



Reconciling thermal and structural data from the polymorphic transitions of malonamide

Eugene Y. Cheung*, Matthew L. Peterson

TransForm Pharmaceuticals, 29 Hartwell Avenue, Lexington, MA 02421, USA

ARTICLE INFO

Article history:

Received 9 September 2008

Received in revised form 17 October 2008

Accepted 22 October 2008

Available online 5 November 2008

Keywords:

Differential scanning calorimetry

X-ray diffraction

Infrared spectroscopy

Polymorphism

Phase transitions

ABSTRACT

Although screening for organic polymorphs has become a hot topic in recent years, polymorph screens continue to be largely based on solution crystallization. Other routes to different crystal forms, such as grinding, annealing, and melt crystallization can also be used to look for polymorphs when chemical stability allows. Thermal analysis is often the first method for identifying polymorphic transitions in solids. However, reconciling the thermal data with the structural data is rarely straightforward without a single crystal X-ray structure. By using differential scanning calorimetry, infrared spectroscopy, and powder X-ray diffraction, the polymorphic transitions of malonamide have now been studied, and two solid state pathways, solid state grinding and annealing, are verified to independently yield the tetragonal polymorph of malonamide from the monoclinic form. In addition, melt recrystallization yields a third polymorph, which has now been confirmed to be the orthorhombic polymorph.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

Thermal analysis is a heavily used method of identifying polymorphic transitions in solids. Differential scanning calorimetry (DSC) can provide the temperature at which a thermal event occurs and also the temperature window for the stability of the phase before the next transition event. The DSC thermogram can be used as a map to identify alternate routes to different crystal forms, such as the use of annealing or melt recrystallization, instead of the more common solution crystallization [1]. However, DSC cannot identify the exact structural nature of the thermal event, whereas techniques catering to solid state analysis, such as infrared spectroscopy (IR) or X-ray diffraction (XRD), provide structural information without the thermal context. When thermal or mechanical routes [2] do not lead to new solid phases that are amenable to structural characterization using single crystal X-ray diffraction, this limitation can now be overcome by advances in powder X-ray diffraction (PXRD), which allows for structure determination directly from polycrystalline samples. Therefore, by applying thermal analysis with PXRD and IR, a complete picture of how each thermal event in a DSC thermogram is related to the individual solid forms is theoretically achievable. In our investigations of alternate pathways to discovering and obtaining polymorphs, we studied the polymorphic nature

of malonamide. Previous DSC and XRD studies of this compound pointed towards the existence of more than one phase [3–5], but structure–thermal relationship were not established and remained elusive, with one form being considered a possible example of a “disappearing polymorph” because it could not be grown or isolated again [5] (Fig. 1).

2. Experimental

A TA Instrument Q1000 DSC was used for the DSC measurements. Specimens were weighed into an aluminum hermetic sample pan and sealed by crimping. The sample pan was loaded into the apparatus and the thermogram was obtained by individually heating the sample from ambient to 200 °C at a rate of 10 °C/min using an empty aluminum hermetic pan as a reference. Dry nitrogen gas was used as a sample purge gas and the flow rate was set at 50 mL/min. Thermal transitions were viewed and analyzed using the TA analysis software provided with the instrument.

X-ray powder diffraction patterns were obtained using the D/Max Rapid X-ray Diffractometer equipped with a copper source (Cu K α 1.5418 Å), manual x – y stage, and 0.3-mm collimator. Specimens were loaded into a 0.7-mm boron rich glass capillary tube. The loaded capillary was mounted in a holder secured into the x – y stage. The diffraction patterns were acquired under ambient conditions at a power setting of 46 kV at 40 mA in reflection mode, while oscillating about the ω -axis from 0° to –5° at 1°/s and spinning about the ϕ -axis at 2°/s. The exposure time was 5 min. The diffraction patterns were integrated over 2θ from 2° to 70° and

* Corresponding author.

E-mail address: echeung@its.jnj.com (E.Y. Cheung).

