polymorphs of the same crystalline chemical entity. Polymorphism is often characterized as the ability of a drug substance, i.e. Active Pharmaceutical Ingredient (API), to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattices giving the crystals different physicochemical properties. The ability to manufacture the selected polymorphic form reliably is a key factor for consistent performance of the drug product.

Regulatory agencies worldwide require a reasonable effort to identify the polymorphs of the drug substance and check for polymorph interconversions. Due to the often unpredictable behavior of polymorphs and their respective differences in physicochemical properties, consistency in manufacturing between batches of the same product must be demonstrated. Proper understanding of the polymorph landscape and nature of the polymorphs of a pharmaceutical will contribute to manufacturing consistency.

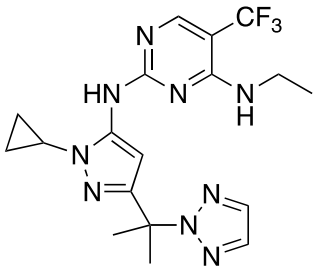
Crystal structure determination at the atomic level and intermolecular interactions offer important information to establish absolute configuration (enantiomers), phase identification, quality control, and process development control and optimization. X-ray diffraction is widely recognized as a reliable tool for the crystal structure analysis of pharmaceutical solids and crystal form identification.

Availability of a single crystal of the drug substance is preferred due to the speed and accuracy of the structure determination. However, it is not always possible to obtain a crystal of suitable size for data collection. Synchrotron X-ray powder diffraction is a useful technique. In such situations the crystal structure can be solved from X-ray powder diffraction data obtained by measurements at ambient conditions and/or at variable temperature or humidity.

There is a need to develop new polymorph forms and cocrystals of drug substances, and methods of preparing them.

SUMMARY

The present disclosure relates to crystalline, amorphous, and cocrystal forms of a LRRK2 inhibitor N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine, referred to herein as the Formula I compound and having the structure:



I.

In one aspect, there is provided a crystalline compound, N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine or a cocrystal thereof.

In one example, provided is a crystalline compound of Formula I, selected from:

a Form A polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.3, 13.8, 15.7, 18.7, 22.1, and 22.6; and

a Form B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 8.0, 9.9, 16.1, 19.9, and 23.2.

In some examples, provided is a Form A polymorph of Formula I exhibiting an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 12.3, 13.8, 15.7, 18.7, 22.1, and 22.6. In other examples, the Form A polymorph further comprises peaks at approximately 5.4 and 7.4 degrees 2-theta.

In some examples, the Form A polymorph has a differential scanning calorimetry DSC shows a melting endotherm at about 107.1 °C onset.

In some examples, the Form A polymorph is an anhydrate.

In some embodiments, the Form A polymorph is characterized by the X-ray powder diffraction pattern shown in Figure 2.

In other examples provided is a Form B polymorph of Formula I that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 8.0, 9.9, 16.1, 19.9, and 23.2.

In some examples, provided is a crystalline compound of Formula I in substantially pure form. In other examples, provided is a cocrystal thereof of Formula I in substantially pure form.

In some examples, the X-ray powder diffraction pattern of a crystalline compound or cocrystal of Formula I is made using CuKα1 radiation.

In another aspect, there is provided a crystalline compound, N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine exhibiting an X-ray powder diffraction pattern having characteristic peaks expressed in ± 0.3 degrees 2-theta at approximately 12.3, 13.8, 15.7, 18.7, 22.1, and 22.6.

In some examples, provided is a pharmaceutical composition comprising a crystalline polymorph of Formula I and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. In some examples, the crystalline polymorph is Form A.

In another aspect, there is provided a pharmaceutical composition comprising the crystalline polymorph as described herein and a pharmaceutically acceptable carrier, glidant, diluent, binder, disintegrant, or lubricant.

In another aspect, there is provided an amorphous compound,

amorphous Form C N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine.

In another aspect, there is provided a pharmaceutical composition comprising the amorphous compound as described herein and a pharmaceutically acceptable carrier, glidant, diluent, binder, disintegrant, or lubricant.

In some examples, provided is a pharmaceutical composition comprising an amorphous compound of Formula I and a pharmaceutically acceptable carrier, glidant, diluent,

or excipient.

In another aspect, there is provided a process for preparing amorphous Form C of the compound N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine, comprising heating a crystalline form of the compound until dissolution followed by cooling to form the amorphous compound.

In another aspect, there is provided a cocrystal comprising N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine and a coformer, and hydrates thereof.

In some examples, provided is a pharmaceutical composition comprising the cocrystal of Formula I and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

In another aspect, there is provided a pharmaceutical composition comprising the cocrystal as described herein and a pharmaceutically acceptable carrier, glidant, diluent, binder, disintegrant, or lubricant.

In some examples, a process for preparing a cocrystal of any one of Formula I comprising contacting N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine with the coformer.

In another aspect, there is provided a process for preparing a cocrystal as described herein comprising contacting N^2-(3-(2-(2*H*-1,2,3-triazol-2-yl)propan-2-yl)-1-cyclopropyl-1*H*-pyrazol-5-yl)-N^4-ethyl-5-(trifluoromethyl)pyrimidine-2,4-diamine with the conformer.

In some examples, the coformer is selected from 4-acetamidobenzoic acid, acetylsalicylic acid, trans-aconitic acid, adipic acid, benzoic acid, butyric acid, cholic acid, gallic acid, glutaric acid, fumaric acid, 4-hydroxybenzoic acid, isobutyric acid, malonic acid, D,L-mandelic acid, propionic acid, salicylic acid, succinic acid, terephthalic acid, and vanillic acid.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the inter-conversion relationships between Formula I compound polymorph Forms A and B and amorphous form C in a schematic diagram.

Figure 2 shows the XRPD pattern of Form A polymorph.

Figure 3 shows an overlay of the XRPD patterns of Formula I compound polymorph Forms A and B.

Figure 4 shows TGA and DSC data of Form A polymorph.

Figure 5 shows the thermal ellipsoid drawing of an asymmetric unit molecule from the single crystal X-ray structure of Form A polymorph.

Figure 6 shows XRPD Diffractogram of amorphous Form C.

Figure 7 shows PLM image of the Form A single crystal.

Figure 8 shows XRPD overlay comparing Form A after 6 months storage at 40 ºC/75%RH and 25 ºC/60%RH.

Figure 9 shows XRPD overlay comparing Form A after 48 months storage at 25 ºC/60%RH.