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PHYSICO-CHEMICAL CHARACTERIZATION OF AN ACTIVE PHARMACEUTICAL INGREDIENT
Crystal polymorphism and structural analysis

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Abstract

The physico-chemical properties and polymorphism of a new active pharmaceutical ingredient entity has been analyzed and the gain of knowledge during the chemical development of the substance is described. Initial crystallization revealed an anhydrous crystal form with good crystallinity and a single, sharp DSC melting peak at 171°C and a straightforward development of this crystal form seemed possible. However, during polymorphism screening, new crystalline forms were detected that were often analyzed as mixtures of crystal forms. The process of characterization and identification of the different crystalline forms and its thermodynamical relationship has been supported by a combination of experimental and computational work including determination of the three-dimensional structures of the crystal forms. The crystal structure of one polymorphic form was solved by single crystal X-ray structure analysis. Unfortunately, Mod B resisted in formation of suitable single crystals, but its structure could be solved by high resolution powder diffraction data analysis using synchrotron radiation. Calculation of the theoretical X-ray powder diffraction pattern from three dimensional crystal coordinates allowed an unambiguous identification of the different crystalline forms. Two polymorphic crystal forms of the API-CG3, named Mod A and Mod B, are enantiotropic whereas Mod B is the most stable polymorph at room temperature up to about 50°C and Mod A at temperatures above 50°C. The mechanism of the solid–solid transition can be explained by analyzing the molecular packing information gained from the single crystal structures. A third crystalline form with the highest melting peak turned out to be not a polymorphic or pseudopolymorphic crystal modification of our API-CG3 but a chemically different substance.

Keywords: crystal packing, crystal polymorphism, differential scanning calorimetry, IR spectroscopy, single crystal structure, synchrotron radiation, X-ray powder diffraction

Introduction

Characterization and monitoring of solid state properties of active pharmaceutical ingredients (API) and excipients are fundamental elements of the pharmaceutical development since batch to batch inconsistency can cause crucial problems in the manufacturing of the pharmaceutical dosage form, the quality of the formulation, the bioavailability and drug stability [1] .

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Polymorphism is the ability of a compound to crystallize in more than one distinct crystal species. Pseudopolymorphism is the name given to solvates or hydrates, when a new compound is formed between the drug substance and a volatile solvent. The aim of a polymorphism study is to find out how many different crystalline forms, polymorphs and pseudopolymorphs of the compound, can be obtained. This is often done by crystallization and equilibration experiments with organic solvents applying different concentrations at different temperatures. Those experiments can result in a completely new crystalline modification or in mixtures of the initial crystalline modification with one or more new crystalline modification [2, 3]. The next step is to scale up the experiments in order to obtain and isolate the new crystalline forms for its characterization. Typical methods for the solid-state characterization are X-ray powder diffraction, differential scanning calorimetry (DSC), thermogravimetry, solubility and dissolution rate measurements, water sorption and desorption behavior, Fourier Transformed - Infrared (FT-IR) and Raman spectroscopy [4]. Based on the results of the comprehensive physico-chemical characterization, the thermodynamic relationship of the different polymorphs can be assessed. The best modification in terms of crystallinity, stability, hygroscopicity and feasibility, usually the thermodynamic most stable modification at room temperature, will be selected for further pharmaceutical development. Furthermore methods for detection and control of the purity of the chosen crystalline modification during development are needed. A frequently used method is X-ray powder diffraction.

A critical aspect is to ensure that the different crystalline modifications identified are pure modifications. Already the initial crystalline modification or the newly obtained crystalline forms can appear as mixtures of different crystalline polymorphs or pseudopolymorphs which is not easily detectable e.g. by several peaks in the DSC curve. An unambiguous identification of a pure crystalline modification can be obtained by three-dimensional single crystal structure analysis. This information provides insights into the conformation of the compound, the molecular packing, solvent molecules, their interaction to each other and the intra- and intermolecular bonds [5, 6]. On the other hand, the experimentally determined single crystal structure can be used to calculate the density of the modification, the crystal morphology and the packing at the different crystal faces and the X-ray powder diffraction pattern. The calculated X-ray powder diffraction pattern can be compared to the experimental X-ray powder diffraction pattern to check the purity of the selected crystal modification.

The current paper describes the physico-chemical characterization and the polymorphism screening of a pharmaceutical compound API-CG3. The process of characterization and identification of the different crystalline forms and its thermodynamical relationship has been supported by a combination of experimental and computational work including determination of the three-dimensional structures of the crystal forms. The crystal structure of one polymorphic form was solved by single crystal X-ray structure analysis. However Mod B resisted in formation of suitable single crystals and its structure was finally solved by high resolution X-ray powder diffraction analysis using synchrotron radiation. Calculation of X-ray powder dif-

fraction pattern from three dimensional crystal coordinates allowed an unambiguous identification of the different crystalline forms.

Materials and methods

Materials

The solvents used were purchased from Fluka and Merck.

Methods

Crystallization and equilibration experiments

The compound is exposed to different solvents or solvent mixtures, at a certain temperature as a suspension or solution. The suspension is stirred for a day, filtered and the solid portion analyzed (equilibration). The solution is cooled or evaporated and the obtained solid portion analyzed (crystallization).

