

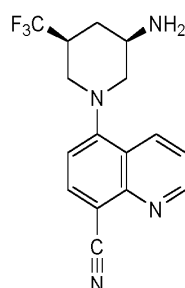
**CRYSTALLINE FORM OF 5-((3R,5S)-3-AMINO-5-TRIFLUOROMETHYL-
PIPERIDIN-1-YL)-QUINOLINE-8-CARBONITRILE**

FIELD

[0001] Crystalline forms of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile are provided herein having a particular morphology. Processes for preparing such particles and pharmaceutical compositions comprising such particles are also disclosed.

BACKGROUND

[0002] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, also named Enpatoran, is a compound having the following structure:



[0003] Enpatoran is a potent and selective dual toll-like receptor (TLR) 7/8 inhibitor in clinical development, including for the treatment of cutaneous and systemic lupus erythematosus (CLE/SLE). The compound may be prepared according to the methods provided in WO 2017/106607.

[0004] Solid forms of a particular chemical compound may differ by polymorphic form and/or by particle morphology or shape. Polymorphism refers to the occurrence of different crystalline forms (i.e., the arrangement of molecules within a crystal) of a single compound. A single compound may give rise to a variety of polymorphic forms, each having different solid-state physical properties, such as different solubility, melting point, stability, dissolution rates and/or different X-ray diffraction peaks. Moreover, crystals having the same polymorphic form or different polymorphic forms may exhibit different crystal habits (i.e., the external shape of the crystalline particle). It may be desirable to investigate solid state forms of a drug, to determine the stability, dissolution and flow properties of each form. Unfortunately, the existence of particular forms and their physical properties is unpredictable.

[0005] When used for treating humans, it is important that a crystalline form of a therapeutic agent, like 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-

carbonitrile, or a salt or hydrate thereof, retains appropriate chemical stability, solubility, and other physicochemical properties over time and among various manufactured batches of the agent. If the physical or chemical properties vary with time and/or among batches, the administration of a therapeutically effective dose may become problematic and may lead to inconsistent dosages or to ineffective therapy. Therefore, it is important to choose a form of the agent that is stable, is manufactured reproducibly, and has properties favorable for its use as a therapeutic agent.

[0006] However, the art remains unable to predict which crystalline form of an agent will have a combination of the desired properties and will be suitable for human administration, and how to make the agent in such a crystalline form.

SUMMARY

[0007] In one aspect, the disclosure provides an equant-shaped particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile. As used herein, the term “particle” refers to a primary particle.

[0008] In another aspect, the disclosure provides a particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile that has an aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

[0009] The particles described herein are useful in the treatment of immune disorders, including TLR7/8-related diseases, such as cutaneous and systemic lupus erythematosus (CLE/SLE).

[0010] In another aspect, the disclosure provides a composition comprising the particles described herein. An embodiment provides a pharmaceutical composition comprising the particles described herein, and one or more pharmaceutically acceptable carriers or excipients.

[0011] In another aspect, the disclosure provides methods of treating diseases responsive to the administration of a dual toll-like receptor (TLR) 7/8 inhibitor by the administration of a pharmaceutical dosage form comprising the particles described herein.

[0012] Another aspect provides methods of treating a disease or disorder modulated by TLR 7/8, comprising administering to a mammal in need of such treatment an effective amount of a composition comprising the particles described herein. The method may comprise the administration of a composition(s) comprising the particles described herein alone or in combination with one or more particles of 5-((3R,5S)-3-amino-5-

(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in other shapes or compounds having inhibitory properties for TLR 7/8.

[0013] Another aspect provides the use of the particles described herein in the manufacture of a medicament for the treatment of an immune disorder.

[0014] Another aspect provides a method of preparing the particles described herein by suspension of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in and/or recrystallization from a solvent comprising (i) one or more organic solvents, and (ii) water.

BRIEF DESCRIPTION OF THE FIGURES

[0015] Figure 1 shows SEM-Images of anisotropic primary particles of Enpatoran (magnification: top: 100x; bottom: 200x).

[0016] Figure 2 shows the ParticleView™ images of anisotropic Enpatoran particles during the cooling crystallization (top: Tr = 53 °C; bottom: Tr = 44 °C).

[0017] Figure 3 shows SEM-Images of the equant Enpatoran particles (magnification: top: 50x; bottom: 200x).

[0018] Figure 4 shows the powder X-ray diffractogram of hemihydrate Form H1.

[0019] Figure 5 shows the single crystal structure of hemihydrate Form H1.

[0020] Figure 6 shows microscope images of Enpatoran particles (magnification: 50x).

[0021] Figure 7 shows microscope images of Enpatoran particles (magnification: 50x).

[0022] Figure 8 shows microscope images of Enpatoran particles (magnification: 20x for Sample 5A, 50x for Sample 5B, 10x for Sample 5C and 20x for Sample 5D).

[0023] Figure 9A depicts the distribution of the aspect ratio of the Enpatoran particles in Sample 5C and Figure 9B shows exemplary particles.

DETAILED DESCRIPTION

[0024] An equant-shaped particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile is provided herein. Equant particles have roughly similar length, width and height, including both cubical particle, spherical particles, and other shapes.

[0025] The present disclosure also provides a particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile that has an aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at

least about 0.8 or at least about 0.9. Aspect ratio is a parameter that describes the sizes of the particle in different dimensions.

[0026] In some embodiments, the equant particle described herein has an aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

[0027] In some embodiments, the aspect ratio is the ratio of the width to the length of a particle. In some embodiments, the length is the maximum Feret diameter and the width is the minimum Feret diameter. In some embodiments, the length is the maximum distance between any two points on the perimeter of the particle parallel to the major axis and the width is the maximum distance between any two points on the perimeter of the particle parallel to the minor axis. The major axis passes through the center of mass of the object at an orientation corresponding to the minimum rotational energy of the shape. The minor axis passes through the center of mass at right angles to the major axis.

[0028] In some embodiments, the aspect ratio is determined from a two-dimensional representation of the particle. In other embodiments, the aspect ratio is determined from a three-dimensional representation of the particle. Preferably, the aspect ratio is determined from a two-dimensional representation of the particle(s) and corresponds to the ratio of the minimum Feret diameter to the maximum Feret diameter.

