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The phase transformation of caffeine: investigation by dynamic X-ray diffraction and emanation thermal analysis

M. Epple [a,1], H.K. Cammenga [a,*], S.M. Sarge [a,2], R. Diedrich [b], V. Balek [c],

[a] *Institute of Physical and Theoretical Chemistry, Technical University of Braunschweig, Hans-Sommer-Strasse 10, D-38106 Braunschweig, Germany*

[b] *Institute of Pharmaceutical Technology, Technical University of Braunschweig, Mendelssohnstrasse 1, D-38106 Braunschweig, Germany*

[c] *Nuclear Research Institute, 25068 Rež, Czech Republic*

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Abstract

The solid–solid phase transformation of caffeine has been studied with time- and temperature-resolved X-ray powder diffractometry (TXRD) and with emanation thermal analysis (ETA). The phase transformation of caffeine at 141 °C has been followed by heating a sample of the low-temperature phase. After cooling again, the high-temperature phase converts only slowly back into the low-temperature phase. This transformation needs weeks or months at room temperature to complete. With TXRD, it was possible to study this slow transformation in situ at elevated temperatures. A nucleation-controlled transformation mechanism appears likely.

Keywords: Caffeine; ETA; Phase transformation; SEM; TXRD

* Corresponding author.

[1] Present address: Institut für Anorganische und Angewandte Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany.

[2] Present address: Physikalisch-Technische Bundesanstalt, Postfach 3345, D-38023 Braunschweig, Germany.

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1. Introduction

Caffeine is an important ingredient of coffee and tea, which is produced in large quantities as a by-product of the technical decaffeination of raw coffee beans. It is used, for example, as a pharmaceutical agent (stimulating effect) and as an additive to some well known soft drinks. Because both the thermodynamics and the phase behaviour are well studied [1–3], it may serve as an example for a pharmaceutically relevant organic solid undergoing dehydration and a phase transition. However, questions still remain about the phase transition kinetics and the morphology changes associated with the phase transition.

In the solid state, caffeine occurs as 4/5 hydrate and in two anhydrous phases. The hydrate is obtained by recrystallization from aqueous solutions at room temperature. It loses its water of crystallization at around 80°C [3,4]. Its thermodynamic stability temperature under its own vapour pressure, the quadruple point, was determined to be 51.5°C (enthalpy of dehydration 7.06 kJ mol^{-1}). At this temperature, solid caffeine hydrate, solid anhydrous caffeine in its low-temperature modification β, saturated aqueous caffeine solution and water vapour are in thermodynamic equilibrium.

Anhydrous β-caffeine undergoes a solid–solid phase transformation at 141°C into the high-temperature phase α-caffeine. This transformation occurs readily on heating and is detectable by differential scanning calorimetry (DSC) [1,4] with a measured enthalpy of phase transition of 4.1 kJ mol^{-1} [4]. The associated volume change is +1.2%. Upon cooling α-caffeine below the transformation temperature, the back-transformation $\alpha \rightarrow \beta$ is kinetically restrained. It typically takes weeks or months at room temperature to complete. Extended investigations on the influence of pharmaceutical unit operations were carried out by Diedrich [5]. He studied the effects on the transformation kinetics of storage at different temperatures, grinding, tabletting and wetting by non-aqueous solvents.

The knowledge of the interconversion rate between the two phases is important for the use of caffeine as a pharmaceutical agent. In addition, caffeine may be considered as a model substance and information gained on caffeine may guide research on other drugs. Because the two anhydrous phases have different Gibbs' energies, the rate of dissolution is higher for the energy-richer high-temperature α-phase. Thus, if a fast metabolic action is desired, one would prefer the metastable α-phase as ingredient. Consequently, the storage stability of anhydrous α-caffeine is important. A conversion into the low temperature phase would also produce undesired mechanical strain in the tablet, due to the different densities of the two modifications.

The driving force of the solid–solid transformation $\alpha \rightarrow \beta$ is the Gibbs' energy difference which increases with falling temperature (distant from the equilibrium temperature 141°C). Considering only this thermodynamic contribution, the conversion rate should be highest at low temperatures. However, a reciprocal action results from kinetics. The rate of conversion drops exponentially with falling temperature, frequently formally according to the Arrhenius equation [6]. These

two effects result in a maximum in the conversion rate of $\alpha \rightarrow \beta$ at an intermediate temperature that must lie somewhere between 0 K and 141°C.