Differential scanning calorimetry

Samples (1.5–2.5 mg) of the original powders were placed in perforated aluminum pans analyzed by DSC (Perkin Elmer DSC -7) under nitrogen purge gas (about 50 mL min^{-1}). Heating-cooling-heating cycles were performed between room temperature and 300°C with different heating rates (e.g. 5, 10 or 20 K min^{-1}) depending on the purpose. The DSC analysis was performed on initial samples, samples after equilibration with saturated solutions in pure solvents and solvent mixtures. The instrument is calibrated with certified standards.

Thermogravimetry

Samples (5–20 mg) of original powders were placed in the sample pans and analyzed by a TGA-7; PerkinElmer or Mettler TGA851e under nitrogen purge gas (20–50 mL min^{-1} with a heating rate between 5–20 K min^{-1}).

Hot stage microscopy and SEM

An Olympus BX-50 microscope connected to a Mettler HFS 91 hot stage and temperature controller was used to observe the sample under polarized light at different heating rates up to the melting of the compound. The SEM investigations were performed using a Jeol JSM 6300.

FT-IR spectroscopy

Infrared spectra were recorded with a Bruker IFS 55 FTIR-spectrometer. Spectra were sampled at potassium bromide disks at an instrument resolution of 2 cm^{-1} in the range from 4000–600 cm^{-1}. Potassium bromide disk was put in a Graseby Specac heating cell applying a temperature range from 25°C–220°C with a heating rate of 5°C min^{-1}.

X-ray powder diffractometry

X-ray powder diffraction patterns were obtained with a Scintag XDS2000 diffractometer (CuK_α-radiation), at a scan rate of 0.5° (2θ) min^{-1} over the 2–40° (2θ). Temperature resolved X-ray powder diffraction experiments were performed using the heating and cooling chamber form Scintag.

Results and discussion

Initial solid-state characterization

The initial samples from manufacturing of the API-CG3 have been characterized. The samples have a high chemical purity of >99% with no significant residual solvent content. The X-ray powder diffraction pattern of the initial samples shows a highly crystalline substance, named Mod A (Fig. 1). In the DSC curve of the API-CG3 Mod A (Fig. 2), a single sharp melting peak at about 171°C is obtained. Mod A is not hygroscopic. The thermogravimetric curve (Fig. 3) and GC analysis did not show significant amounts of residual solvents (<0.05%). No significant loss on drying is obtained by thermogravimetry up to the melting of the compound. However a continuous loss on drying is obtained after the melting point.

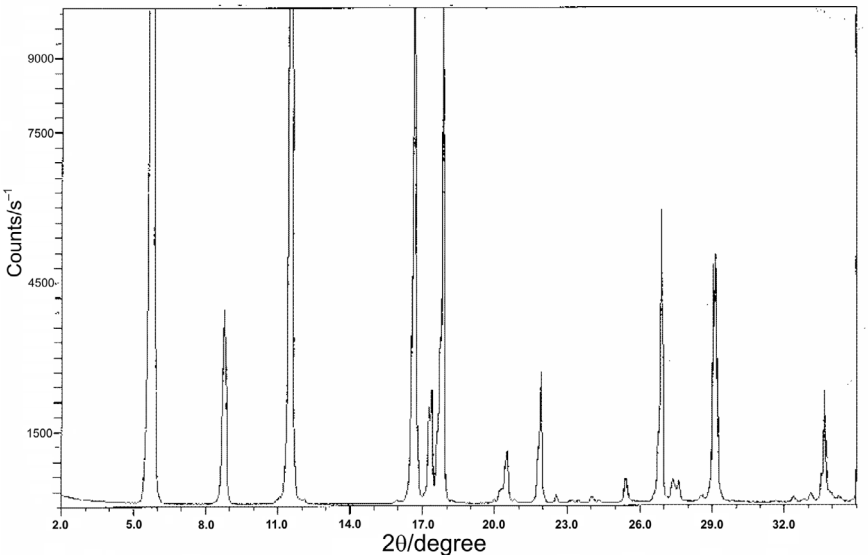

Fig. 1 X-ray powder diffraction pattern of the API-CG3, Mod A

Based on the initial results, the requirement of a screening for crystal polymorphism was questioned as the current crystalline form seems to be a suitable crystal form for further development. Nevertheless a polymorphism screening was performed.