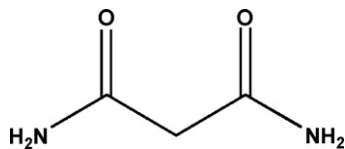


Fig. 1. Structure of malonamide.

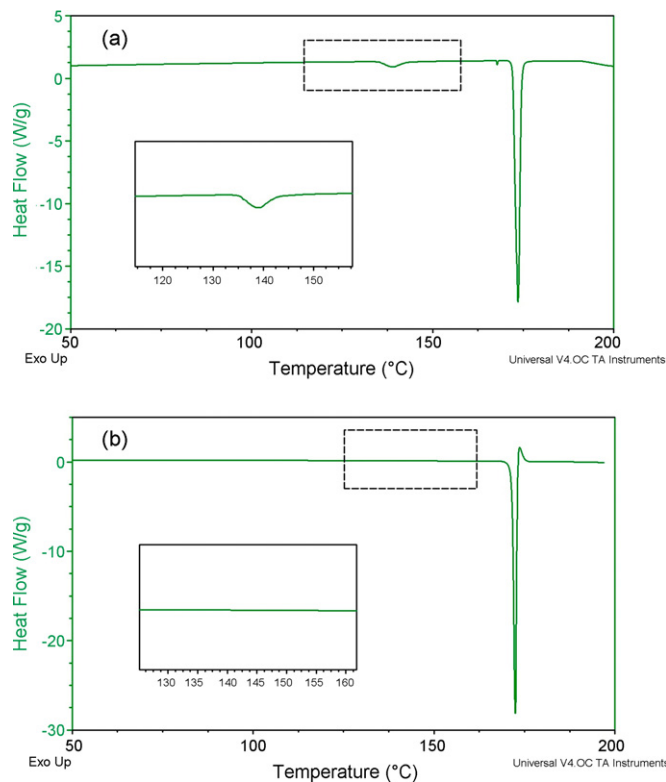


Fig. 2. DSC traces of the commercial phase (a) and the phase obtained from grinding (b).

χ (1 segment) from 0° to -360° at a step size of 0.02° using the *cyllint* utility in the RINT Rapid display software provided with the instrument. The dark counts value was set to 8 as per the system calibration; normalization was set to average; the ω offset was set to 180° .

Malonamide was obtained from Sigma–Aldrich. The tetragonal form of malonamide was obtained in two ways, by annealing or by grinding. In the former, 100 mg of the commercial form of malonamide was placed in a 10 mL vial in an oven set at 136°C and incubated for 18 h. Grinding experiments were performed by the addition of 40 mg of malonamide and stainless steel bearings into 1.5 mL stainless steel capsules, followed by shaking for ca. 10 min

Table 1
Unit cell data from the polymorphs of malonamide.

| Unit cell data | Monoclinic [6] | Tetragonal [4] | Orthorhombic [5] |
|-----------------------|----------------|----------------|------------------|
| a (Å) | 13.07(2) | 5.3140(3) | 5.3602(9) |
| b (Å) | 9.45(2) | 5.3140(3) | 7.5178(8) |
| c (Å) | 8.04(2) | 15.5360(12) | 11.791(2) |
| β ($^\circ$) | 73.0(2) | 90.0000 | 90.0000 |
| V (Å ³) | 949.6 | 438.7 | 475.1 |
| Z | 8 | 4 | 4 |
| Space group | $P2_1/c$ | $P4_32_12$ | $Pbcn$ |

