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New crystal modification of CDCH, a process for its preparation and pharmaceutical formulations comprising this modification

The invention relates to the new monohydrate of 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid hydrochloride (CDCH), a process for its preparation and pharmaceutical formulations which comprise this monohydrate as the active compound.

CDCH is a chemotherapeutic for humans and animals which has a broad spectrum of antibacterial action. The active compound can also be employed in the preservation of materials. CDCH shows a low toxicity and is particularly effective against Enterobacteriacea, and especially against antibiotic resistant strains: S. aureus, Ps. aeruginosa, Enterococcus faecalis and E. coli. CDCH and its preparation as a betaine is described in EP-A-550 903 and EP-A-591 808.

An anhydrous form of CDCH is the only crystal modification known to date. However, this crystal modification is not entirely satisfactory in the preparation of various medicament forms. CDCH is hygroscopic and absorbs water under adverse storage conditions and during pharmaceutical processing of the active compound to medicament forms. This impairs the dosing accuracy and quality of the preparations. Subsequent changes in the crystal structure of the anhydrous form when CDCH is stored in aqueous suspensions or at ambient humidity are the reason for the physical instability of CDCH. It is therefore of great importance to use a crystal form which is as stable as possible for the preparation of medicament forms comprising CDCH.

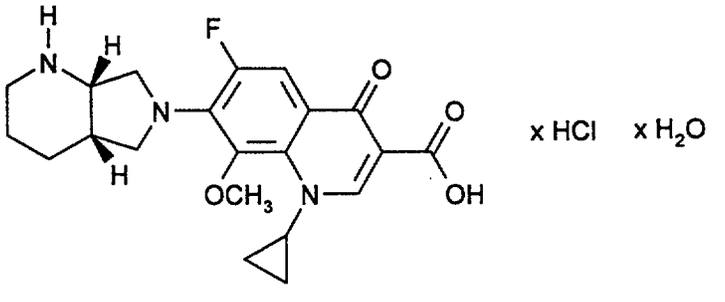
It has now been found that CDCH can be converted into a new water-containing

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crystalline modification which is distinguished by an increased stability, in particular during storage at high humidities, compared with the known anhydrous form and is particularly suitable for the preparation of stable pharmaceutical preparations.

During preparation of the monohydrate from aqueous media, the active compound crystallizes in the form of needles which become severely matted. Surprisingly, the crystal habit can be modified in a controlled manner under certain crystallization conditions. The prisms thus formed represent a preferred embodiment of the present invention, since they do not mat and are significantly more free-flowing than the monohydrate in the form of needles. This has considerable advantages in the preparation of medicament forms. By using a non-hygroscopic, free-flowing active compound, a satisfactory dosing accuracy is achieved during the preparation of medicaments, which increases safety and therefore minimizes the risk to the patient.

The invention accordingly relates to the new monohydrate of CDCH of the formula I



and to a process for its preparation, which is characterized in that anhydrous, crystalline CDCH is treated with an amount of water sufficient for thorough mixing and for formation of the monohydrate at temperatures below 80°C until the stoichiometric content of water of crystallization has been absorbed and conversion of the crystals is complete, and the crystals thus obtained are separated off and dried to the constant weight of the monohydrate in order to remove the adsorbed water present. To avoid the formation of the anhydrous form, the humidity during drying should be not less than 30 % relative humidity. The monohydrate crystallizes in the form of needles from

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water-containing media with a water content of more than 10 %.

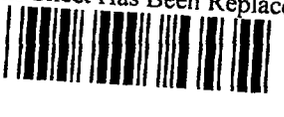
The preferred monohydrate form which crystallizes as prisms can be obtained by suspending anhydrous crystalline CDCH in ethanol/water mixtures, especially preferably in ethanol/water with a maximum of 10 % of water, thorough mixing of the solid contents with the amount of water added being ensured until the required content of water of crystallization has been absorbed and conversion of the crystals is complete, for example by stirring the suspension or shaking, swirling, rotating the reaction vessel and the like. If the water content in the ethanol/water mixture is a maximum of 10 %, the monohydrate crystallizes in the form of prisms.