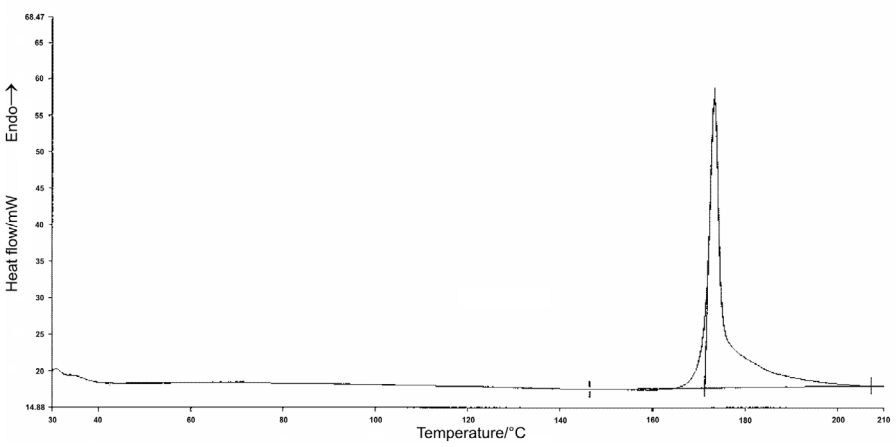

Fig. 2 DSC curve of the API-CG3, Mod A

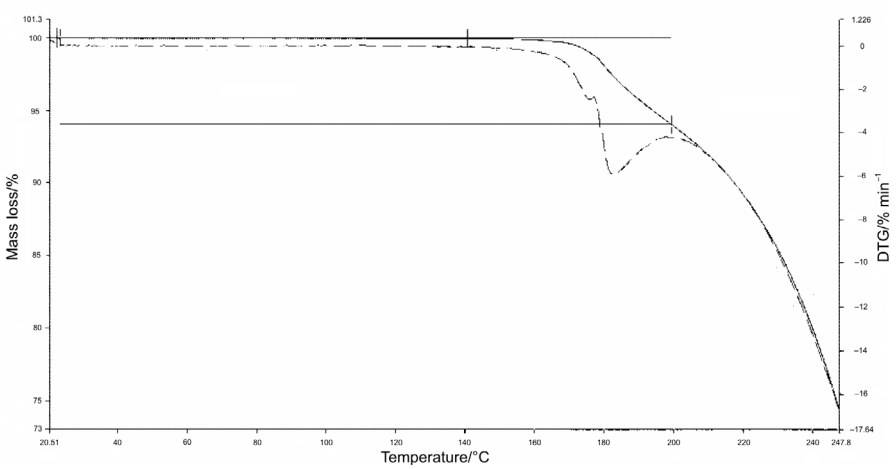

Fig. 3 TG/DTG curves of the API-CG3, Mod A

Polymorphism screening

The polymorphism screening included crystallization and equilibration experiments using a range of organic solvents. Those experiments were performed in a temperature range between 0°C and 80°C. The solid portion of the experiments was filtered and analyzed by X-ray powder diffraction. Already in the first series of solvent screening experiments at 60°C with different solvents, one completely new X-ray powder diffraction pattern as well as Mod A with additional diffraction peaks was observed (Table 1).

The experiments that yielded new X-ray powder diffraction pattern were repeated. In addition, the crystallization conditions were further modified, optimized

Table 1 Solvent screening of API-CG3 Mod A at 60°C

Solvent	X-ray powder diffraction results
Acetone	Mod B
Isopropanol	Mod A and traces of B
Ethanol	Mod B
Ethyl acetate	Mod A & additional diffraction peaks
Toluene	Mod A & additional diffraction peaks
Methanol	Mod A
Ethanol/water	Mod A

and scaled up to obtain pure samples of the new crystalline forms amendable for further characterization.

Solid-state characterization of Mod B

After isolation of pure Mod B of the API-CG3, it has been characterized by DSC, TG, X-ray powder diffraction (XRPD) and DVS (water sorption – desorption measurements to evaluate the hygroscopicity) as well as spectroscopic methods. Mod B is an anhydrous, non-hygroscopic, highly crystalline form which exhibits in the DSC curves two endothermic transitions, at about 120 and 168°C with melting enthalpies of 15 and 197 J g^{-1}, respectively (Fig. 4). The X-ray powder diffraction pattern can clearly be differentiated to Mod A (compare Fig. 1 and Fig. 5, respectively).

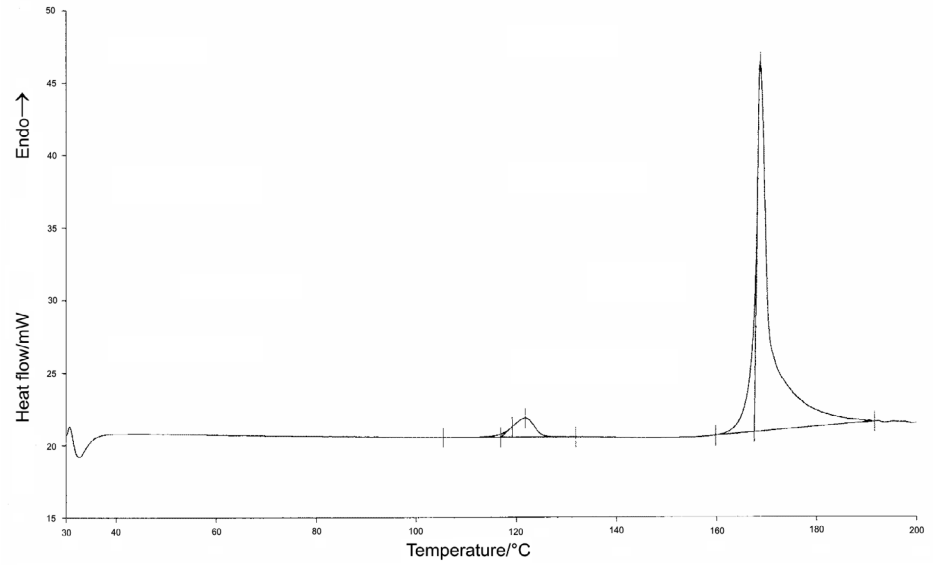

Fig. 4 DSC curve of Mod B (heating rate: 10 K min^{-1})