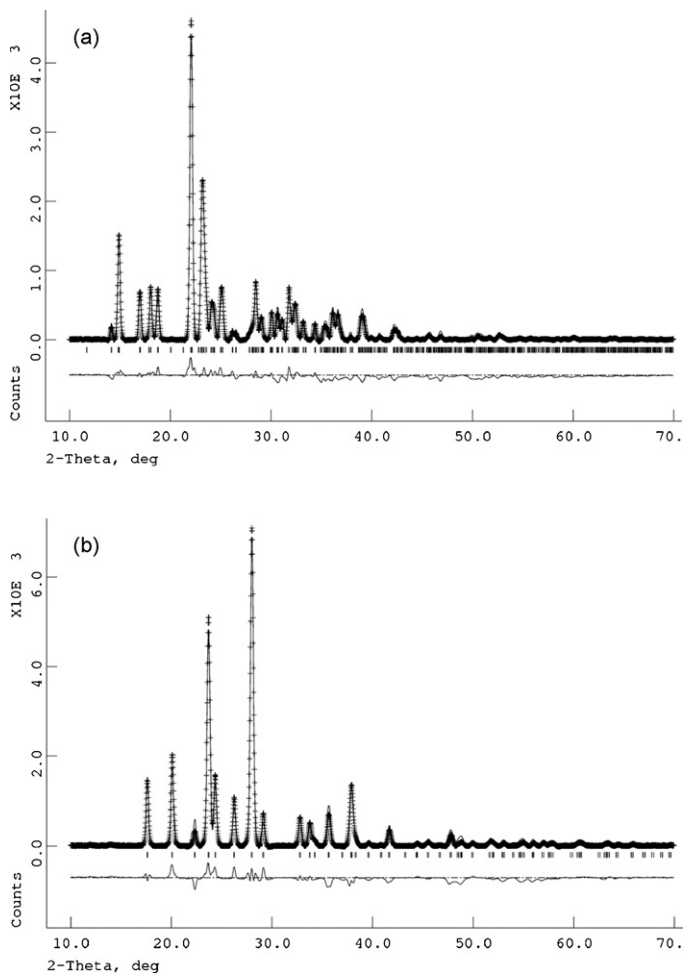


Fig. 3. (a) The Rietveld difference plot for the commercial (monoclinic) phase of malonamide. (b) The Rietveld difference plot for the malonamide phase obtained from grinding (tetragonal).

at ca. 2000 rpm in an in-house modified mechanical shaker. The orthorhombic form was obtained by melting the commercial phase at 184°C and allowing the sample to cool in the oven to room temperature.

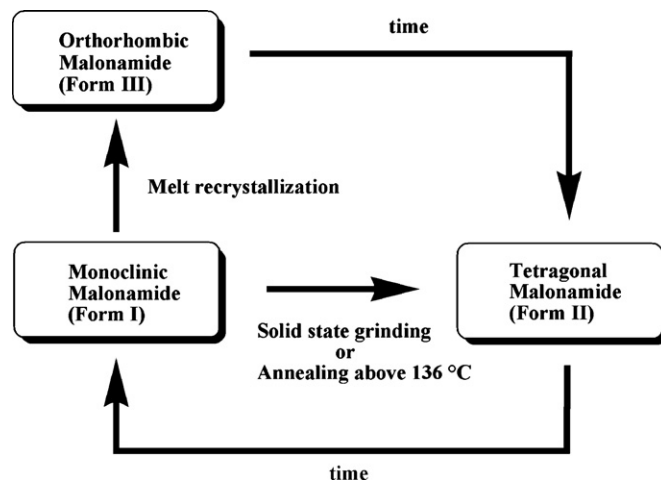


Fig. 4. Flowchart outlining the relationships among the three polymorphs of malonamide.

3. Results and discussion

The DSC thermogram and powder X-ray diffraction pattern of a commercial sample of malonamide were obtained. The DSC trace gave a clear indication that a small endotherm (endotherm range 135.48–139.21 °C; $\Delta H = 13.67$ J/g) precedes the melt at ca. 170 °C (melting range 172.09–173.53 °C; $\Delta H = 227.4$ J/g) (Fig. 2a).

For many years, the only known polymorph was monoclinic, with two molecules in the asymmetric unit ($Z = 2$), obtained by crystallization from water (Table 1) [6]. Comparison of the pow-

der X-ray diffraction pattern of commercial malonamide with the simulated powder X-ray diffraction pattern using the structural coordinates of the originally discovered monoclinic phase indicated very good overlap. A full Rietveld refinement of this phase with the powder X-ray diffraction data of the recrystallized material gave a good Rietveld difference plot (Fig. 3a), clearly demonstrating that the monoclinic phase (Form I) is actually the commercial phase [7].