[0029] The three-dimensional shape of particles can be determined, e.g., by using X-ray microtomography (see Yin et al., Sci Rep. 2016 Apr 21:6:24763) and other 3D imaging systems such as dynamic image analysis using two cameras (see Liu et al., Chem. Eng. J., 438 (2022) and Rajagopalan et al., Volume 321, November 2017, Pages 479-493). The two-dimensional shape of particles can be determined, e.g., by optical microscopy. The dimensions and morphology of the particles may also be determined by, e.g., optical microscopy as described in USP, Method 776.

[0030] Processes for preparing the particles described herein and pharmaceutical compositions comprising such particles are also disclosed.

[0031] The particles described herein show improved bulk properties with markedly improved manufacturability. The particles may have one or more of higher bulk density, higher flowability, improved manufacturing properties for tableting, and/or other improved properties.

[0032] The processing or handling of the active pharmaceutical ingredient during the formulation and manufacturing process may be greatly improved by using the particles provided herein. The particles can thus provide desirable processing properties. They can be

easier to handle during manufacturing of dosage forms allowing for improved API consistency in the dosage form.

[0033] The particles disclosed herein may show good tableting behavior, including one or more of (i) low tendency to stick to manufacturing equipment, such as the punches of the tableting press, and/or (ii) have good flowability, in order to homogeneously and reproducibly fill the tableting die. The particles disclosed herein may show good flowability in order to allow for a smooth and reproducible tableting of the drug.

Compositions

[0034] The present invention also provides compositions, e.g., pharmaceutical compositions as further described below, comprising the particles described herein.

[0035] Provided herein is a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles, wherein the majority of these particles are equant-shaped particles. For instance, more than about 60%, more than about 70%, more than about 75%, more than about 80%, more than about 85%, more than about 90% or more than about 95% of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles in such composition are equant shaped particles. In some embodiments, the equant shaped particles in the composition have a mean, mode or median aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

[0036] Provided herein is a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles, wherein the mean, mode or median aspect ratio of the particles in the composition is at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9. In some embodiments, the mean, mode or median aspect ratio is determined from a three-dimensional representation of the particles. Preferably, the mean, mode or median aspect ratio is determined from a two-dimensional representation of the particles.

[0037] The mean, mode or median aspect ratio can be determined by selecting a representative number of primary particles, determining the aspect ratio of each individual particle and calculating the mean, mode or median value on this basis.

Bulk Properties

[0038] The particles of 5-((3R,5S)-3-amino-5-trifluoromethyl-piperidin-1-yl)-quinoline-8-carbonitrile described herein and resulting compositions were found to show improved bulk

properties, improved manufacturability, as well as other improved particle properties such as flowability. The particles and compositions described herein may have one or more of higher bulk density, higher flowability, improved manufacturing properties for tableting, and/or other improved properties.

[0039] The compositions comprising the particles described herein may have a bulk density greater than about 0.3 g/cm³, greater than about 0.4 g/cm³, greater than about 0.5 g/cm³, greater than about 0.55 g/cm³, greater than about 0.6 g/cm³, greater than about 0.65 g/cm³, or greater than about 0.7 g/cm³. In a further embodiment, the compositions comprising the particles described herein have a bulk density less than about 0.95 g/cm³, less than about 0.9 g/cm³, less than about 0.85 g/cm³, or less than about 0.8 g/cm³. In some embodiments, the compositions comprising particles described herein have a bulk density from about 0.5 g/cm³ to about 0.95 g/cm³, from about 0.55 g/cm³ to about 0.9 g/cm³, from about 0.6 g/cm³ to about 0.85 g/cm³, or from about 0.7 g/cm³ to about 0.8 g/cm³. The bulk density of the compositions may be determined as the ratio of the mass of an untapped powder sample and its volume including the contribution of the inter-particulate void volume. Accordingly, the bulk density depends on both the density of particles and the spatial arrangement of particles in the sample.

[0040] As used herein, the term “about” when used in relationship to a value, e.g., the upper limit of a range or a reference value, such as the reference expression level of a biomarker, refers to any value that is reasonably close to the value referred to, for instance, any value that is less than 10% below or above the value referred to. In some embodiments, the term “around” means the exact value.

[0041] The compositions of the compositions described herein may additionally have a flow function coefficient (ffc) greater than about 4; greater than about 5; greater than about 6; greater than about 7; or greater than about 8. Powder flow is important during tableting to ensure uniformity of the API powder flow and distribution into the tablet dies. This ensures tablet weight uniformity and production of tablets with consistent and reproducible properties.

[0042] The flow function coefficient (ffc) tests are performed under controlled environmental conditions (i.e., 22 °C and 35% relative humidity) to reduce or prevent bias on flowability due to hygroscopicity effects. Conformity of the environmental conditions ($\pm 2^{\circ}\text{C}$; $\pm 5\%\text{r.h.}$) should be checked directly prior to starting the measurement. The measurement can be performed with $n=1$. The shear cell bottom ring is filled. If needed, pre-processing (e.g. sieving for de-agglomeration) is performed. For very fine bulk solids, it can

be advantageous to perform filling of the bottom ring with the help of a sieve. The parameters (e.g. material, batch number, method) for testing is entered into the RST Control software, and the instructions of the RST Control Software are followed during the measurement. The measurement may be saved as an Input-file (.inp) for further analysis and an Output-file (.out) for raw data documentation as pdf-file. Additionally, a Datetime-file (.FTD) may be saved to review the raw data. Evaluation of ffc and cohesion values are determined from construction of the Mohr circles by the software RST-Control 95 XS. The standard data evaluation parameters are:

#	Configuration
Regression Yield locus	Straight section
Auto correction	Deactivated
Prorating	Activated
Bulk Density correction	Activated

[0043] In further embodiments, the mean, mode or median particle diameter d₉₀ of the particles of 5-((3R,5S)-3-amino-5- trifluoromethyl-piperidin-1-yl)-quinoline-8-carbonitrile of the compositions described herein is less than about 600 µm, less than about 500 µm, less than about 450 µm, or less than about 400 µm. In further embodiments, the mean, mode or median particle diameter d₉₀ of the particles of 5-((3R,5S)-3-amino-5- trifluoromethyl-piperidin-1-yl)-quinoline-8-carbonitrile of the compositions described herein is greater than about 1 µm, greater than about 10 µm, greater than about 50 µm; or greater than about 100 µm. In further embodiments, the mean, mode or median particle diameter d₉₀ of the particles of 5-((3R,5S)-3-amino-5- trifluoromethyl-piperidin-1-yl)-quinoline-8-carbonitrile of the compositions described herein is from about 1 to about 600 µm, from about 10 to about 500 µm, from about 50 to about 450 µm, or from about 100 to about 400 µm.