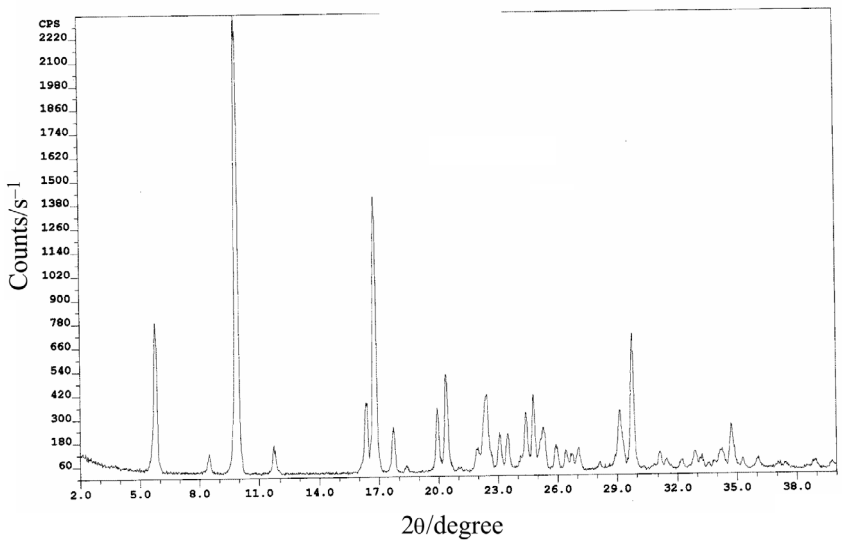

Fig. 5 X-ray powder diffraction pattern of Mod B

Characterization of Mod B by thermal microscopy

Mod B has been investigated by temperature resolved polarized light-microscopy to check whether at about 120°C a solid-solid transition or a melting of the compound occurs.

It could be shown (Fig. 6) that at about 120°C no melting occurs but the polarization of the crystals is changing. Only at about 171°C a melting of the crystal could be obtained followed by a re-crystallization at higher temperatures with subsequent melting. This is in good agreement with further DSC or temperature resolved X-ray powder diffraction observations.

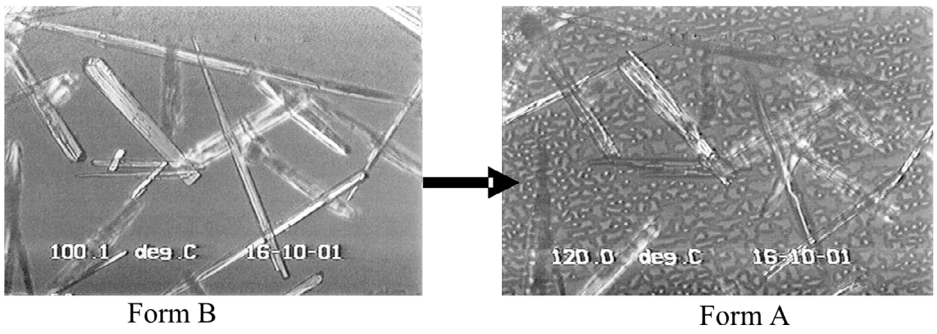

Fig. 6 Light microscopy pictures of API-CG3 Mod B at room temperature and 120°C

Temperature resolved X-ray powder diffraction and DSC experiments of Mod B

Similar experiments were performed with X-ray powder diffraction technique. X-ray powder diffraction pattern were recorded in 10° temperature steps between room temperature, 30 to 220°C starting with Mod B. After heating of Mod B a solid-solid transition could be observed from Mod B to Mod A. After further heating melting of Mod A is obtained. However, after further heating a re-crystallization has been obtained to a new crystalline compound. The X-ray powder diffraction pattern of this compound is equal to the X-ray powder diffraction pattern obtained at 60°C in polymorphism screening experiments as a mixture with Mod A (Table 1). This compound melts at about 190°C.

A DSC curve of Mod B was recorded with 20 K min^{-1} between room temperature and 210°C resulting in 3 endothermic transitions (Fig. 7). It could be shown in combined DSC, thermal microscopy and X-ray powder diffraction experiments that

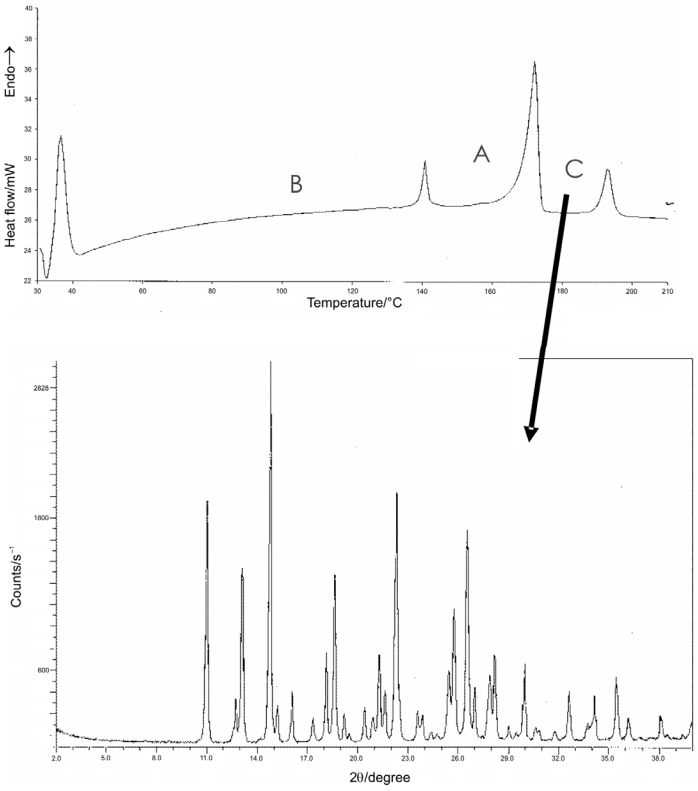

Fig. 7 DSC curve of Mod B recorded with 20 K min^{-1} between 30 and 210°C. The three peaks in DSC correspond to three different crystal forms termed B (Mod B), A (Mod A) and C for the new crystalline form with the corresponding X-ray powder pattern in Fig. 1 (Mod A), Fig. 5 (Mod B) and at the bottom of this figure for the new crystalline form, respectively

