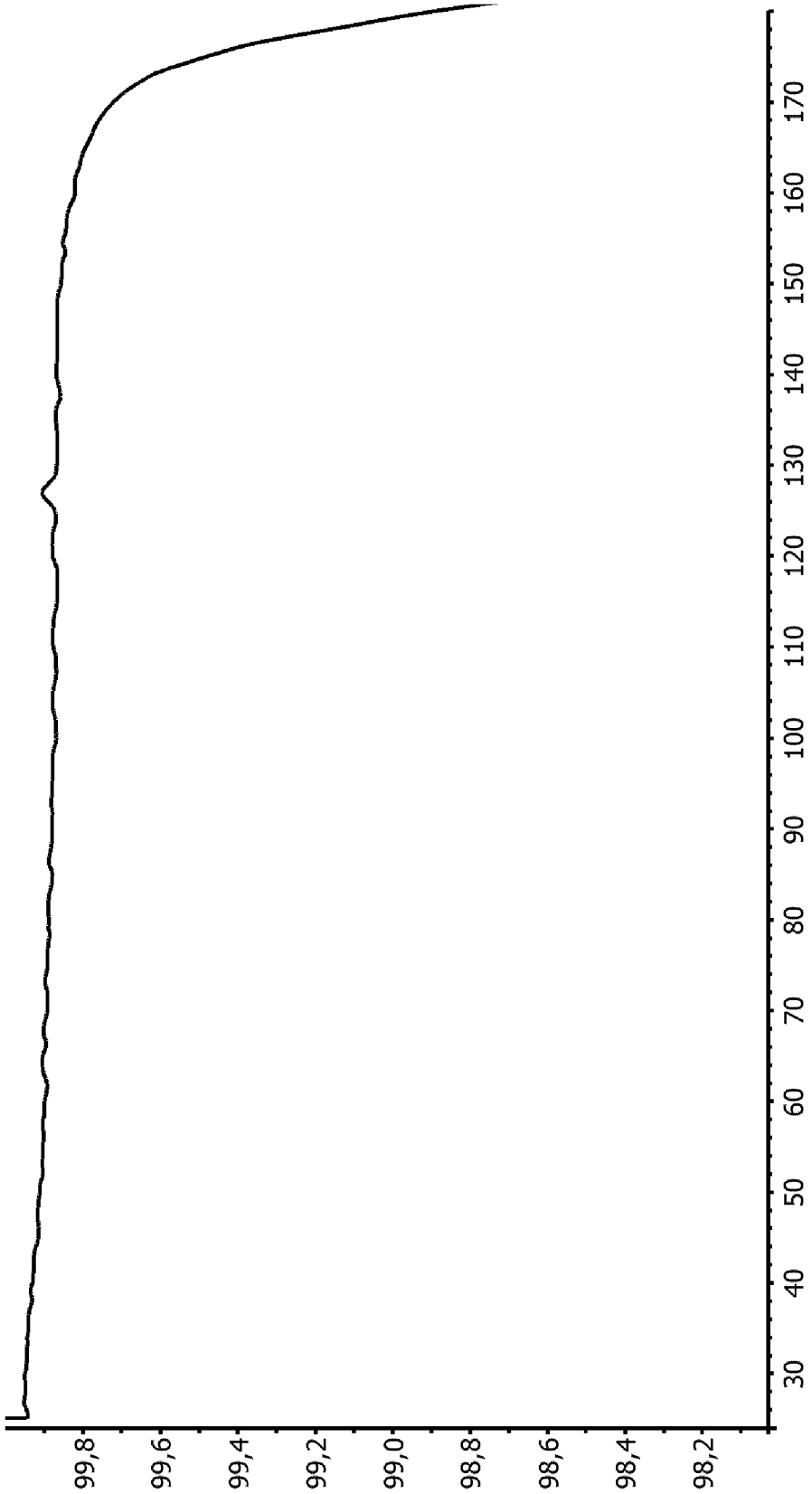
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Figure 5

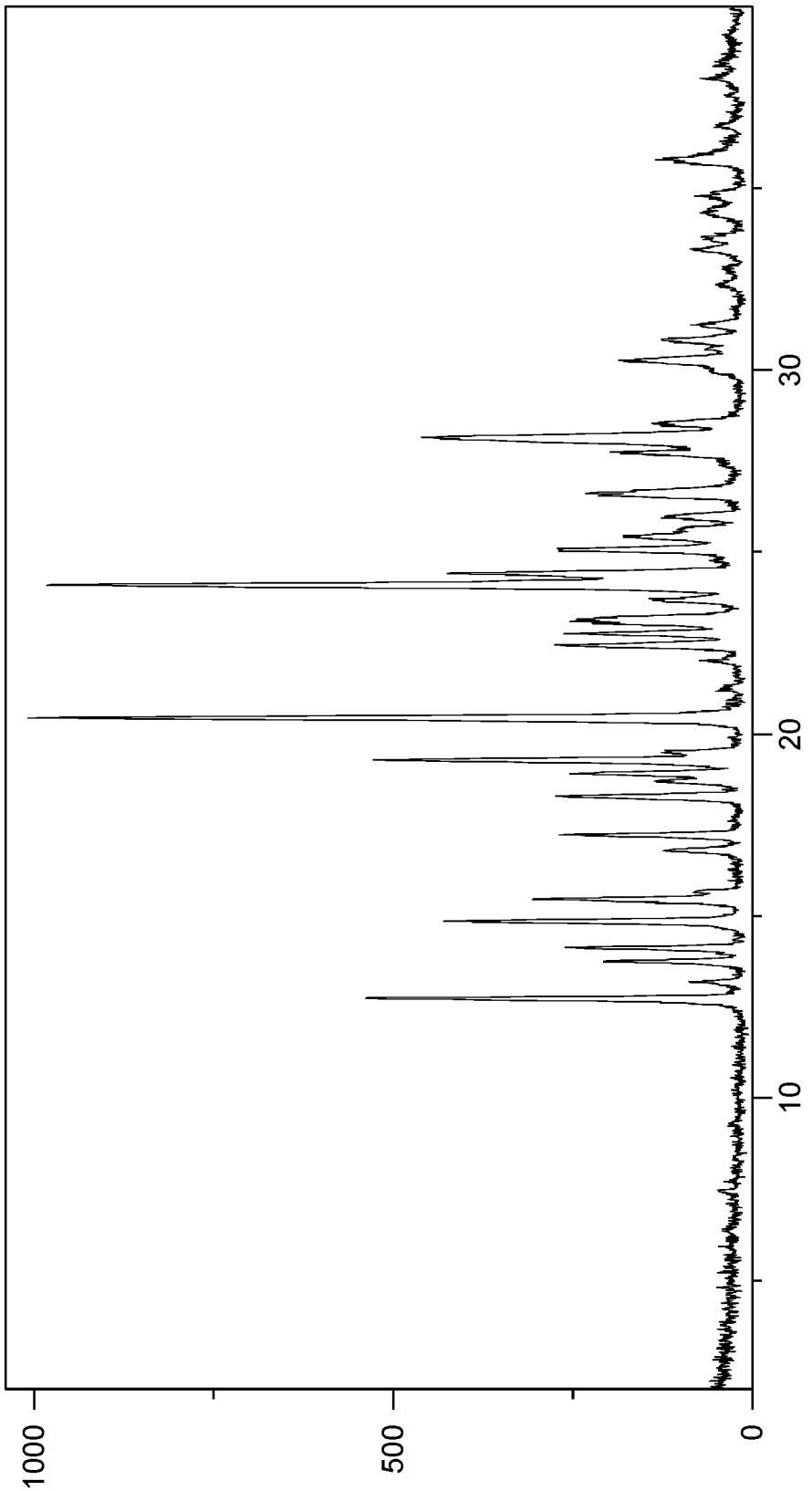

Figure 6