Process for the preparation of particles

[0044] The inventors have found that suspension or crystallization of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in organic solvents without water led to highly anisotropic particles. However, suspension or crystallization in water, or mixtures of organic solvents with water, have been found to produce more isotropic, equant particles. The solubility of the compound in water is poor, and thus a crystallization from water is not efficient and control of the particle size distribution from an aqueous suspension was low. In contrast, the usage of organic solvents in mixtures with water for the suspension

or crystallization of the compound provides improved control of the particles size and provides the preferred particle shapes.

[0045] Thus, one process for preparing the particles involves the dissolution and/or suspension of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in a solvent as described below, optionally wet milling the suspension/solution, optionally heating and cooling the suspension/solution, and separating the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile from the solvent.

[0046] A process for preparing the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile comprises the steps:

- (i) preparing a suspension of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in a solvent comprising water, more preferably comprising one or more organic solvents and water;
- (ii) optionally heating the suspension to a recrystallization temperature;
- (iii) stirring the suspension for a period of time at ambient temperature or at the recrystallization temperature;
- (iv) optionally cooling the suspension; and
- (v) separating the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile from the solvent.

[0047] Optionally, there is a further wet milling step, for instance, directly after conversion to the equant habit. The wet milling step may take place directly after step (iii) of the process of the preceding paragraph.

[0048] Heating the suspension may facilitate partially or fully dissolving the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in the solvent. The optional heating may be at a temperature from room temperature (for example, 25 °C) to the boiling temperature of the solvent. In embodiments, the suspension is heated to a temperature at or above 35 °C, at or above 35 °C, at or above, 40 °C, at or above 45 °C, or at or above 50 °C. Preferably, stirring or other mixing is applied to the suspension during the heating. The suspension is stirred at the selected recrystallization temperature for a period of time from 30 minutes to a day or more. In embodiments, the suspension is stirred for a period of time from 30 minutes to about 24 hours, from 1 hour to 24 hours, or from 2 hours to 24 hours.

[0049] The suspension is optionally cooled to a temperature of room temperature or below. In embodiments, the suspension is cooled to a final temperature of room temperature to 0 °C, to 0 °C to 10 °C, or to 0 °C to 5 °C. Preferably the cooling temperature is achieved slowly, i.e., by cooling the suspension at a rate of 1 °C/minute or less, at a rate of 0.5

°C/minute or less, at a rate of 0.4 °C/minute less or at a rate of 0.3 °C/minute less, or at a rate of 0.2 °C/minute less. Preferably, stirring or other mixing is applied to the suspension during the cooling. The suspension may be held at the cooling temperature for a period of time prior to the separation of the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile from the solvent. The suspension may be held at the cooling temperature for from 10 minutes to 4 hours, from 20 minutes to 2 hours, or from 30 minutes to 1.5 hours.

[0050] The particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile may be separated from the solvent by any means known in the art, including for example, filtration or centrifugation.

[0051] The solvent for producing the particles is water, preferably in combination with one or more organic solvents. The organic solvent may be miscible with at least 0.1 % (v/v) water; miscible with at least 0.5 % (v/v) water; miscible with at least 1 % (v/v) water; or miscible with at least 2 % (v/v) water.

[0052] The solvent comprising the one or more organic solvents and water may comprise from 80 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 20 % (v/v) water; from 85 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 15 % (v/v) water; from 90 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 10 % (v/v) water; from 98 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 2 % (v/v) water; or from 99 to 99.8 % (v/v) of the one or more organic solvents and from 0.5 to 1.5 % (v/v) water.

[0053] The organic solvent may be an ester, ether, alcohol, ketone, or combination thereof.

[0054] The ester solvent may have the formula $R^1-O-C(=O)-R^2$, in which R^1 is selected from C_1 to C_5 alkyl or C_2 to C_5 alkenyl; and R^2 is selected from C_1 to C_5 alkyl or C_2 to C_5 alkenyl. Exemplary ester solvents include, but are not limited to, methyl acetate, ethyl acetate; n-propyl acetate; isopropyl acetate; n-butyl acetate; isobutyl acetate; sec-butyl acetate; tert butyl acetate; and the like.

[0055] The ether solvent may have the formula R^3-O-R^4 , in which R^3 is selected from C_1 to C_5 alkyl or C_2 to C_5 alkenyl; and R^4 is selected from C_1 to C_5 alkyl or C_2 to C_5 alkenyl. Exemplary ether solvents include, but are not limited to, methyl tert-butyl ether; methyl isopropyl ether; ethyl isopropyl ether; diisopropyl ether; and the like.

[0056] The alcohol solvent may be selected from C₂ to C₆ alcohols, diols and triols. Exemplary alcohol solvents include, but are not limited to, ethanol, n-propanol, isopropanol, n-butanol, sec-butyl alcohol, isobutyl alcohol, tert butyl alcohol, and the like.

[0057] The ketone solvent may be selected from C₃ to C₆ ketones. Exemplary ketone solvents include, but are not limited to, acetone, methyl ethyl ketone, 2-butanone, 2-pentanone, 3-pentanone, and the like.

[0058] A preferred solvent for the preparation of the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile is a mixture comprising isopropyl acetate and water. The water may be present in the isopropyl acetate at a concentration of between 0.1 % to 2 % (v/v); from 0.5 % to 2 % (v/v); or from 0.5 % to 1.5 % (v/v). In an embodiment, the solvent is isopropyl acetate with 1 % water (v/v).

[0059] Wet milling may be used control or reduce the size of the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile and/or to ensure a more uniform particle size distribution. In the wet milling process the particles are suspended in a liquid and passed through the wet mill. The mixture may be recirculated through the wet mill until the desired properties, such as particle size and/or uniformity, are obtained. The liquid for the wet milling is a solvent as described herein.

[0060] Wet milling may be performed using techniques, apparatus and conditions that are known in the art, including, for example, using a planetary mill, colloid mill, media mill, ball mills, disc mills, and conical mills. The skilled person appreciates that various aspects of the milling process, such as the milling time, milling speed (rotation speed), temperature, etc. may be varied in order to achieve the desired particle size and/or uniformity.

[0061] The wet milling time may vary from minutes to hours depending on the particle size desired. The wet milling time may be from 5 minutes to 200 minutes. In some embodiments, the wet milling is conducted at a speed of from about 500 rpm to about 50000 rpm, such as 3000 rpm to 25000 rpm. The temperature of the wet milling is not particularly limited. It may be conducted at low temperatures, e.g., 0°C, and at high temperatures, e.g., 60°C. Preferably, the wet milling is conducted at a temperature below 50°C, such as 25°C.