after the first endothermic peak Mod A is formed by a solid-solid transition. The 2nd endothermic peak corresponds to the melting of Mod A. After melting of Mod A at about 171°C a re-crystallization to another crystalline form is obtained.

Enantiotropic relationship between Mod B and A

Based on the results of thermal microscopy, DSC and temperature resolved X-ray powder diffraction experiments Mod A and Mod B are enantiotropic to each other. The endothermic transition at about 120°C recorded by DSC with a heating rate of 10 K min^{-1} corresponds to a solid-solid transition from Mod B to Mod A. This transition is not spontaneous reversible. In order to determine the enantiotropic transition temperature of Mod B to Mod A, 1:1 mixtures of Mod B and Mod A were exposed to different solvents as a suspension at different temperatures. The experimental transition temperature is between 50–60°C for most solvents (Table 2).

Table 2 Equilibration of a 1:1 mixture Mod A and B at different temperatures and in different solvents

Temperature/°C	Solvent	X-ray powder diffraction results
0	ethanol	Mod B
25	ethanol	Mod B
50	ethanol	Mod B & additional peaks
60	ethanol	new X-ray powder pattern
70	ethanol	new X-ray powder pattern
0	toluene	Mod B
25	toluene	Mod B
50	toluene	Mod B
60	toluene	Mod A & additional peaks
70	toluene	Mod A & additional peaks

Identification of a new chemical entity corresponding to the crystalline form obtained at high temperatures

After melting of Mod A and further heating a subsequent re-crystallization to a new crystalline compound is obtained. The X-ray powder diffraction pattern of this compound is equal to the X-ray powder diffraction pattern obtained e.g. at 60°C in polymorphism screening experiments as a mixture with Mod A (Table 1). This compound melts at about 190°C.

In order to gain structural information of this compound, temperature resolved FT-IR spectroscopy was performed (Table 3).

Above 140°C Mod B transforms into Mod A. Further heating above 170°C causes a lactam ring formation by an intramolecular dehydration, accompanied by a release of 1 mol water. Thus the new crystalline form with the highest melting peak is

Table 3 Temperature resolved FT-IR spectroscopy starting with Mod B

Temperature/°C	FT-IR spectrum
25–100	Corresponds to Mod B
140–160	Corresponds to Mod A
Above 170	New compound

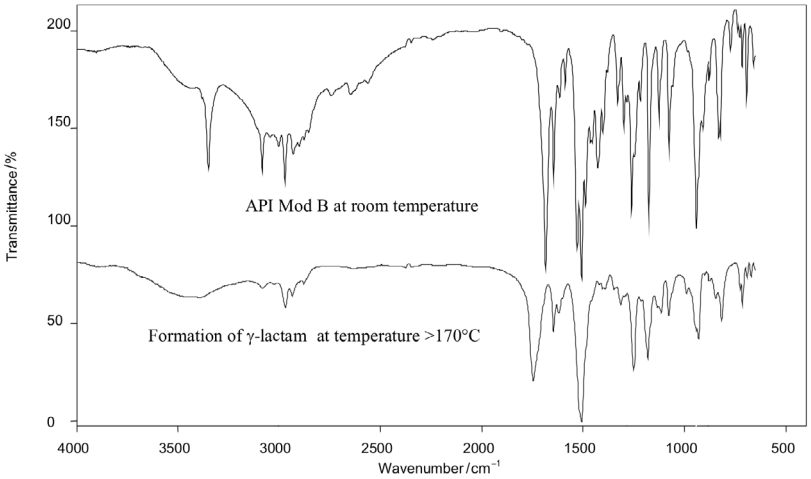

Fig. 8 FT-IR spectra of Mod B (black, at the top) and crystalline compound recrystallized from Mod A melt

not a polymorphic or pseudopolymorphic crystal modification of our API-CG3 but a chemically different substance (Fig. 8). This was confirmed by other complementary methods e.g. NMR, HPLC and MS.

Three-dimensional crystal structure analysis

In order to gain more insight into the structural basis for the polymorphism of API-CG3, the molecular packing, solvent molecules, their interaction to each other and the intra- and intermolecular bonds, the crystal structure of the two modifications of the API-CG3 were determined. Mod A was determined by single crystal X-ray diffraction, while Mod B was characterized from synchrotron powder data by means of the program PowderSolve.