It is difficult to measure the transformation rate of α-caffeine into β-caffeine because the transformation takes hours, even at higher temperatures. Therefore, it is not possible to cool a sample of α-caffeine in the differential scanning calorimeter to record a transition peak. Because no mass change occurs, thermogravimetry is not applicable either. We found that time-resolved and temperature-resolved X-ray diffractometry (TXRD) is an ideal tool by which to examine such a transformation. We report here experiments carried out with this technique, together with kinetic evaluations.

The morphological structure of a solid may also strongly influence the stability and the rate of dissolution of a pharmaceutical. Changes in the surface and bulk structure, which are often not easily observed with the common thermoanalytical methods, can be detected by emanation thermal analysis. We carried out experiments to characterize the dehydration of caffeine hydrate, the phase transformation β to α and vice versa, and the melting process.

The aim of our experiments was to gain insight into the kinetic and morphological features of this solid–solid phase transformation. Conclusions should be drawn on the storage stability and the properties of caffeine samples for pharmaceutical purposes.

2. Experimental

Time-resolved and temperature-resolved X-ray diffraction (TXRD) experiments were carried out with a laboratory-constructed heating stage that was adapted to a Philips PW 1050/81 goniometer. Nickel-filtered copper $K\alpha$ radiation ($\lambda = 154.18$ pm) was employed. Construction details and theoretical background of the technique can be found in Ref. [7].

Emanation thermal analysis (ETA) was performed according to the procedures described in Ref. [8]. With this method, radioactive radon is brought into the sample crystals by co-crystallization with a radium salt from aqueous solution. The rate of release is followed when the sample temperature changes. This method is very sensitive to morphological changes, e.g. to the formation of grain boundaries and cracks during recrystallizations and solid state reactions. Scanning electron microscopy was performed on a Stereoscan 600 (Cambridge Scientific Instruments Ltd.). The samples were sputtered with gold. The acceleration voltage was between 7.5 and 15 kV.

The caffeine sample was zone-refined. Calorimetric purity analysis of the melting peak [9] indicated a purity of more than 99.99 mol%. The anhydrous β-caffeine was ground in an agate mortar to yield a fine powder for X-ray diffractometry (particle size approximately 10 μm). The caffeine hydrate sample was recrystallized from distilled water. The crystals were centrifuged off and conditioned for some weeks over saturated caffeine solution.