Provided that the amount of water is sufficient for formation of a stoichiometric monohydrate and for thorough mixing of the amount of CDCH employed with the water, any desired amount of water can be used for formation of the monohydrate in the form of needles, since the absorption of water of crystallization, which proceeds with conversion of the crystals, ends with the formation of the monohydrate, and furthermore no further hydrates are obtained. The amount of water is expediently limited such that although thorough mixing can take place, no or low solubility losses occur. The preparation of the monohydrate is preferably carried out at room temperature, but can also be carried out at elevated temperature, for example 30°C to 60°C, or a low temperature, for example 5°C to 20°C. The preparation of the monohydrate from the anhydrous form also takes place successfully at humidities greater than 30 % relative humidity. However, this process is not suitable for the preparation of the preferred monohydrate which crystallizes as prisms.

The crystals of the monohydrate are separated off from the excess solvent by customary methods, for example by filtering, decanting, centrifuging and the like. The crystals of the monohydrate which have been separated off are advantageously dried at room temperature or at elevated temperature up to 50°C at humidities of at least 30 % relative humidity.

The CDCH monohydrate according to the invention has a characteristic IR spectrum (Figure 1), which shows characteristic absorption bands of the water of crystallization

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in the region of the OH valency vibrations (3600 - 3100 cm^{-1}), which are absent in the anhydrous crystal modification. It also differs from the anhydrous CDCH in other frequency ranges, so that a completely different arrangement of the molecules in the crystal lattices of the two modifications can be concluded.

The determination of the water content confirms the presence of a stoichiometric monohydrate of CDCH. The thermogravimetric weight loss determined in several samples of the monohydrate is 1 mol of water (3.9 %, Figure 2). The thermogram of the monohydrate (Figure 3) recorded by means of DSC (Differential Scanning Calorimetry) under atmospheric pressure shows, in agreement with the thermogravimetric measurements, the release of water by a broad endothermal peak which indicates the rearrangement of the crystal lattice of the monohydrate analysed, the dissociation of CDCH and water and the enthalpy of vaporization of the liberated water of crystallization. The X-ray diffractograms and ^{13}C-NMR, Raman and FIR spectra of the anhydrous form and of the monohydrate show characteristic differences (Figures 4-7, Tables 2-5): thus, for example, the ^{13}C-NMR spectrum has a characteristic peak at 168.1 ppm and the X-ray diffractogram a line at $2\Theta = 26.7$.

The DSC and TGA thermograms were obtained using thermoanalysers (DSC 7 and TGA 7) from Perkin-Elmer. The X-ray diffractograms were recorded with a Stoe transmission diffractometer. The IR, FIR and Raman spectra were recorded with Fourier-IR spectrometers IFS 66 (IR), IFS 66v (FIR) and IFS 88 (Raman) from Bruker. The ^{13}C-solid-NMR spectra were recorded with a Bruker MSL 300. The microscopic photographs were taken with a Laborlux S microscope from Leitz.

During storage, the CDCH monohydrate according to the invention shows a higher physical stability compared with the anhydrous crystal modification, and is therefore more suitable for the preparation of various medicament forms. The preferred monohydrate, which crystallizes in the form of prisms, furthermore imparts to CDCH excellent trickling and flow properties, which is of great advantage in the preparation of pharmaceutical formulations (Figure 8). The invention therefore also relates to liquid and solid pharmaceutical formulations which comprise the CDCH monohydrate according to the invention, such as, for example, suspensions, emulsions, tablets, coated

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tablets, coated tablet cores, suppositories, hard or soft gelatin capsules and the like. Aqueous suspensions and tablets for oral administration preferably comprise the monohydrate according to the invention, particularly preferably in the prismatic crystal form.

CDCH can be present in these pharmaceutical formulations as the only active compound or can be combined with other antibacterially active substances.

Pharmaceutical formulations can comprise the CDCH monohydrate according to the invention by itself or in combination with several other active compounds, or be formulated together with auxiliaries and additives usually employed in pharmacy, such as tablet binders, fillers, preservatives, tablet disintegrating agents, flow regulating agents, plasticizers, wetting agents, dispersing agents, emulsifiers, solvents, flavourings and the like, to give presentation forms for oral, parenteral or rectal administration.