Polymorphic form

[0062] The particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile described herein may comprise one or more crystalline polymorphic forms of the compound. In embodiments, the polymorphic form may be an anhydrous form of the compound. More preferably, the crystalline polymorphic form of the compound is a hydrate

or hemihydrate, and most preferably is a hemihydrate. In embodiments, the particles comprise different crystalline polymorphic forms of the compound. In some embodiments, the crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in the majority of particles of a composition is a hemihydrate, such as the Form H1 referred to below. In some embodiments, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% of the particles have 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in the hemihydrate form, such as the Form H1.

[0063] As used herein, the term “polymorph” or “polymorphic form” refer to a crystallographically distinct form of a substance. The practical physical characteristics of a polymorphic form are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. Different polymorphs of the same compound may have different physical, chemical, biological and/or spectroscopic properties. For example, and without limitation, different polymorphic forms may have different stability properties. A particular polymorphic form may be more sensitive to relative humidity, heat and/or light. In some cases, differences in stability result from changes in chemical reactivity, such as and without limitation, differential oxidation. Such properties may provide for more suitable product qualities such as a dosage form that is more resistant to discoloration when comprised of a particular polymorph. Alternatively or additionally, a particular polymorphic form may have a different dissolution rate thereby providing, for example, a more desirable bioavailability. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, powder X-ray diffractometry (PXRD), single crystal X-ray diffractometry, differential scanning calorimetry (DSC), thermogravimetry (TGA), vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography, quantitative analysis, solubility, and rate of dissolution.

[0064] As used herein when referring to a spectrum and/or to data presented in a graph, the term “peak” refers a feature that one skilled in the art would recognize as not attributable to background noise.

[0065] In embodiments, the crystalline form of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile of the particle is the crystalline hemihydrate in polymorphic form H1, as described herein.

[0066] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by one or more peaks from the powder X-ray diffraction (PXRD) (Cu-K α_1 radiation), presented in degrees $2\theta \pm 0.2^\circ$, wherein the peaks comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9. A powder X-Ray diffraction pattern may be obtained by standard techniques as described in the European Pharmacopeia 6th Edition chapter 2.9.33, and characterized by the X-ray powder diffractogram of Figure 4 (monochromatic Cu-K α_1 radiation, $\lambda = 1.5406 \text{ \AA}$, Stoe StadiP 611 KL transmission diffractometer).

[0067] Single crystal X-Ray structure data may be obtained on Form H1 form (Oxford Diffraction Supernova Single Crystal X-ray Diffractometer with Graphite monochromator and CCD Detector) at 298 K. Hemi-hydrate Form H1 crystallises in the orthorhombic space group $P2_12_12_1$ with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$. As can be seen from the single crystal structure of Figure 5, Form H1 represents a hemi-hydrate form.

[0068] Form H1 is characterised by the following physical properties. Thermal behaviour shows dehydration $< 100^\circ\text{C}$, followed by melting of anhydrous form A1 at $\sim 165^\circ\text{C}$. TGA shows weight loss of $\sim 2.9\%$ (w/w) up to 130°C which can be assigned to degradation of 0.5 mol water. The DSC scan of Form H1 was acquired on a Mettler-Toledo DSC1 with a heating rate of 5 K/min, using nitrogen purge gas at 50 mL/min. The TGA scan of Form H1 was acquired on a Mettler-Toledo TGA 851 with a heating rate of 5 K/min, using nitrogen purge gas at 50 mL/min.

[0069] Water Vapour Sorption behaviour reveals water uptake levels $\sim 0.5\%$ (w/w) in the full relative humidity (RH) range 0-98% RH. Hemi-hydrate form H1 can be classified as non-hygroscopic according to Ph. Eur. Criteria (section 5.11.). Water Vapour Sorption isotherm was acquired on a DVS Intrinsic system from SMS.

[0070] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more, sixteen or more, seventeen or more, eighteen or more, nineteen or more, or each of the PXRD peaks 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9. All PXRD peaks provided herein are measured with Cu-K α_1 radiation in degrees 2θ and include ± 0.2 degrees.

[0071] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by PXRD peaks comprising a peak at 13.4.

[0072] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by PXRD peaks comprising peaks at 9.7 and 13.4.

[0073] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by PXRD peaks comprising peaks at 7.2, 9.7 and 13.4.

[0074] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by PXRD peaks comprising peaks at 7.2, 9.7, 13.4 and 22.2.

[0075] The crystalline polymorph of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile hemihydrate Form H1 may be characterized by PXRD peaks comprising peaks at 7.2, 9.7, 13.4, 21.5 and 22.2.

[0076] The particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile having polymorphic hemihydrate form H1, as described herein, provide improved physical stability and high chemical stability. For example, at ambient conditions the particles of form H1 provide improved stability as compared to the enantiotropic behavior of certain anhydrous polymorphic forms. Based on the high physical stability, no protective packaging material may be necessary for the pharmaceutical formulations of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile of the polymorphic hemihydrate form H1.

Pharmaceutical composition

[0077] Further aspects provide a pharmaceutical composition comprising the particles described herein, and one or more pharmaceutically acceptable carriers or excipients. The term “pharmaceutically acceptable carrier or excipient” refers to a non-toxic carrier, adjuvant, excipient or vehicle that does not interfere with the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers or excipients that may be used in the pharmaceutical compositions include any such excipients known in the art.

[0078] Pharmaceutically acceptable compositions may be orally administered in any orally acceptable dosage form. Exemplary oral dosage forms are capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include

lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient may be combined with emulsifying and suspending agents. If desired, sweetening, flavoring or coloring agents are optionally also added.

[0079] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the particles described herein may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form also optionally comprises buffering agents.

[0080] Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0081] In another aspect, the disclosure provides the pharmaceutical composition disclosed herein for use as a medicament.

[0082] In another aspect, the disclosure provides methods of treating diseases responsive to the administration of a dual toll-like receptor (TLR) 7/8 inhibitor by the administration to a patient in need thereof of a pharmaceutical dosage form comprising the particles described

herein. The term “patient” or “subject” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0083] Another aspect provides methods of treating a disease or disorder modulated by TLR 7/8, comprising administering to a mammal in need of such treatment an effective amount of a composition comprising the particles described herein. The method may comprise the administration of a composition(s) comprising the particles described herein, alone or in combination with one or more particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in other shapes or compounds having inhibitory properties for TLR 7/8.