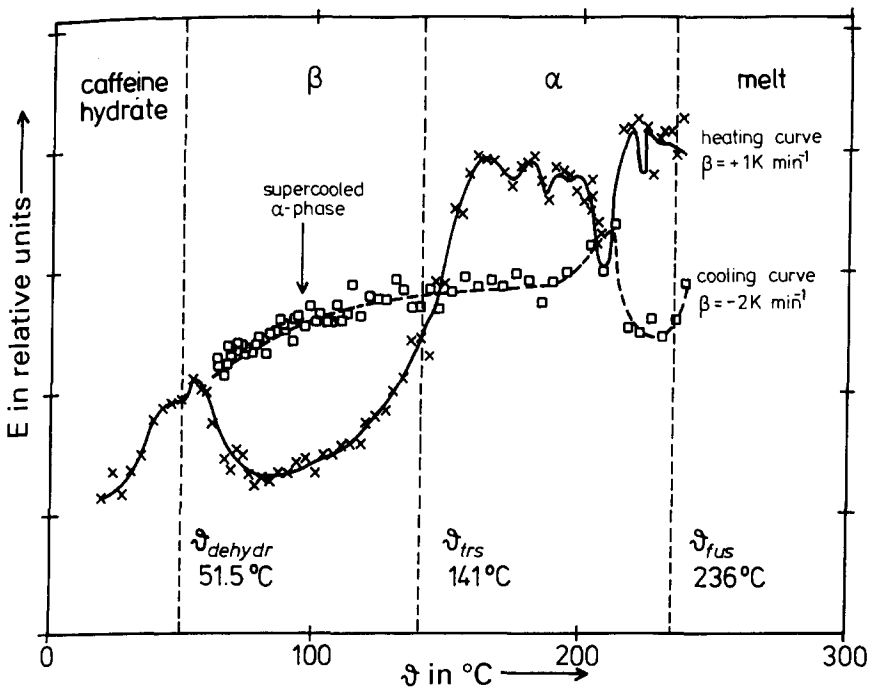

Fig. 1. Emanation thermal analysis of a sample of caffeine hydrate. The sample was heated from room temperature to 250°C at 1 K min^{-1} and cooled at 2 K min^{-1}. Visible during the heating process are the dehydration around 50°C (temporary increase in emanation rate), the $\beta \rightarrow \alpha$ phase transformation around 141°C (rise in emanation rate due to an increase of porosity), a pre-melting process starting at 200°C (drop in emanation rate) and the melting process at 236°C (rise in emanation rate). Upon cooling, the sample solidifies at around 200°C. No $\alpha \rightarrow \beta$ transformation can be observed due to the sluggish back-transformation. ϑ, sample temperature; E, emanation rate.

3. Results and discussion

3.1. Emanation thermal analysis (ETA) and scanning electron microscopy (SEM)

Caffeine hydrate was heated at 1 K min^{-1} from room temperature to 250°C. The results are shown in Fig. 1. Clearly visible is the dehydration around 50°C that leads to a change in the crystal lattice and to an increased release of radon. After the dehydration, the emanation rate drops again. It starts to rise during the solid–solid phase transformation ($\beta \rightarrow \alpha$), as the crystal lattice changes again. The emanation rate remains high after the transformation, indicating the formation of (permanent) new diffusion paths. The drop in emanation rate above 200°C can be ascribed to pre-melting (sintering) which clogs these pathways. The melting leads to a liquid that allows more radon to escape (rise of the emanation rate).

Upon cooling at 2 K min^{-1}, the melt solidifies after supercooling for a few degrees. The emanation rate drops. The transition of the α-phase to the β-phase is

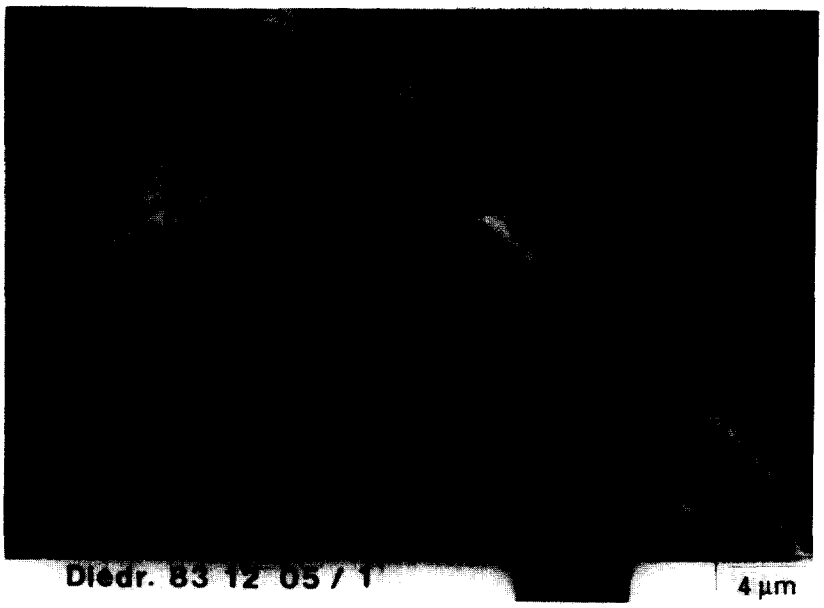

Fig. 2. Scanning electron micrograph of a sample of β-caffeine. The black bar on the bottom represents 4 μm. The sample consists of agglomerates of needles with a smooth surface.