The commercial material can be used as the starting point for solid-state grinding in the stainless steel capsules (Fig. 4), after which we found complete and reproducible conversion to a

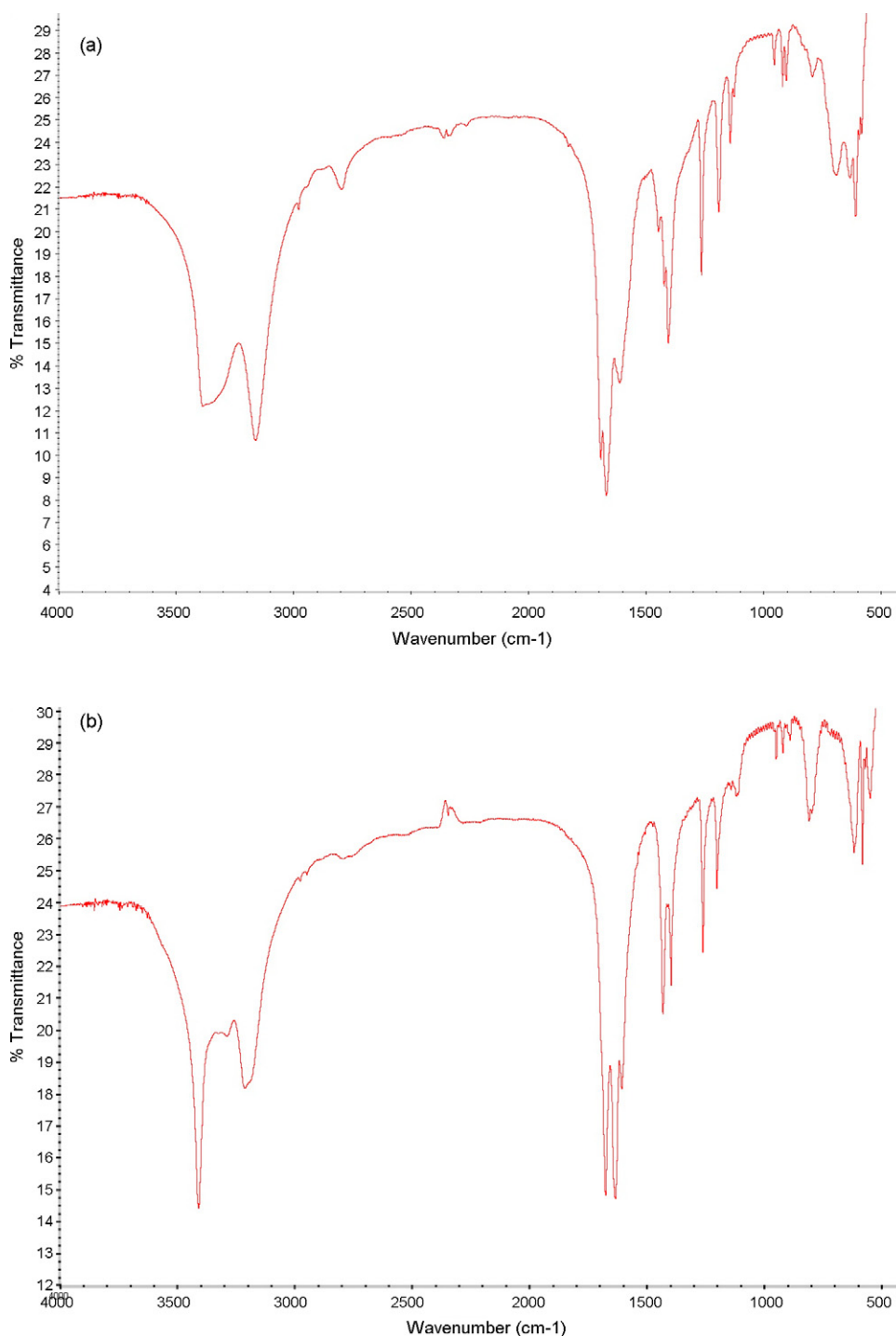


Fig. 5. The IR spectra for the commercial phase (a) and the phase obtained from grinding (b).