[0084] The present disclosure furthermore relates to a method for treating or preventing a disease or disorder in a subject, such as a TLR7/8 related disease or disorder, comprising administering to said subject an effective amount of a composition(s) comprising the particles described herein.

[0085] The disease or disorder to be treated or prevented by administering a composition comprising the particles described herein may be an autoimmune disease, for instance, one characterized by joint pain, antinuclear antibody positivity, malar rash, or discoid rash. In some aspects, the autoimmune disease is associated with the skin, muscle tissue, and/or connective tissue. In some embodiments, the autoimmune disease is not evidenced in the individual by skin, muscle tissue, and/or connective tissue symptoms. In some embodiments, the autoimmune disease is systemic. Autoimmune diseases that may be treated or prevented by administering a composition comprising 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile include, without limitation, rheumatoid arthritis (RA), autoimmune pancreatitis (AIP), lupus, such as systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE), type I diabetes mellitus, multiple sclerosis (MS), antiphospholipid syndrome (APS), sclerosing cholangitis, systemic onset arthritis, irritable bowel disease (IBD), scleroderma, Sjogren's disease, vitiligo, myositis, such as dermatomyositis or polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease including Crohn's disease and ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease (GvHD), autoimmune skin diseases, uveitis, pernicious anemia, and hypoparathyroidism. The autoimmune disease may also be, without limitation, polyangiitis overlap syndrome, Kawasaki's disease, sarcoidosis, glomerulonephritis, and cryopathies.

[0086] In some aspects, the autoimmune disease is selected from the group consisting of arthritis, pancreatitis, mixed connective tissue disease (MCTD), lupus, antiphospholipid syndrome (APS), systemic onset arthritis, and irritable bowel syndrome.

[0087] In other aspects, the autoimmune disease is selected from the group consisting of pancreatitis, glomerulonephritis, pyelitis, sclerosing cholangitis, and type I diabetes. In some aspects, the autoimmune disease is rheumatoid arthritis. In some aspects, the autoimmune disease is autoimmune pancreatitis (AIP). In some aspects, the autoimmune disease is glomerulonephritis. In some aspects, the autoimmune disease is pyelitis. In some aspects, the autoimmune disease is sclerosing cholangitis. In some aspects the autoimmune disorder is psoriasis. In some aspects, the autoimmune disease is a rheumatoid disease or disorder.

[0088] In other aspects, the autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune skin disease, and multiple sclerosis. The autoimmune disease may be cutaneous and systemic lupus erythematosus (CLE/SLE). In some aspects, any of the above-mentioned autoimmune diseases is a TLR7/8-related autoimmune disease.

Further embodiments

[0089] The present disclosure further provides the following embodiments E1 to E50:

E1. An equant-shaped particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile.

E2. A particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, wherein the particle has an aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

E3. The particle of E1 or E2, wherein the crystalline form of the particle is a hydrate or hemihydrate, and most preferably is a hemihydrate.

E4. The particle of E3, wherein the crystalline form of the particle is a crystalline hemihydrate polymorph characterized by one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9.

E5. The particle of E4, wherein the crystalline hemihydrate polymorph is characterized by two or more, three or more, four or more, five or more, six or more, seven or more, eight or

more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more, sixteen or more, seventeen or more, eighteen or more, nineteen or more, or each of the PXRD peaks, expressed in degrees $2\theta \pm 0.2^\circ$, 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9.

E6. The particle of E4 or E5, wherein the crystalline hemihydrate polymorph is characterized by an orthorhombic space group P212121 with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$.

E7. A particle of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, wherein the particle has an aspect ratio of at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9, and

wherein the crystalline form of the particle is a crystalline hemihydrate polymorph characterized by (1) one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9, and (2) an orthorhombic space group P212121 with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$.

E8. A composition comprising particles according to any one of E1 to E7.

E9. A composition comprising particles of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, wherein the mean, mode or median aspect ratio of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles in the composition is at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

E10. A composition comprising particles of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, wherein more than about 50%, more than about 60%, more than about 70%, more than about 75%, more than about 80%, more than about 85%, more than about 90% or more than about 95% of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles in the composition are equant shaped particles. **E11.** The composition according to any one of E8 to E10, wherein more than about 50%, more than about 60%, more than about 70%, more than about 75%, more than about 80%, more than about 85%, more than about 90% or more than about 95% of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles in the composition are of a crystalline form as described in any one of E3 to E6.

E12. A composition comprising particles of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile,

wherein the mean aspect ratio of the particles in the composition is at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9, and

wherein the crystalline form of more than about 50%, more than about 60%, more than about 70%, more than about 75%, more than about 80%, more than about 85%, more than about 90% or more than about 95% of the particles is a crystalline hemihydrate polymorph characterized by (1) one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9, and (2) an orthorhombic space group P212121 with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$.

E13. A composition comprising particles of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile,

wherein the mean aspect ratio of the particles in the composition is at least about 0.5, and

wherein the crystalline form of more than about 80% of the particles is a crystalline hemihydrate polymorph characterized by (1) one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9, and (2) an orthorhombic space group P212121 with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$.

E14. The composition according to any one of E8 to E13, wherein the composition has a bulk density greater than about 0.3 g/cm^3 ; greater than about 0.4 g/cm^3 ; greater than about 0.5 g/cm^3 ; greater than about 0.55 g/cm^3 ; greater than about 0.6 g/cm^3 ; greater than about 0.65 g/cm^3 ; or greater than about 0.7 g/cm^3 .

E15. The composition according to any one of E8 to E14, wherein the composition has a bulk density less than about 0.95 g/cm^3 , less than about 0.9 g/cm^3 , less than about 0.85 g/cm^3 , or less than about 0.8 g/cm^3 .

E16. The composition according to any one of E8 to E13, wherein the composition has a bulk density from about 0.5 g/cm^3 to about 0.95 g/cm^3 , from about 0.55 g/cm^3 to about 0.9 g/cm^3 , from about 0.6 g/cm^3 to about 0.85 g/cm^3 , or from about 0.7 g/cm^3 to about 0.8 g/cm^3 .

E17. The composition according to any one of E8 to E16, wherein the composition has a flow function coefficient (ffc) greater than about 4; greater than about 5; greater than about 6; greater than about 7; or greater than about 8.

E18. The composition according to any one of E8 to E17, wherein the mean, mode or median particle diameter d90 of the particles in the composition is less than about 600 μm , less than about 500 μm , or less than about 400 μm .