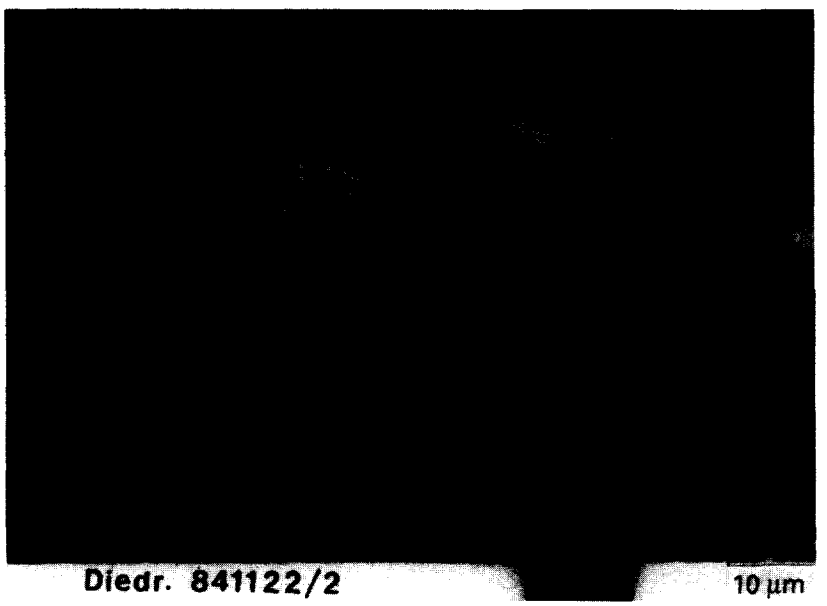

Fig. 3. Scanning electron micrograph of freshly prepared α-caffeine. The sample was prepared by heating β-caffeine above the transition temperature (141°C) and quenching to room temperature. Owing to sublimation, larger aggregates have formed. They have a porous structure that corresponds to a higher surface area. The black bar on the bottom represents 10 μm.