The pharmaceutical formulations are prepared in a manner known per se, for example by mixing, stirring, suspending, dispersing, emulsifying, and the like, the active compounds with or in the pharmaceutical auxiliaries and processing the components to pharmaceutically suitable presentation forms for oral, parenteral or rectal administration.

Preparation of crystalline CDCH (needles, prisms)

Example 1 (prisms)

1 g of anhydrous CDCH is dissolved in 150 ml of absolute ethanol and the solution is filtered. The solution is heat treated at 60°C until the solvent has evaporated completely. The crystals which have precipitated out are dried at room temperature/ambient humidity.

Example 2 (prisms)

0.1 g of anhydrous CDCH is dissolved in 10 ml of ethanol (10 % water content). The solution is heat treated at 60°C until the solvent has evaporated completely. The

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crystals which have precipitated out are dried at room temperature/ambient humidity.

Example 3 (prisms)

4 g of anhydrous CDCH are dissolved in 300 ml of ethanol (96 %). The solvent is distilled off in a rotary evaporator at 60°C under 120 mbar. The crystals are dried in a vacuum drying cabinet under 80 mbar at 105°C for 2 hours and then exposed to ambient humidity.

Example 4 (needles)

0.3 g of anhydrous CDCH is dissolved in 6 ml of water:ethanol (1:1). The solution is heat treated at 70°C until the solvent has evaporated completely. The crystals which have precipitated out are dried at room temperature in vacuo and then left to stand at room temperature/85% relative humidity overnight.

Example 5 (needles)

0.1 g of anhydrous CDCH is dissolved in 5 ml of methanol. The solution is left to stand at RT until the solvent has evaporated completely. The crystals are dried in vacuo at room temperature and then left to stand at room temperature/85% relative humidity overnight.

Example 6 (needles)

0.1 g of anhydrous CDCH is dissolved in 5 ml of water. The solution is left to stand at room temperature until the solvent has evaporated completely. The crystals are dried at room temperature in vacuo and then left to stand at room temperature/85% relative humidity overnight.

Example 7

25.1 g of CDCH monohydrate (prisms), 3.3 g of Avicel PH 101 and 1.7 g of maize

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starch are mixed in a highshear mixer and then granulated with 13 g of water. After rasping (4 mm), the granules are dried in a mini-fluidized bed dryer (intake air temperature 80°C) and sieved over a 0.8 mm sieve. Subsequent mixing is carried out with 0.19 g of Ac-Di-Sol and 0.01 g of magnesium stearate. The mixture is then pressed on a single punch tabletting machine (tablet format 5.5 r 9, tablet weight 68.5 mg).

Example 8

196.6 g of micronized CDCH monohydrate (needles) are mixed with 88 g of Avicel in a highshear mixer (powder mixture). 3.6 g of PVP 25 are dissolved in 97.2 g of water (granulating liquid). The powder mixture is granulated with the granulation liquid. After rasping (3 mm), the granules are dried in a dryer (intake air temperature 90°C) and sieved over a 1 mm sieve. Subsequent mixing is carried out with 1.8 g of Ac-Di-Sol and 0.1 g of magnesium stearate. The mixture is then pressed on a rotary press (tablet format 5.5 r 9, tablet weight 83.4 mg).

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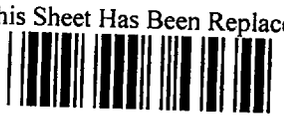


Table 1: Ir spectroscopy

Anhydrous form [cm^{-1}]	Hydrate [cm^{-1}]
722	722
804	804
834	835
938	875
957	938
994	994
1048	1045
1186	1082
1319	1163
1354	1184
1372	1319
1453	1352
1513	1372
1622	1394
1709	1432
2427	1456
2524	1517
2700	1624
2929	1709
3469	2427
3527	2456
	2524
	2634
	2925
	2698
	2745
	2893
	2925
	3472
	3530

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Table 2: X-ray diffractometry