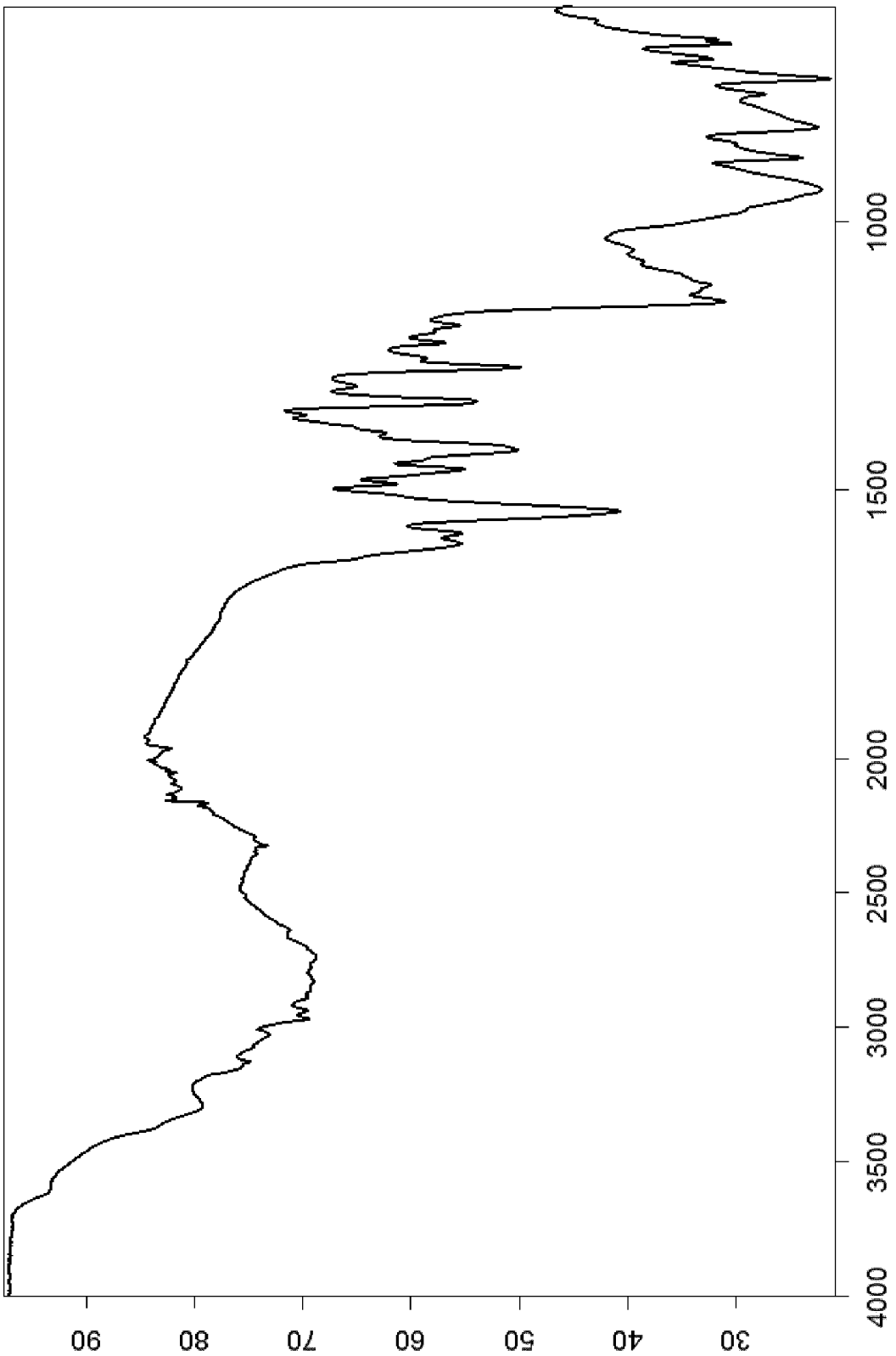

Figure 7

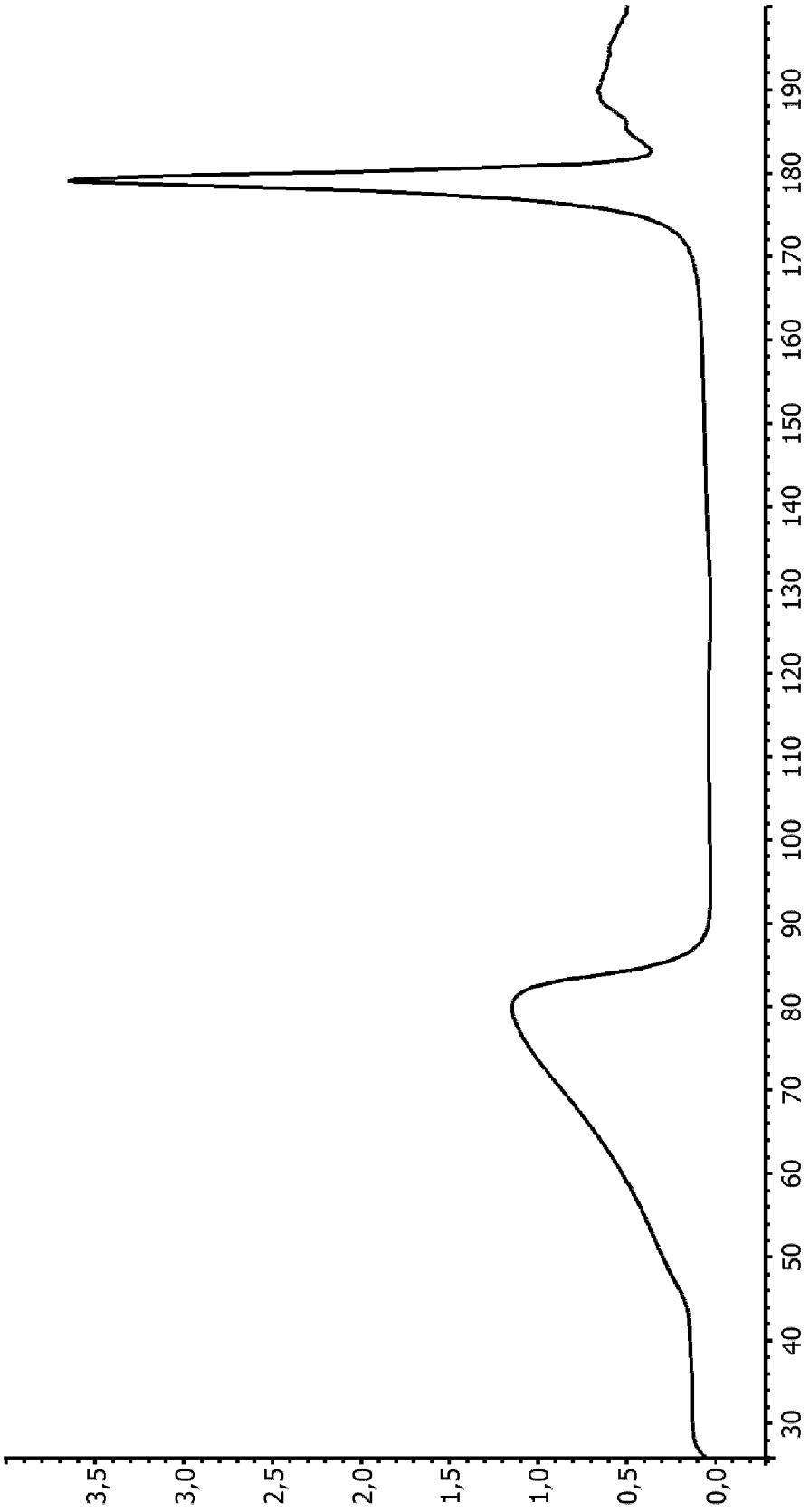
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Figure 8

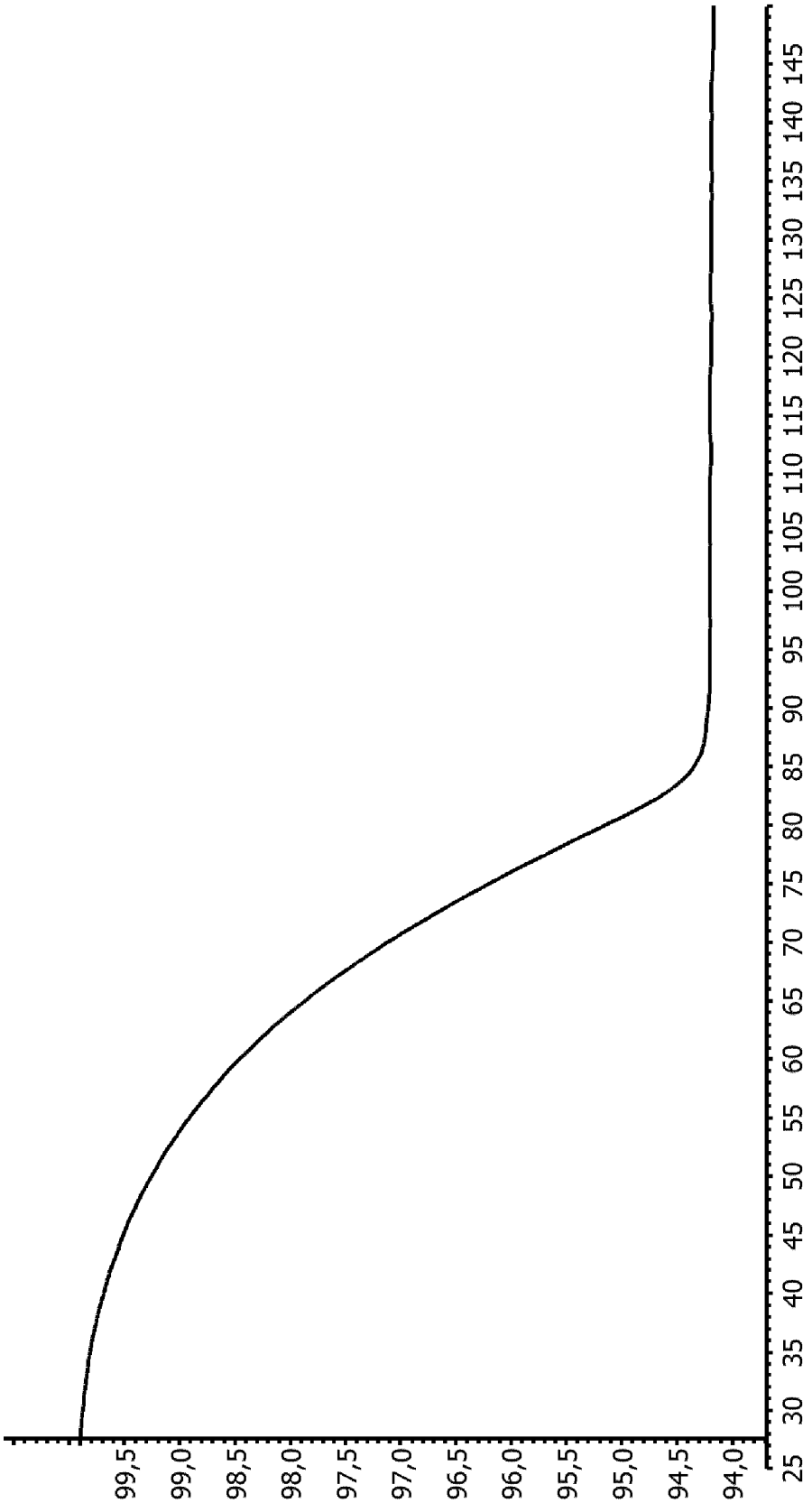