E19. The composition according to any one of E8 to E17, wherein the mean, mode or median particle diameter d90 of the particles in the composition is from about 50 to about 500 μm , from about 100 to about 450 μm , or from about 150 to about 400 μm .

E20. The composition according to any one of E8 to E19, wherein the composition is a pharmaceutical composition and comprises one or more pharmaceutically acceptable carriers.

E21. The pharmaceutical composition of E20, wherein the composition is a tablet for oral ingestion.

E22. The pharmaceutical composition of E20 or E21 for use as a medicament.

E23. The pharmaceutical composition of E20 or E21 for use in a method of treating or preventing a TLR7/8-related autoimmune disease.

E24. The pharmaceutical composition of E23, wherein the TLR7/8-related autoimmune disease is selected from the group consisting of rheumatoid arthritis, autoimmune pancreatitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, type I diabetes mellitus, multiple sclerosis, antiphospholipid syndrome, sclerosing cholangitis, systemic onset arthritis, irritable bowel disease, scleroderma, Sjogren's disease, vitiligo, myositis, dermatomyositis, polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease, autoimmune skin diseases, uveitis, pernicious anemia, and hypoparathyroidism.

E25. A process for preparing particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile comprising the steps:

- (i) preparing a suspension of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in a solvent comprising water and, optionally, one or more organic solvents, preferably both one or more organic solvents and water;
- (ii) optionally heating the suspension to a recrystallization temperature;
- (iii) stirring the suspension for a period of time at ambient temperature or at the recrystallization temperature;

- (iv) optionally wet milling the suspension;
- (v) optionally cooling the suspension; and
- (vi) separating the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile from the solvent.

E26. The process of E25, wherein the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile are a crystalline hemihydrate.

E27. The process of E26, wherein the crystalline hemihydrate is polymorphic form H1.

E28. The process according to any one of E25 to E27, wherein the heating of step (ii) comprises heating the suspension to a recrystallization temperature above at or above 35 °C, or at or above 40 °C, or at or above 45 °C, or at or above 50 °C.

E29. The process according to any one of E25 to E28, wherein step (iii) comprises stirring the suspension for a period of time from 30 minutes to about 24 hours, from 1 hour to 24 hours, or from 2 hours to 24 hours.

E30. The process according to any one of E25 to E29, wherein step (iv) comprises cooling the suspension to a temperature from below room temperature to 0 °C, from 0 °C to 10 °C, or from 0 °C to 5 °C.

E31. The process according to E30, wherein the cooling temperature is achieved by cooling the suspension at a rate of 1 °C/minute or less, at a rate of 0.5 °C/minute or less, at a rate of 0.4 °C/minute less, at a rate of 0.3 °C/minute less, or at a rate of 0.2 °C/minute less.

E32. The process according to any one of E25 to E31, wherein the suspension may be held at the cooling temperature for from 10 minutes to 4 hours, from 20 minutes to 2 hours, or from 30 minutes to 1.5 hours.

E33. The process according to any one of E25 to E32, wherein the solvent comprises one or more organic solvents and water.

E34. The process of E33, wherein the one or more organic solvents and water may comprise from 80 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 20 % (v/v) water; or from 85 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 15 % (v/v) water; or from 90 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 10 % (v/v) water; or from 98 to 99.9 % (v/v) of the one or more organic solvents and from 0.1 to 2 % (v/v) water; or from 99 to 99.8 % (v/v) of the one or more organic solvents and from 0.5 to 1.5 % (v/v) water.

E35. The process according to E33 or E34, wherein the one or more organic solvents are selected from an ester, ether, alcohol, ketone, or combination thereof.

E36. The process according to any one of E25 to E35, wherein more than 50%, more than 60%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90% or more than 95% of the particles are equant-shaped.

E37. The process according to any one of E25 to E36, wherein the mean, mode or median aspect ratio of the particles is at least about 0.3, at least about 0.4, at least about 0.5, at least about 0.6, at least about 0.7, at least about 0.8 or at least about 0.9.

E38. The process according to any one of E25 to E37, wherein the bulk density of the resulting particle composition is greater than about 0.3 g/cm³, greater than about 0.4 g/cm³, greater than about 0.5 g/cm³, greater than about 0.55 g/cm³, greater than about 0.6 g/cm³, greater than about 0.65 g/cm³, or greater than about 0.7 g/cm³.

E39. The process according to any one of E25 to E38, wherein the bulk density of the resulting particle composition is less than about 0.95 g/cm³, less than about 0.9 g/cm³, less than about 0.85 g/cm³, or less than about 0.8 g/cm³.

E40. The process according to any one of E25 to E39, wherein the flow function coefficient (ffc) of the resulting particle composition is greater than about 4; or greater than about 5; or greater than about 6; or greater than about 7; or greater than about 8.

E41. The process according to any one of E25 to E40, wherein the mean, mode or median particle diameter d₉₀ of the particles in the resulting composition is less than about 600 μm, less than about 500 μm, or less than about 400 μm.

E42. The process according to any one of E25 to E40, wherein the mean, mode or median particle diameter d₉₀ of the particles in the resulting composition is from about 50 to about 500 μm, from about 100 to about 450 μm, or from about 150 to about 400 μm.

E43. A particle of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile that is obtainable by the process according to any one of E25 to E42.

E44. The particle of E43 having the characteristics of the particle according to any one of E1 to E7.

E45. A composition comprising particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile that is obtainable by the process according to any one of E25 to E42.

E46. The composition of E45, wherein the composition is a pharmaceutical composition and comprises one or more pharmaceutically acceptable carriers.

E47. The pharmaceutical composition of E46, wherein the composition is a tablet for oral ingestion.

E48. The pharmaceutical composition of E46 or E47 for use as a medicament.

E49. The pharmaceutical composition of E46 or E47 for use in a method of treating or preventing a TLR7/8-related autoimmune disease.

E50. The pharmaceutical composition of E49, wherein the TLR7/8-related autoimmune disease is selected from the group consisting of rheumatoid arthritis, autoimmune pancreatitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, type I diabetes mellitus, multiple sclerosis, antiphospholipid syndrome, sclerosing cholangitis, systemic onset arthritis, irritable bowel disease, scleroderma, Sjogren's disease, vitiligo, myositis, dermatomyositis, polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease, autoimmune skin diseases, uveitis, pernicious anemia, and hypoparathyroidism.

EXAMPLES

Example 1: Preparation of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Anisotropic Forms

[0090] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile (API) was prepared according to the method of WO 2017/106607 (compound 73).

