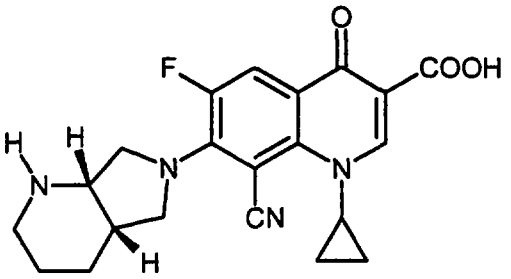
Crystal modification D of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

The present invention relates to a defined crystal modification of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, to processes for its preparation and to its use in pharmaceutical preparations.

Hereinbelow, 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (I) is referred to as CCDC.



(I)





CCDC is known from DE-A 19 633 805 or PCT Appl. No. 97 903 260.4. According to these publications, it is prepared by reacting 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid with (1S,6S)-2,8-diazabicyclo[4.3.0]nonane in a mixture of dimethylformamide and acetonitrile in the presence of an auxiliary base. Water is added to the mixture and CCDC is then extracted from water using dichloromethane and is isolated by removing the extractant. This gives a powder whose crystal modification is not unambiguous. On the contrary, the powder is largely amorphous and can contain mixtures of different crystal modifications. If, by chance, a uniform crystal modification is formed, it is not clear how it can be extracted and obtained in a defined form. However, it is the precondition for preparing medicaments that, for an active compound which can be present in different crystal modifications, it can be stated unamibiguously which of its crystal modifications is used for preparing the medicament.

The partially amorphous powder which is obtained by the preparation process outlined above is furthermore hygroscopic. However, amorphous solids, and in particular hygroscopic solids, are difficult to handle when being processed pharmaceutically since, for example, they have low bulk densities and unsatisfactory flow properties. Moreover, the handling of hygroscopic solids requires special work techniques and apparatuses to obtain reproducible results, for example with respect to the active compound content or the stability of the solid formulations produced.

It is therefore an object of the invention to prepare a crystalline form of a defined modification of CCDC which, owing to its physical properties, in particular its crystal properties, is easy to handle in pharmaceutical formulations.

This object is achieved according to the invention by a novel crystalline form of CCDC which is referred to as modification D hereinbelow.

The invention accordingly provides the crystalline modification D of CCDC which is characterized in that it has an X-ray powder diffractogram with the reflection signals (2 theta) of high and medium intensity (> 30% relative intensity) listed in Table 1 below.

Table 1:

X-ray powder diffractogram of CCDC of the modification D

2 θ (2 theta)
7.6
9.5
12.8
14.2
17.5
19
19.3
19.5
20.4
21
21.8
22.6
25.2
27.5

The X-ray powder diffractogram of the modification D is also shown in Figure 1.

Moreover, the CCDC modification D according to the invention differs from other forms of CCDC in a number of further properties. These properties, on their own or together with the other parameters, may also serve for characterizing the CCDC modification D according to the invention.

CCDC of the modification D is characterized by a melting point, determined with the aid of differential thermoanalysis (DTA), of from 261°C to 265°C. A characteristic differential thermodiagram is shown in Figure 2.

CCDC of the modification D is characterized in that it has an infrared spectrum, measured in KBr, as shown in Figure 3.

Crystal modification D of CCDC is obtained by dissolving CCDC of an unknown modification or amorphous CCDC at a concentration between 1 and 3 per cent by weight in water, allowing the solution to stand until a solid precipitates out, filtering off this solid, drying the resulting water-containing product, followed by heating to a temperature above the rearrangement temperature.

The water-containing product can be dried by customary methods. Thus, the water-containing product can be dried, for example, at elevated temperature under reduced pressure. It is also possible to carry out the drying in the presence of a customary drying agent, such as, for example, phosphorus pentoxide.

The temperature required for rearranging the dried sample into modification D can be determined by DTA of the dried substance. It is generally between 130°C and 160°C.

CCDC of the crystal modification D is surprisingly stable and does not change into another crystal modification or the amorphous form, even on prolonged storage. For these reasons, it is highly suitable for preparing tablets or other solid formulations. Owing to its stability, it gives these formulations the desired long-lasting storage stability. Using the crystal modification D, it is therefore possible to prepare, in a defined and targeted manner, stable solid preparations of CCDC.

CCDC of the crystal modification D is highly active against pathogenic bacteria in the area of human or veterinary medicine. Its broad area of use corresponds to that of CCDC.

The X-ray powder diffractogram for characterizing the crystal modification D of CCDC was obtained using a transmission diffractometer STADI-P with a location-sensitive detector (PSD2) from Stoe.