Crystal structure determination of Mod A from single crystals

Single crystals of high quality were grown by slow evaporation at room temperature of an ethanol/water (50:50) solution for Mod A. Data collection and structural determina-

Table 4 Three-dimensional structure parameter for Mod A and Mod B

	Mod A	Mod B
λ/Å	1.54178	0.94953
Space group	$P2_1/c$	$P2_1/a$
Z	4	4
a/Å	16.131(3)	11.2875(1)
b/Å	4.656(1)	29.7356(2)
c/Å	21.114(4)	4.51097(2)
β/°	108.43(1)	104.8038(5)
V_{cell}/Å3	1504.5(5)	1463.81(2)
ρ(calc)/g cm^{-3}	1.445	1.485
R^{α}	0.069	0.156
C1-C4-C5-C6, °	79.8	70.6
C10-C9-C11-C12, °	55.7	–110.5
N13-C14-C15-F16, °	–60.0	–67.6
N···O_{intra}/Å	2.978	2.906
O···O_{inter}/Å	2.680	2.610

tion were carried out using standard crystallographic techniques [7, 11]. The most relevant crystal data and geometrical features for Mod A are summarized in Table 4.

Mod A crystallizes in the monoclinic space group $P2_1/c$, with four molecules in the unit cell. A comparison between the experimental and the simulated powder X-ray pattern using the single-crystal structure has been performed. Although the experimental X-ray powder diffractogram is severely affected by preferred orientation (i.e. there is a mismatch of intensity in some peak), all the peak position in 2θ are essentially identical. This confirms that the experimental X-ray diffraction pattern consists of a single pure phase, crystal modification A.

Crystal structure determination of Mod B from high resolution powder diffraction pattern

Mod B of the API-CG3 forms only very tiny crystallites, and it was impossible to obtain crystals of sufficient quality for single crystal X-ray diffraction. Therefore, synchrotron powder X-ray data were recorded at the ESRF in Grenoble (BM16 beamline, λ = 0.9495313 Å). Data collection was carried out in a 2θ range of 0–40°, step size of 0.005° in a total measurement time of 6 h.

The synchrotron powder pattern was indexed with a monoclinic cell by the programs DICVOL and ITO leading to the same result, and systematic absences indicated the space group $P2_1/a$. A Pawley refinement carried out on this cell using PowderFit in Cerius^2 [10] gave an agreement factor of $R_{wp} = 0.1942$.

From these data, structure solution of Mod B was attempted with the program PowderSolve (Cerius^2 program package), utilizing as starting model the molecular

geometry of the API-CG3 as determined from the single crystal structure of Mod A. During the Simulated Annealing run, 11 degrees of freedom (position and overall orientation of the molecule, and 5 torsion angles) were varied, and the calculation was performed for 20 cycles, each one comprising 10^6 steps.

The best solution (R_{wp} = 0.2509) from PowderSolve was refined using the Rietveld method as implemented in the program GSAS [8]. Bond lengths and angles were constrained to standard values and planar restrains were applied to non-hydrogen atoms belonging to the aromatic moieties. Towards the end of the refinement, a preferred orientation parameter was taken into account, and hydrogen as placed in calculated positions but not refined. The final Rietveld cycle yielded a good R_{wp} factor of 0.1556, and the corresponding lattice parameters are reported in Table 4. All peaks in the powder pattern are accounted for by the structural model. That means that the reference batch of the API-CG3 Mod B contains a polymorphic pure modification.

Crystal packing of Mod A and B

The three-dimensional structures of the two polymorphs, Mod A and Mod B, show similarities regarding the inter-molecular interactions and crystal packing (Table 4). In both cases, the unit cell is monoclinic, with a short axis (the [010] direction in Mod A, the [001] direction in Mod B) of ca. 4.5 Å, and two longer ones. Both structures were determined at room temperature. The calculated density of Mod B (1.485 g cm^{-3}) is higher than that of Mod A (1.445 g cm^{-3}), which is in accordance with the relative stability of the two polymorphs.

The molecular conformation of the API-CG3 in the solid-state is quite similar in both modifications, as illustrated in Fig. 9. There is a considerable twisting of the two rings (measured, for instance, by the N13-C14-C15-F16 torsion angle), as already observed in this family of diclofenac derivatives. In Mod B, the carboxylic moiety is closer to the amine group than in Mod A (C1-C4-C5-C6 is 70.6° in the former polymorph *vs*. 79.8° in the latter one), due to a shorter N–H···O intramolecular hydrogen bond (Table 5). The main difference is the conformation of the ethyl group, which lies on the same side of the carboxylic group with respect to the aromatic ring in Mod A, whilst it points upwards in Mod B (compare Figs 9a and b).

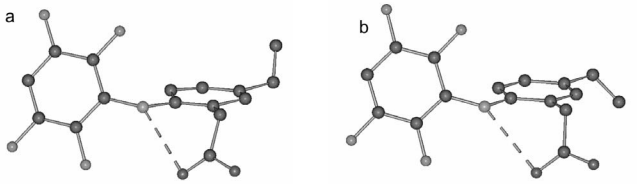

Fig. 9 Conformation of the API-CG3 determined by structural analysis for view of molecules for a – Mod A and b – Mod B in the crystal lattice. Hydrogens are omitted for clarity