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Figure 9

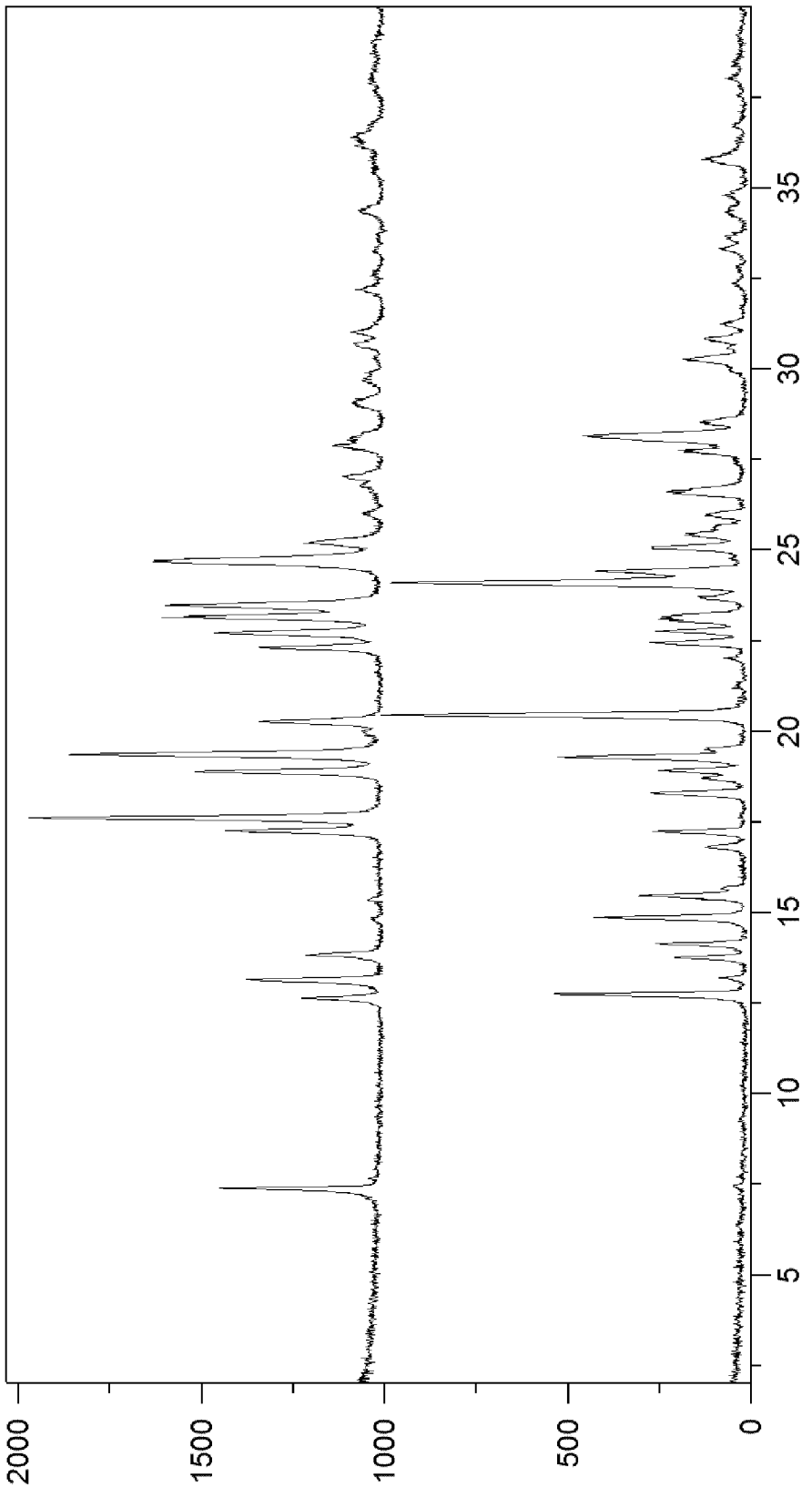


Figure 10

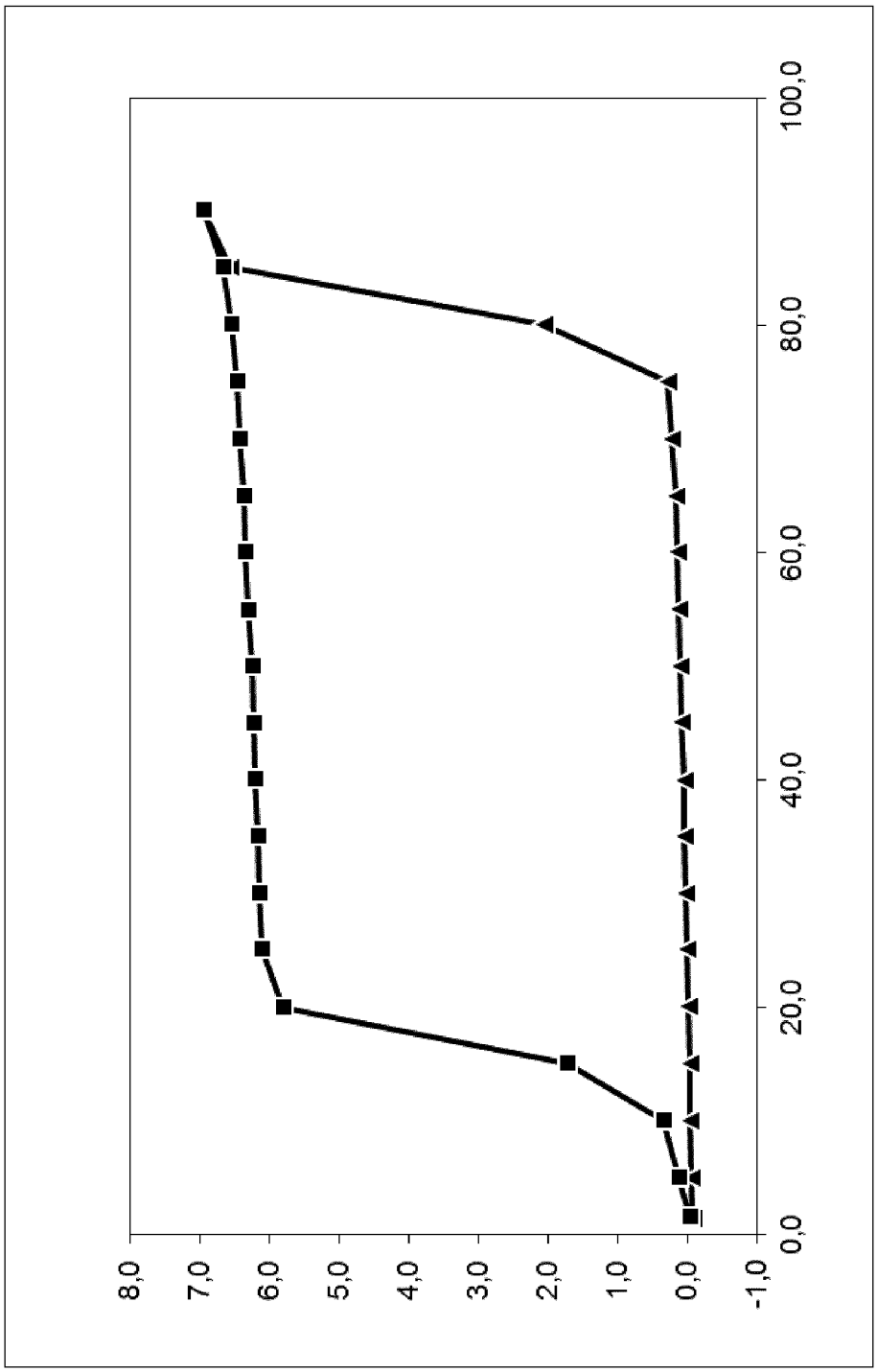