The melting point of the differential thermoanalysis was obtained using the DSC 820 unit from Mettler-Toledo. Here, the sample of CCDC of the crystal modification D was heated exposed to the atmosphere in an aluminium crucible at 5 K/min.

The KBr IR spectrum was obtained using the 881 unit from Perkin-Elmer.

The examples below illustrate the invention without limiting it. The solvent/base systems used in the examples below are particularly preferred.

Comparative Example

A mixture of 3.07 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 1.39 g of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane, 2.24 g of 1,4-diazabicyclo[2.2.2]octane (DABCO), 29.5 ml dimethylformamide and 29.5 ml of acetonitrile is stirred at room temperature for 16 hours. The reaction mixture is concentrated at a bath temperature of 60°C using a rotary evaporator, and the residue is taken up in 10 ml of water. The resulting solution is adjusted to pH 7 using dilute hydrochloric acid, and the solid is filtered off. The filtrate is extracted three times using 20 ml of dichloromethane each time. The organic phase is dried over sodium sulphate and filtered and the filtrate is concentrated at a bath temperature of 60°C using a rotary evaporator. This gives 2.4 g of a light-brown solid which has the X-ray powder diffractogram shown in Figure 4 and is therefore predominantly amorphous.

Example 1

1012 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are initially charged in a mixture of 3300 ml of ethanol, 1980 ml of N-methyl-pyrrolidone and 534 g of Hünig base. The mixture is heated under reflux, and 459 g of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane are then added dropwise. After the dropwise addition has ended, the mixture is stirred under reflux for another 3 hours and then allowed to cool to room temperature, and the solid is filtered off with suction and washed with a total of 1800 ml of ethanol.

The resulting solid is suspended in a mixture of 4650 ml of ethanol and 41 g of Hünig base, and the reaction mixture is heated under reflux for 3 hours. The reaction mixture is allowed to cool again to room temperature, and the solid is filtered off with suction, washed with a total of 1000 ml of EtOH and dried at from 60 to 70°C in a vacuum drying cabinet until the weight remains constant. This gives 1130 g of a beige solid which has the X-ray powder diffractogram shown in Figure 5.

From 450 g of this solid and 29 450 g of doubly distilled water, a 1.5% strength (w/w) aqueous solution is prepared, which is filtered through a 0.2 µm filter to remove any undissolved particles. This solution is then stored at room temperature under exclusion of light in canisters of polyethylene for 4 weeks. After this period of time, the precipitated solid is filtered off through a 0.8 µm filter and dried at 75°C overnight.

This gives 2 g of a solid which, according to X-ray powder diffractogram, is predominantly amorphous (Figure 6) and has the DTA shown in Fig. 7.

30 mg of the solid obtained in this manner are heated at 160°C under nitrogen for 2 hours. This gives 28 mg of a solid which has the X-ray powder diffractogram shown in Figure 1, the differential thermodiagram shown in Figure 2 and the IR spectrum shown in Figure 3.

Patent Claims

1. 8-Cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (CCDC) of the crystal modification D, characterized in that it has an X-ray powder diffractogram with the following reflection signals (2 theta) of high and medium intensity

2 θ (2 theta)
7.6
9.5
12.8
14.2
17.5
19
19.3
19.5
20.4
21
21.8
22.6
25.2
27.5

2. 8-Cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (CCDC) of the crystal modification D, characterized in that it has an X-ray powder diffractogram with the following reflection signals (2 theta) of high and medium intensity

2 θ (2 theta)
7.6
9.5
12.8
14.2
17.5
19
19.3
19.5
20.4
21
21.8
22.6
25.2
27.5

and a melting point, determined by DTA, of from 261°C to 265°C.

3. 8-Cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (CCDC) of the crystal modification D, obtainable by dissolving 1 to 3 per cent by weight of CCDC of unknown modification or amorphous CCDC in water, filtering off the solid which precipitates out after a while, drying this solid and heating it to a temperature above the rearrangement temperature.

4. Process for preparing CCDC of the modification D, characterized in that 1 to 3 per cent by weight of CCDC of unknown modification or amorphous CCDC is dissolved in water, and the solid which precipitates out after a while is filtered off, dried and heated to a temperature above the rearrangement temperature.

5. Medicament, characterized in that it comprises, in addition to customary auxiliaries and excipients, CCDC of the modification D according to either of Claims 1 and 2.

6. The use of CCDC of the modification D according to either of Claims 1 and 2 for preparing medicaments.

7. The use of CCDC of the modification D according to either of Claims 1 and 2 for preparing antibacterial compositions.