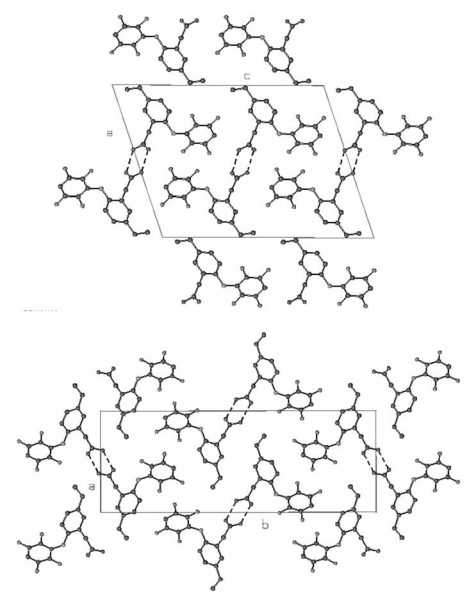

Fig. 10 Crystal arrangement of the API-CG3 in the solid-state. View of Mod A (top) along the b axis and of Mod B (bottom) along the c axis. Hydrogens are omitted for clarity

The two polymorphs of the API-CG3 show many analogies in their crystal lattice arrangements. In both crystals, the most important hydrogen bond motif is the dimer formed by two neighboring carboxylic groups, interacting through short O–H···O interactions (O···O distance of 2.680 Å in Mod A, 2.601 Å in Mod B (Fig. 9). This common structural feature, i.e. the presence of molecules in the lattice tightly bound by strong intermolecular contacts, suggest that in the API-CG3 these dimers are formed in the early stage of nucleation (as outlined by Gavezzotti in his crystal structure prediction strategy, [9]. Layers of these nuclei are formed via interaction between neighboring aromatic moieties, and then molecules stack along the short axis in a similar manner in both modifications.

A rationalization of the polymorphism behavior of the API-CG3 can be attempted by careful examination of the three-dimensional crystal structures of the two polymorphs. From the above analysis, it seems clear that the two modifications must differ by the relative orientation of the hydrogen bond dimers within each layer, i.e. in the ac plane for Mod A, and in the ab plane for Mod B. Figure 11 shows the same packing view of the two modifications as in Fig. 10, but a space filling mode is utilized, and the molecular dimers within each row are shaded alternatively in red and blue. In Mod A (Fig. 11, left), the fluorinated rings are in close contact between molecules in the same row (either between red or blue molecules), while the interaction between different rows are due to the phenyl rings bearing ethyl groups (i.e. between red and blue molecules).

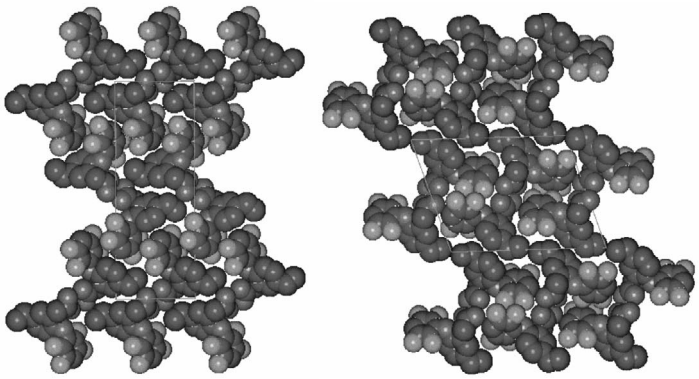

Fig. 11 Crystal lattice view of the API-CG3 Mod A (left) and Mod B (right). Molecular dimers linked by O–H···O contacts within each row are depicted alternatively in red and blue

On the other hand, in Mod B these contacts are reversed (Fig. 11, right), namely the stacking of perfluoro-phenyl groups characterize the row-to-row interaction, whereas molecules belonging to the same row possess ethyl-to-phenyl close contacts. How does the API-CG3 go from Mod B to A in the solid-state? The answer is visible from Fig. 11, i.e. a concerted anti-clockwise rotation of molecules within the same row along the short axis relates the two crystalline modifications. In that way Mod B transforms as a solid-solid transition into Mod A.

This hypothesis has been confirmed by an experiment using hot stage polarized-light microscopy. When crystals of Mod B were heated from room temperature to 120°C, we observed a change in the color, but no melting. This points to rearrangements of the molecules in the crystal lattice.

Morphology investigations of Mod A and B

The similarity in crystal packing of Mod A and Mod B of the API-CG3 is reflected in analogous crystal shapes. Optical and electron microscopy images of crystals of Mod A are shown in Fig. 12, where it is evident that this modification crystallizes as

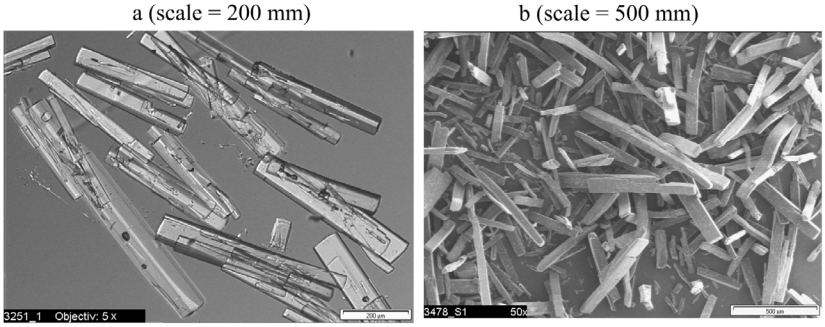

Fig. 12 Light a – and electron b – microscopy images of crystalline API-CG3 Mod A

elongated platelets. The relative orientation of the lattice parameters with respect to the crystal faces has been measured (Fig. 13). It was found that the [010] direction coincides with the fastest growth direction, while the most developed face is {100}, i.e. the *a* axis is perpendicular to it.