[0091] Cooling crystallization in Isopropyl acetate: Approximately 35 g API were weighted into a 400 mL reactor of an EasyMax 402 station, equipped with overhead stirrer and reflux. The reactor was closed by a PTFE cover and filled with 256 g Isopropyl acetate. A 4-blade propeller-stirrer was set to 200 rpm. The reactor was heated to 60 °C as fast as possible and the further to 75 °C at 0.5 K/min. At approximately 70 °C a clear solution was observed. The solution was cooled down to 65 °C at 0.5 K/min and further to 5 °C at 0.1 K/min. Nucleation occurred at approximately 53 °C and growth of fiber-like particles could be observed. ParticleView™ images of anisotropic particles during the cooling crystallisation are shown in Figure 2 (top: Tr = 53 °C; bottom: Tr = 44 °C). The suspension was filtered by vacuum filtration using a Büchner funnel and cellulose filter paper (Whatman size 2). The obtained powder was dried at 40 °C and dry nitrogen flow for 24 h.

[0092] SEM-Images of the anisotropic primary particles are shown in Figure 1 (magnification: left: 100x; right: 200x). The bulk properties of the anisotropic particles are reported in Table 1.

Table 1

Bulk density	0.14 g/cm ³
Flow Function Coefficient (ffc)	2.5

Example 2: Preparation of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Anisotropic Forms

[0093] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile (API) was prepared according to the method of WO 2017/106607 (compound 73).

[0094] Respective amount of the API was suspended in the organic solvent(s) at ambient temperature or at 50 °C, as reported in Table2. Each suspension was stirred for 1 day using a magnetic stirring bar and then isolated by filtration.

Table 2

Sample	Temp.	Weight API [mg]	Solvent (volume [mL])	Morphology
2A	ambient	75.3	Isopropyl acetate (0.5)	Anisotropic
2B	50 °C	86.4	Isopropyl acetate (0.5)	Anisotropic
2C	ambient	86.8	Isopropyl acetate / 2 % n-Heptane (0.5)	Anisotropic
2D	50 °C	136.8	Isopropyl acetate / 2 % n-Heptane (0.5)	Anisotropic
2E	ambient	83.1	n-Propyl acetate (0.5)	Anisotropic
2F	50 °C	107.0	n-Propyl acetate (0.5)	Anisotropic
2G	ambient	74.4	Ethyl acetate (0.5)	Anisotropic
2H	50 °C	97.2	Ethyl acetate (0.5)	Anisotropic
2I	ambient	64.5	Methyl acetate (0.5)	Anisotropic
2J	50 °C	80.4	Methyl acetate (0.5)	Anisotropic

[0095] The samples were analyzed by optical microscopy, the results of which are reflected in Figure 6. As reflected by this figure, it was found that suspensions or crystallizations from organic solvents without water led to anisotropic particles.

Example 3: Preparation of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Equant Particles

[0096] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile (API) was prepared according to the method of WO 2017/106607 (compound 73).

[0097] Suspension in isopropyl acetate and water (1 % v/v): Approximately 20 g API were weighted into a 100 mL reactor of an EasyMax 402 station, equipped with overhead stirrer and reflux. The reactor was closed by a PTFE cover and filled with 105 mL isopropyl acetate. The jacketed temperature was set to 25 °C and the suspension was stirred at 250 rpm (propeller 4 blades upwards). The suspension was stirred for 30 min, then the stirrer was set to 400 rpm and the suspension was stirred for 90 min. Then the reactor temperature was cooled to 5 °C at 0.2 K/min. The suspension was stirred at 5 °C for 30 min and filtered by vacuum filtration using a Büchner funnel and cellulose filter paper (Whatman size 2). The obtained powder was dried at ambient temperature under a dry nitrogen flow for 18 h.

[0098] SEM-Images of the equant particles are shown in Figure 3 (magnification: top: 50x; bottom: 200x).

[0099] The bulk properties of the equant particles produced by this method are reported in Table 3.

Table 3

Bulk density (sieved)	0.75 g/cm ⁻³
Flow Function Coefficient (ffc)	8.3

Example 4: Preparation of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Equant Particles

[00100] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile (API) was prepared according to the method of WO 2017/106607 (compound 73).

[00101] Suspensions in organic solvents/water in mg-scale: Respective amount of the API was suspended in the recited solvents at ambient temperature and 50 °C, as reported in Table 4. Each suspension was stirred for 1 day using a magnetic stirring bar.

Table 4

Sample	Temp.	Weight API [mg]	Solvent (volume [mL])	Morphology
4A	50 °C	28.3	Water (0.5)	equant
4B	ambient	23.8	Methyl tert butyl ether / 2 % (v/v) Water (0.5)	equant
4C	50 °C	48.3	Methyl tert butyl ether / 2 % (v/v) Water (0.5)	equant
4D	ambient	43.2	n-Propyl acetate / 1 % (v/v) Water (0.5)	equant
4E	50 °C	76.9	n-Propyl acetate / 1 % (v/v) Water (0.5)	equant

[00102] The results of the analysis are reflected in Figure 7. As reflected by this figure, suspensions or crystallization in water or mixtures of organic solvents with water – even in very small amounts – showed more isotropic, equant particles. The solubility of the compound in water is very poor and thus, a crystallization from water is not efficient and control of the particle size distribution in the suspension was poor. Usage of organic solvents in mixture with water allows for the control of the particles size of the preferred equant shaped particles.

Example 5: Preparation of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile Particles

[00103] 5-((3R,5S)-3-Amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile (API) was prepared according to the method of WO 2017/106607 (compound 73).

[00104] The API was then further processed in four different ways.

[00105] Sample 5A: API was suspended in water and heated up to 30 °C. Suspension was stirred for 18 hours and subsequently filtered. Drying under vacuum (20-50 mbar) at 70 °C for 35 hours.

[00106] Sample 5B: API was suspended in EtOH and 1 M solution of K₂CO₃, heated up to 60 °C and stirred for 60 min. Solution was cooled down to 25 °C as fast as possible, polish filtration. Solution was heated up to 60 °C, again water was added in 40 min. Suspension was stirred for 60 min and cooled down to 10 °C with 1K/min. Cooled suspension was finally stirred for 4 hours and filtered. The filter cake was dried at 70 °C and 320 to 70 mbar for 36 hours.

[00107] Sample 5C: API was slurried in I-PrOAc/water (1%) at 25 °C for 120 min and subsequently cooled down to 5 °C with 0.2 K/min, solid/liquid separation by filtration.