Anhydrous form [2 Theta]	Hydrate [2 Theta]
5,8	5,8
8,6	8,5
10,3	10,1
11,6	11,6
13,6	13,4
14,5	14,5
15,0	14,8
15,8	15,6
17,3	17,0
17,5	17,2
18,3	17,4
18,9	17,5
19,3	17,9
19,6	18,6
20,6	19,1
21,5	19,6
22,5	20,4
22,8	21,1
23,0	21,8
23,8	22,7
24,2	23,0
24,7	23,6
25,0	24,1
26,3	24,5
27,0	26,5
27,4	26,7
27,8	27,0
28,2	27,3
29,4	27,5
29,7	27,8
30,0	28,5
30,3	28,9
31,3	29,2
31,8	29,7
34,5	31,4
35,3	31,9
37,1	32,3
	32,6
	34,2
	35,1
	35,5
	36,8
	37,5

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Table 3: ^{13}C solid-state NMR spectroscopy

Anhydrous form [ppm]	Hydrate [ppm]
8,5	7,7
12,3	8,3
14,1	9,0
18,2	10,8
20,0	12,1
22,8	18,2
35,2	19,8
39,7	22,9
46,5	34,9
49,5	40,2
52,3	47,0
55,9	49,5
59,2	50,1
62,6	52,6
65,8	55,9
105,4	56,8
108,1	59,4
116,9	64,1
117,5	66,8
134,7	105,0
136,0	107,1
137,3	116,3
140,1	117,4
142,6	135,2
150,1	136,1
152,6	137,4
165,3	140,8
166,0	143,5
175,5	149,3
	150,9
	168,1
	175,5

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Table 4: Raman spectroscopy

Anhydrous form [cm^{-1}]	Hydrate [cm^{-1}]
110	109
147	148
243	243
278	278
388	309
425	425
496	496
543	543
723	724
833	833
964	962
1031	1031
1191	1191
1267	1305
1305	1321
1320	1352
1354	1376
1376	1433
1433	1490
1491	1554
2891	1619
2922	1711
2957	2835
2991	2888
3020	2923
3054	2942
3069	2958
3082	2977
3088	2990
3110	3019
	3056
	3069
	3089
	3106

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Table 5: FIR spectroscopy

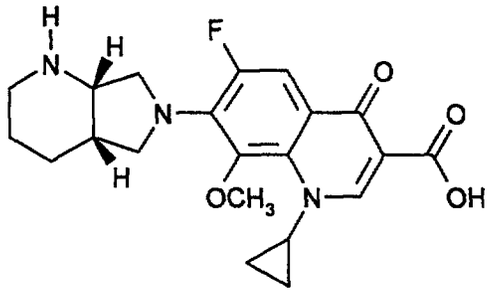
Anhydrous form [cm^{-1}]	Hydrate [cm^{-1}]
137	95
165	111
187	139
219	145
230	163
248	185
279	220
289	230
311	277
342	313
370	340
386	369
396	388
412	399
423	412
436	423
456	436
474	459
494	476
	494

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* C L M S *

Patent Claims

1. Monohydrate of CDCH, of the formula



x HCl x H_2O

which has a characteristic peak at 168.1 ppm in the ^{13}C-NMR spectrum and a band at $2\Theta = 26.7$ in the X-ray diffractogram.

2. Compound according to Claim 1 in the prismatic crystal form.

3. Process for the preparation of the CDCH monohydrate according to Claim 1, characterized in that anhydrous CDCH is treated with an amount of water which is at least sufficient for thorough mixing and hydration until the stoichiometric content of water of crystallization has been absorbed and conversion of the crystals is complete, the crystals of the monohydrate thus obtained are separated off and the adsorbed water present is removed.

4. Process according to Claim 3, characterized in that a suspension of the anhydrous CDCH in aqueous media is stirred until hydration and conversion of the crystals is complete.

5. Process according to Claim 3, characterized in that, to prepare the monohydrate in the form of prisms, anhydrous CDCH or CDCH monohydrate in the form of needles is dissolved in media having a water content which is stoichiometrically sufficient but limited to 10 %, and the solvent is then removed.

6. Process according to Claim 3, characterized in that anhydrous CDCH is exposed

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to humidity until the crystals have been converted quantitatively.

7. Medicaments comprising compounds according to Claims 1 and 2.

8. Antibacterial compositions comprising compounds according to Claims 1 and 2.

9. Use of compounds according to Claims 1 and 2.

10. Use of compounds according to Claims 1 and 2 in the preparation of medicaments.

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