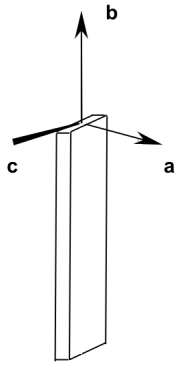

Fig. 13 Orientation of the lattice parameters with respect to the crystal faces in the API-CG3 Mod A

In Mod B, a needle-like morphology was observed e.g. by scanning electron microscopy (Fig. 14).

The morphology of both crystals was calculated by means of the Attachment Energy approach available in Cerius[2]. The force field utilized was DREIDING 2.21, with ESP charges computed by the program MOPAC (MNDO level). The result is shown in Fig. 15, where we can see that the predicted morphology is in excellent accordance with the experimental characterization. The habit of Mod A reveals the following order of importance of crystal faces: {1 0 0} > {1 0 –2} > {0 1 1} ≈ {-1 1 1}, while in Mod B is the following: {0 2 0} > {1 1 0}≈ {1 -1 0} > {0 0 1} ≈ {1 1 1} ≈

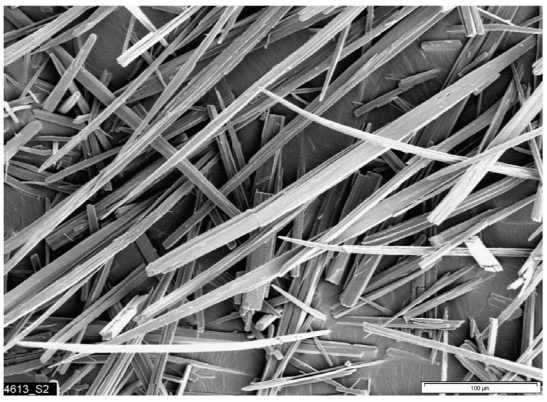

Fig. 14 SEM picture of the API-CG3 Mod B (scale = 100 µm)

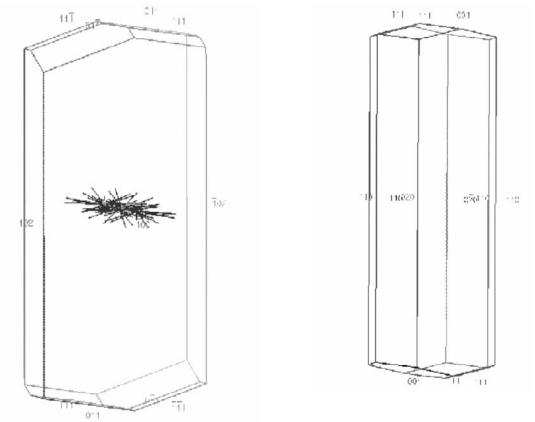

Fig. 15 Calculated morphology of the API-CG3 Mod A (left) and Mod B (right) using the Attachment Energy model

{1-1 -1}. In both cases, the fastest crystal growth occurs along the stacking of molecules in the crystal lattice, thus apolar solvents (e.g. toluene) may reduce the elongation of crystallites in the two modifications of the API-CG3.

Conclusions

The solid-state characterization and polymorphism investigations show that this compound can crystallize in at least three different crystalline forms. One turned out to be not a polymorph but a chemically different compound. Neither solvates nor hydrates were detected.

The two polymorphic crystal modifications, Mod B and Mod A are enantiotropic to each other. Mod B is the most stable modification at ambient temperature up to about 50°C. Mod A is the most stable crystal modification at temperatures higher than 60°C.

Mod B is not a hygroscopic, highly crystalline, anhydrous substance which is stable in most solvents at ambient temperatures. At higher temperature or after fast crystallization Mod A or mixtures of Mod A and B or mixtures with the chemically different compound can be obtained.

It has been possible to elucidate the 3D crystal structure of the two polymorphs of the API-CG3. Mod A has been characterized by single crystal X-ray diffraction, while the structure determination of the second polymorph has been carried out successfully by PowderSolve, using high resolution (synchrotron) powder X-ray data. Mod B has a slightly higher density (1.49 *vs.*1.45) *vs.* Mod A.

Comparison of the calculated X-ray powder diffraction pattern with the experimental pattern shows that both modifications of the API-CG3 are single phases. The two modifications show a similar conformation in the solid-state, the main difference being the orientation of the ethyl group. The packing organization is governed by

short hydrogen bonds (intramolecular N–H···O and intermolecular O–H···O contacts), and by molecular stacking along the short axis. A rationalization of the polymorphism behavior of the API-CG3 is proposed.

The 3D structure has been used to calculate the morphology, and there is agreement with the experimental crystal habit characterized by light and electron microscopy. The API-CG3 Mod A has a platelet crystal shape, whereas Mod B shows a more needle-like morphology.

This study shows that a polymorphism screening is useful even if the current known crystalline form looks very suitable for development since it might not be the thermodynamic stable form under the desired conditions. Furthermore, structure proof for new crystalline forms has been shown to be essential. On the other hand, a combination of solid-state characterization methods is necessary for a complete picture and structure determination and analysis of molecular packing is a very helpful tool for the explanation of like in this case solid-solid transitions and the physico-chemical properties of the different crystal forms.

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