different phase as monitored by IR spectroscopy (Fig. 5) and powder X-ray diffraction (Fig. 3b). Although localized heating is possible at the point of impact between the steel bearing, compound, and the container, the internal temperature of the stainless steel capsule was measured to rise no higher than 30 °C, well below 170 °C, the melting point of malonamide. The IR spectra of the two phases differ considerably, especially in the carbonyl stretching and the N–H stretching regions (Fig. 5). In the IR spectrum of the monoclinic phase, the region from 3000 to 3500 cm^{-1} , which encompasses the N–H stretching bands, shows a broad band at 3400 cm^{-1} followed by a sharper band at 3200 cm^{-1} . The IR spectrum of the sample after grinding shows that the intensities of the two main peaks in this region are reversed, and that the band at the higher frequency is now narrow instead of broad. These two spectra illustrate that the two phases have dissimilar hydrogen bonding environments.

As this new phase can be prepared reproducibly by grinding, a DSC thermogram of the pure phase could be recorded and compared with that of the commercial product (Fig. 2). The small endotherm evident at ca. 135–139 °C in the commercial material is no longer present in the thermogram of the new phase. Other than the loss of this feature, the two DSC traces are identical (melting endotherm of the new phase = 171.59–172.48 °C; $\Delta H = 285.0 \text{ J/g}$). The endotherm in the DSC data of the commercial material is therefore suggestive of a phase transition. The commercial phase is stable until this transition temperature, after which it converts to the new phase which then melts. To prove this, a sample of commercial malonamide was annealed at 136 °C for 18 h (Fig. 4) and its powder X-ray diffraction pattern was recorded. The diffractogram matched that of the phase obtained by solid state grinding. Clearly, the new polymorph can be obtained by either grinding or by incubation above the phase transition.

Because this new phase did not yield crystals suitable for single crystal X-ray diffraction, structure determination directly from powder X-ray diffraction data was carried out using the powder pattern from the ground sample. Unit cell indexing followed by Pawley refinement enabled structure solution of a tetragonal polymorph (Form II) from the powder X-ray data [8]. This tetragonal phase had been observed from solution crystallization. The authors reported that the tetragonal phase could not be grown again from solution even after crystallization attempts at different locations (calling it “a disappearing polymorph”). They observed an orthorhombic phase during their repeated attempts instead of the tetragonal or monoclinic phases. Using our diffraction data, a full Rietveld refinement [9] was carried out using the structural coordinates of the published tetragonal polymorph. The success of the refinement (Fig. 3b) demonstrates without doubt that the tetragonal polymorph obtained either through grinding or high temperature annealing is the same tetragonal polymorph that had previously eluded attempts at isolation.

The DSC thermograms of the pure monoclinic and pure tetragonal phases offer an important clue to establishing the relationship between them and the orthorhombic form. Because no other features are found in the DSC data from these two phases, it is probable that the phase transition to the orthorhombic phase occurs above the melting point of tetragonal malonamide, and that a monotropic relationship exists between the two phases. Commercial malonamide was melted, held at 180 °C for 20 min prior to cooling, and the DSC thermogram, IR spectrum, and powder X-ray diffraction pattern were recorded for the recrystallized solid (Fig. 6). The data from all three techniques show that the solid is distinct from the monoclinic and tetragonal phases. The DSC result gives the melting value as 160.66–163.78 °C ($\Delta H = 277.4 \text{ J/g}$). Full Rietveld refinement [10] using the powder diffraction data and the coordinates of the orthorhombic phase (Form III) result in an excellent refinement and Rietveld difference plot (Fig. 6c), thereby confirming that recrystal-