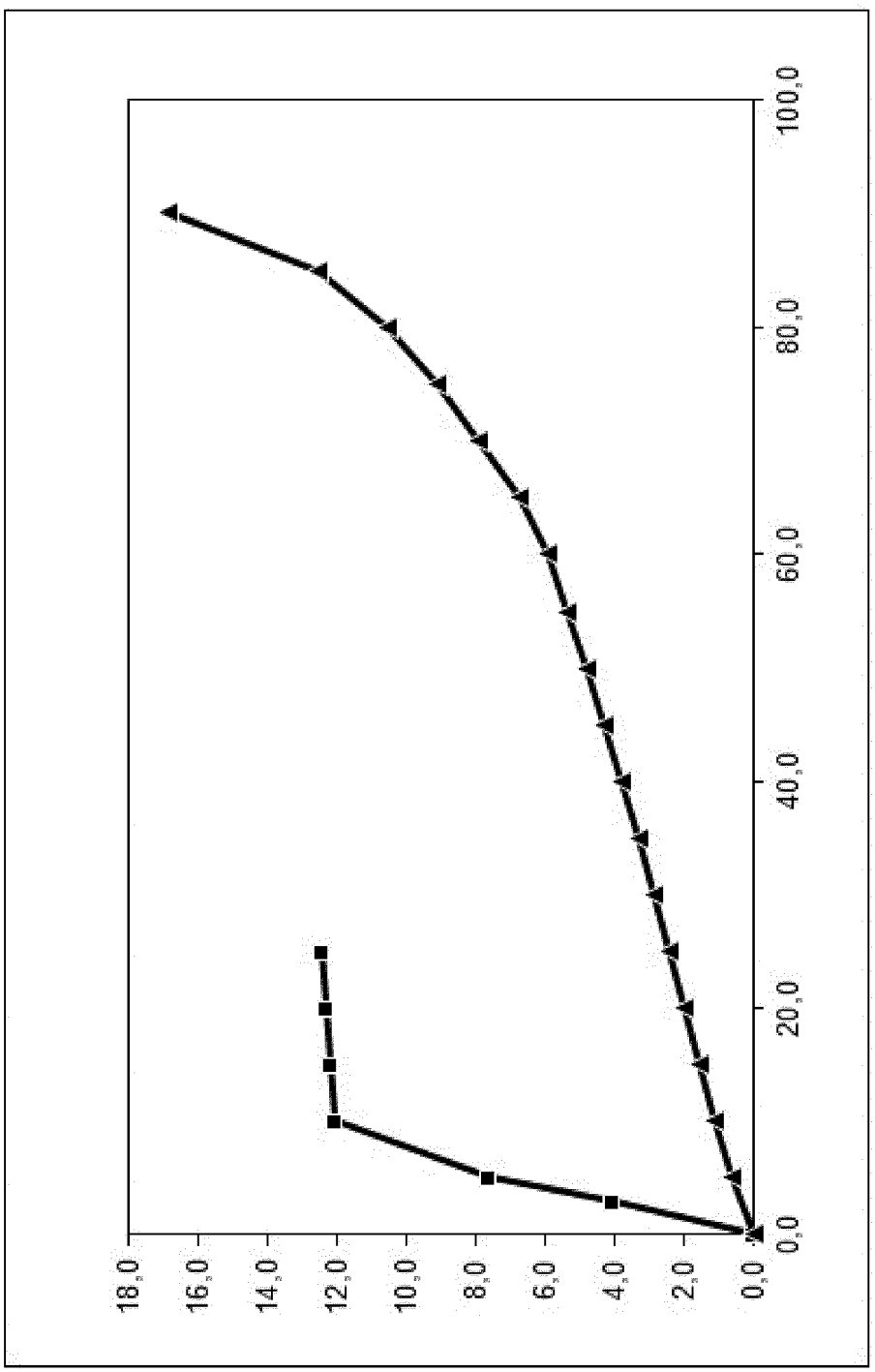


Figure 11



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/083830

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4985 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/165581 A1 (ABBVIE INC [US]) 13 September 2018 (2018-09-13) paragraphs [0018], [0288], [0289], [0486] - [0591]; examples 1-6; table 13 -----	1-15
A	WO 2017/066775 A1 (ABBVIE INC [US]; ABBVIE PHARMACEUTICAL TRADING CO [CN]) 20 April 2017 (2017-04-20) cited in the application paragraphs [0004], [0334] - [0525], [0526], [0528], [0833] - [0844]; examples 5-15; table 15A -----	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2020	11/02/2020

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/083830

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018165581 A1	13-09-2018	AU 2018230500 A1	19-09-2019
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