[00108] Sample 5D: API was slurried in I-PrOAc/water (1%) at 50 °C, wet milling was performed at ambient conditions, after milling the suspension was heated up to 60 °C with 0.5 K/min, holding time @60 °C: 1 h, Ostwald ripening was performed by cooling down to 5 °C with 0.2 K/min, solid/liquid separation by filtration.

[00109] The particle size of the samples then became determined.

[00110] Optical microscopy: For determination of particle size by optical microscopy, a calibrated microscope Leica DM was used. The sample was dispersed in silicon oil to ensure that the particles are well-distributed and not agglomerated. An aliquot of the dispersed sample was prepared on a microscope slide and covered with a cover slip. The dimensions of the particles, i.e. the maximum and minimum Feret diameters, were measured using the image analysis software Leica Application Suite Version 4.12.0. Calculation of aspect ratio

was performed according to following equation: aspect ratio=minimum Feret diameter/maximum Feret diameter. The results of the analysis are shown in Table 5 and a representative image is shown in Figure 8.

Table 5

Sample	Morphology	Mean aspect ratio	Standard deviation	Number of counted particles
5A	Columnar	0.28	0.12	96
5B	Acicular	0.14	0.08	103
5C	Equant	0.59	0.14	86
5D	Equant	0.70	0.18	116

[00111] As reflected by Table 5, the suspension of the API in organic solvent and water, as reflected by Samples 5C and 5D, yielded equant shaped particles and a mean aspect ratio above 0.3, whereas the Samples that used water alone or an organic solvent for suspending the API lead to columnar or acicular particles with a lower aspect ratio.

[00112] Morphologi G3: The automated image analysis system Morphologi G3 (Malvern) was used for determining the aspect ratio of Sample 5C (calculated as ratio of the width to the length, wherein length is the maximum distance between any two points on the perimeter of the particle parallel to the major axis and the width is the maximum distance between any two points on the perimeter of the particle parallel to the minor axis). Approx. 19 mm³ of the sample was dispersed with 1 bar pressure, injection time of 20 ms and sampling time of 60 s on the image plate. Measurement was performed in Z-stacking mode with a magnification of 5x. Particle properties were determined by using the software Morphologi Ver. 8.23. The following filters were applied to exclude secondary particles and particles of insufficient quality:

Circularity: <0.85
 Convexity: <0.90
 Length: <100 µm
 Area Pixel: <1300

[00113] The calculated aspect ratio after volume transformation was then determined to be as follows:

D[V, 0.1]: 0.49 (10 % of volume weighted particles have a smaller aspect ratio than 0.49)

$D[v, 0.5]$: 0.62 (50 % of volume weighted particles have a smaller aspect ratio than 0.62)

$D[v, 0.9]$: 0.83 (90 % of volume weighted particles have a smaller aspect ratio than 0.83)

[00114] The distribution of the aspect ratio of the particles and exemplary particles are shown in Figure 9.

[00115] As reflected by this data, the aspect ratio as determined by automated image analysis is in conformity with the mean aspect ratio determined for Sample 5C with the optical microscope (value of 0.59 $\pm$ 0.14).

We Claim:

1. A composition comprising particles of a crystalline form of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile, wherein the mean aspect ratio of the 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile particles in the composition is at least about 0.3.
2. The composition according to claim 1, wherein the crystalline form of the majority of particles is a hydrate or hemihydrate.
3. The composition according to claim 2, wherein the crystalline form of the majority of particles is a crystalline hemihydrate polymorph characterized by one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9.
4. The composition according to claim 2, wherein the crystalline form of the majority of particles is a crystalline hemihydrate polymorph characterized by one or more peaks from the powder X-ray diffraction (PXRD), wherein the peaks, expressed in degrees $2\theta \pm 0.2^\circ$, comprise 7.2, 9.7, 13.4, 14.3, 17.0, 17.8, 19.9, 20.6, 21.5, 21.9, 22.2, 22.6, 23.0, 23.5, 24.1, 25.1, 25.5, 25.8, 26.4 and 26.9 and further characterized by an orthorhombic space group P212121 with the lattice parameters $a = 10.7499 \pm 0.1 \text{ \AA}$, $b = 16.4119 \pm 0.1 \text{ \AA}$, $c = 17.5927 \pm 0.1 \text{ \AA}$, and $\alpha = \gamma = \beta = 90^\circ$.
5. The composition according to any one of claims 1 to 4, wherein the composition has a bulk density greater than about 0.3 g/cm^3 .
6. The composition according to any one of claims 1 to 5, wherein the composition has a bulk density less than about 0.95 g/cm^3 .
7. The composition according to any one of claims 1 to 6, wherein the composition has a flow function coefficient (ffc) greater than about 4.
8. The composition according to any one of claims 1 to 7, wherein the mean particle diameter d_{90} of the particles in the composition is less than about $600 \text{ }\mu\text{m}$.
9. A process for preparing particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile comprising the steps:
 - (i) preparing a suspension of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile in a solvent comprising one or more organic solvents and water;
 - (ii) optionally heating the suspension to a recrystallization temperature;

- (iii) stirring the suspension for a period of time at ambient temperature or at the recrystallization temperature;
 - (iv) optionally wet milling the suspension;
 - (v) optionally cooling the suspension; and
 - (vi) separating the particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile from the solvent.
10. A composition comprising particles of 5-((3R,5S)-3-amino-5-(trifluoromethyl)piperidin-1-yl)quinoline-8-carbonitrile that is obtainable by the process according to claim 9.
11. The composition of claim 10, wherein the composition has the characteristics of the composition of any one of claims 1 to 8.
12. The composition of any one of claims 1 to 8, 10 and 11, wherein the composition is a pharmaceutical composition and comprises one or more pharmaceutically acceptable carriers.
13. The pharmaceutical composition of claim 12 for use as a medicament.
14. The pharmaceutical composition of claim 12 for use in a method of treating or preventing a TLR7/8-related autoimmune disease.
15. The pharmaceutical composition of claim 14, wherein the TLR7/8-related autoimmune disease is selected from the group consisting of rheumatoid arthritis, autoimmune pancreatitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, type I diabetes mellitus, multiple sclerosis, antiphospholipid syndrome, sclerosing cholangitis, systemic onset arthritis, irritable bowel disease, scleroderma, Sjogren's disease, vitiligo, myositis, dermatomyositis, polymyositis, pemphigus vulgaris, pemphigus foliaceus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, hypopituitarism, graft-versus-host disease, autoimmune skin diseases, uveitis, pernicious anemia, and hypoparathyroidism.