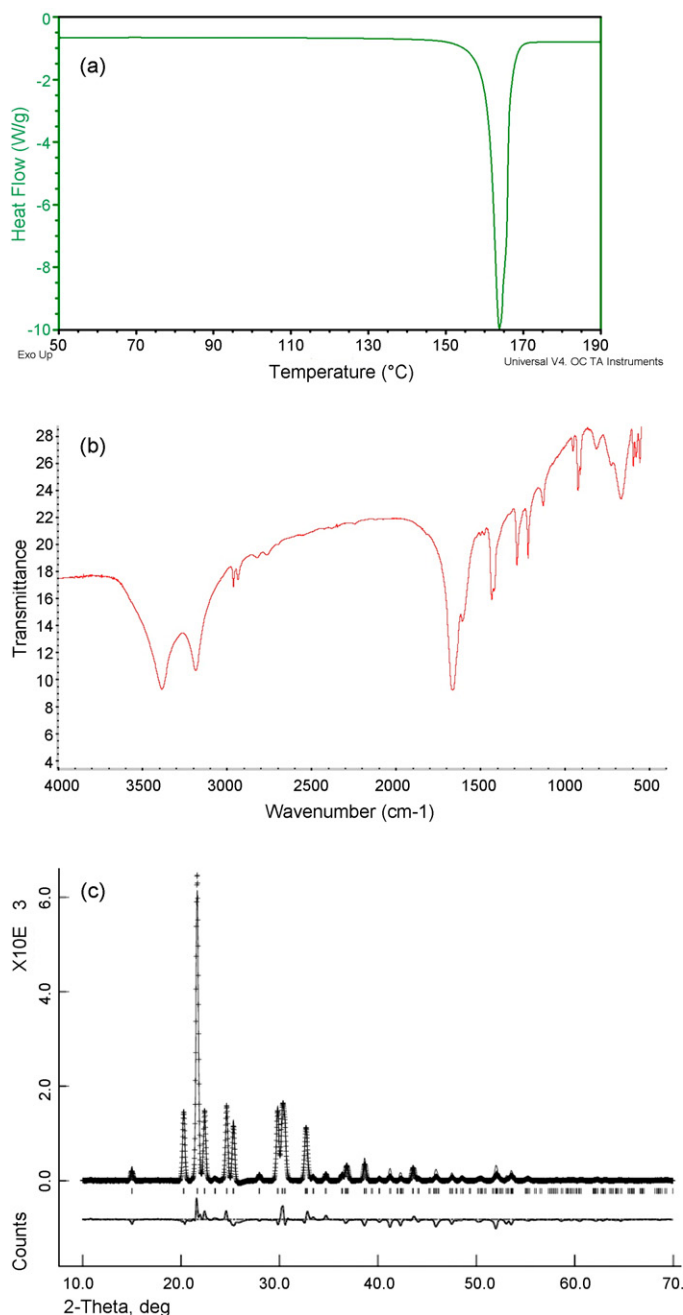


Fig. 6. DSC, IR, and PXRD data for the melt recrystallized phase of malonamide.

lization via the melt provides a straightforward avenue to obtaining this third polymorph.

The physical stability of the metastable tetragonal and orthorhombic phases was monitored at room temperature, and it was found that the tetragonal phase kept at ambient conditions slowly converts to the monoclinic phase over the course of weeks. The orthorhombic polymorph seems to be less stable, and converts to the tetragonal phase over a matter of days or less, which then reverts slowly to the monoclinic phase. Thus, the monoclinic form can always be obtained under ambient conditions, and the identity of the form which is isolated depends on when the crystals are harvested.

In conclusion, easy and reproducible access to the three known polymorphs of malonamide are now possible. By using PXRD and Rietveld analysis in conjunction with the thermal and IR data, the

form assignments could be resolved. In addition, we have uncovered two routes to the tetragonal phase, which was considered as a “disappearing polymorph”. One notable aspect of the study is that the polymorphic nature of this system has resulted in the melting point of the metastable tetragonal phase of malonamide being reported as the melting point of the commercially available monoclinic form of malonamide in the chemical literature. The results in this paper thus emphasize that reported chemical or physical properties in the literature for a compound may inadvertently be assembled from several distinct solid phases.

References

- [1] (a) S.-Y. Lin, W.-T. Cheng, S.-L. Wang, *Int. J. Pharm.* 318 (2006) 86;
(b) S. Yada, M. Ohya, Y. Ohuchi, T. Hamaura, N. Wakiyama, F. Usui, A. Kusai, K. Yamamoto, *Int. J. Pharm.* 255 (2003) 69;
(c) P. Taddei, A. Torreggiani, G. Fini, *J. Mol. Struct.* 642 (2002) 63;
(d) A. Miyamae, H. Kema, T. Kawabata, T. Yasuda, M. Otsuka, Y. Matsuda, *Drug Dev. Ind. Pharm.* 20 (1994) 2881;
(e) M. Otsuka, K. Otsuka, N. Kaneniwa, *Drug Dev. Ind. Pharm.* 20 (1994) 1649;
(f) J. Pirttimaki, E. Laine, J. Ketolainen, P. Paronen, *Int. J. Pharm.* 95 (1993) 93.
- [2] (a) K.L. Chan, S.G. Kazarian, D. Vassou, V. Gionis, G.D. Chryssikos, *Vibration Spectrosc.* 43 (2007) 221;
(b) E. Yonemochi, *Pharm. Tech. Jpn.* 22 (2006) 1703–1709;
(c) R. Storey, R. Docherty, P. Higginson, C. Dallman, C. Gilmore, G. Barr, W. Dong, *Cryst. Revs.* 10 (2004) 45;
(d) S. Morissette, Ö. Almarsson, M.L. Peterson, J.F. Remenar, M. Read, A.V. Lemmo, S. Ellis, M.J. Cima, C.R. Gardner, *Adv. Drug Deliv. Rev.* 56 (2004) 275.
- [3] M. Sakiyama, A. Imamura, *Thermochim. Acta* 142 (1989) 365.
- [4] G.S. Nichol, W. Clegg, *Acta Crystallogr. E* 61 (2005) o3427.
- [5] G.S. Nichol, W. Clegg, *Acta Crystallogr. E* 61 (2005) o3424.
- [6] P.C. Chieh, E. Subramanian, J. Trotter, *J. Chem. Soc. A* 35 (1970) 179.
- [7] Rietveld refinement details for the monoclinic phase: $a = 13.0990(9) \text{ \AA}$, $b = 9.4582(4) \text{ \AA}$, $c = 8.0421(5) \text{ \AA}$, $\beta = 72.941(5)$, $V = 952.53(7) \text{ \AA}^3$, $R_p = 0.0242$, $R_{wp} = 0.0318$ [46 variables, 3324 profile points].
- [8] Tetragonal space group, $P4_32_12$, unit cell after Pawley refinement $a = 5.3087 \text{ \AA}$, $c = 15.9326 \text{ \AA}$, $V = 449.02 \text{ \AA}^3$, after 50 cycles of simulated annealing $R_{wp} = 5.81\%$.
- [9] Rietveld refinement details for the tetragonal phase: $a = 5.30828(31) \text{ \AA}$, $c = 15.9306(10) \text{ \AA}$, $V = 448.89(4) \text{ \AA}^3$, $R_p = 0.0298$, $R_{wp} = 0.0461$ [16 variables, 3324 profile points].
- [10] Rietveld refinement details for the orthorhombic phase: $a = 5.36283(29) \text{ \AA}$, $b = 7.5879(5) \text{ \AA}$, $c = 11.8039(8) \text{ \AA}$, $V = 480.330(31) \text{ \AA}^3$, $R_p = 0.0220$, $R_{wp} = 0.0366$ [16 variables, 3324 profile points].