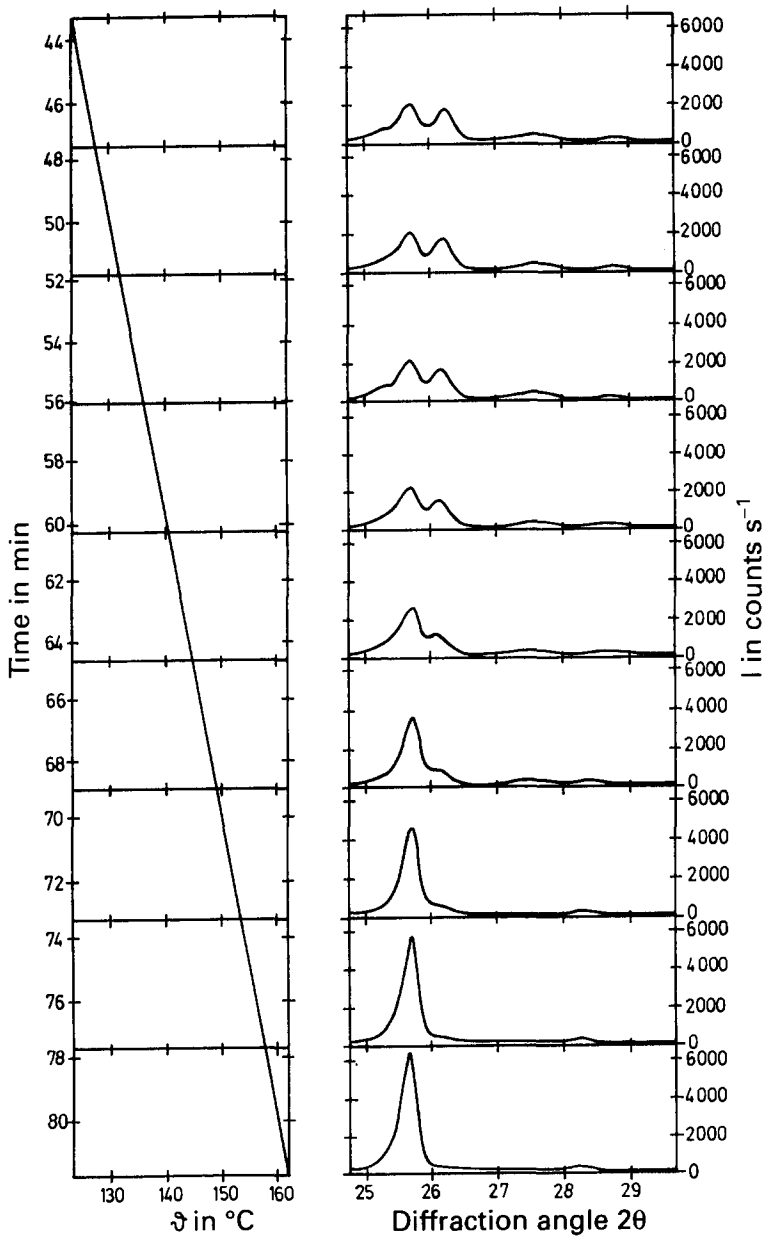

Fig. 4. Temperature-resolved diffraction data, recorded during the transformation $\beta \rightarrow \alpha$ of anhydrous caffeine (low-temperature phase to high-temperature phase). The phase transformation occurs around 130–150°C. The heating rate was 1 K min^{-1}. A diffraction angle range of 25–30° 2θ was scanned with 0.02° 2θ s^{-1} (one diffractogram every 4.3 min). The temperature is plotted on the left, the corresponding X-ray diffractograms on the right. Only the temperature range 120–165°C is shown. ϑ, sample temperature; I, X-ray scattering intensity in counts per second (cps).

too slow to be detected during the experiment. Accordingly, no discontinuity in the emanation rate curve is visible.

The porous structure of α-caffeine was also detected by SEM. Figure 2 shows a sample of β-caffeine. It occurs as agglomerate of long needles that are approximately 10–20 μm long and 1–2 μm thick. The surface is smooth. This is visible under higher magnification (not shown).

In Fig. 3, a sample of freshly prepared α-caffeine is displayed. This was prepared by annealing β-caffeine above the transition temperature, but below the melting temperature. The increasing vapour pressure of caffeine leads to the formation of large polycrystalline aggregates. The surface structure displays long cracks and pores. Upon cooling below the transformation temperature and annealing around 100°C, the original structure of β-caffeine is restored. The surface becomes smooth again (not shown).

3.2. Time- and temperature-resolved X-ray powder diffractometry (TXRD)

Figure 4 displays a set of powder diffractograms, recorded during heating a sample of the anhydrous low-temperature phase β-caffeine at 1 K min^{-1}. Every 4.3 min a diffractogram was recorded. Around 130–140°C, the start of the transformation $\beta \rightarrow \alpha$ can be detected, especially in the region 25–26.5° 2θ, where two educt peaks vanish and one product peak emerges.

The changes in higher angular regions are difficult to detect, because the diffraction peaks are comparatively small. In this case, the data can be better presented in the form of a film-analogous plot as shown in Fig. 5. This resembles an old-fashioned heating-camera plot where a film is transported within the diffractometer during the heating process. To create such a plot, suitable peak functions (modified Lorentzians) are fitted to the measured diffractograms. All detected peaks are plotted vertically in the diffraction angle versus time-temperature diagram. The line widths in Fig. 5 are chosen to be approximately proportional to the logarithm of the peak intensity (=height). Although this graph does not allow one to quantitatively evaluate the change in peak intensities, it readily shows in which temperature range changes are taking place. Small and overlapping peaks are clearly visible, and the transformation can be assigned to the temperature range 130–150°C.

The transformation $\beta \rightarrow \alpha$ is completed at about 150°C, but the main product phase peak at 25.7° 2θ continues to grow. Other experiments showed that it can reach intensities of 25 000 counts s^{-1} and more. We assume that this unrestricted growth is due to a rearrangement of the caffeine crystals within the powder. Because the vapour pressure of caffeine is not negligible above 150°C, a partial rearrangement, for example, by sublimation and condensation, could lead to a preferential orientation in the powder sample which favours the corresponding crystal plane [10].

To quantitatively evaluate the kinetics of the back-transformation of the high-temperature phase α-caffeine into β-caffeine, the peak intensities must be evaluated. In this case of a unimolecular transformation without mass loss, the peak intensity

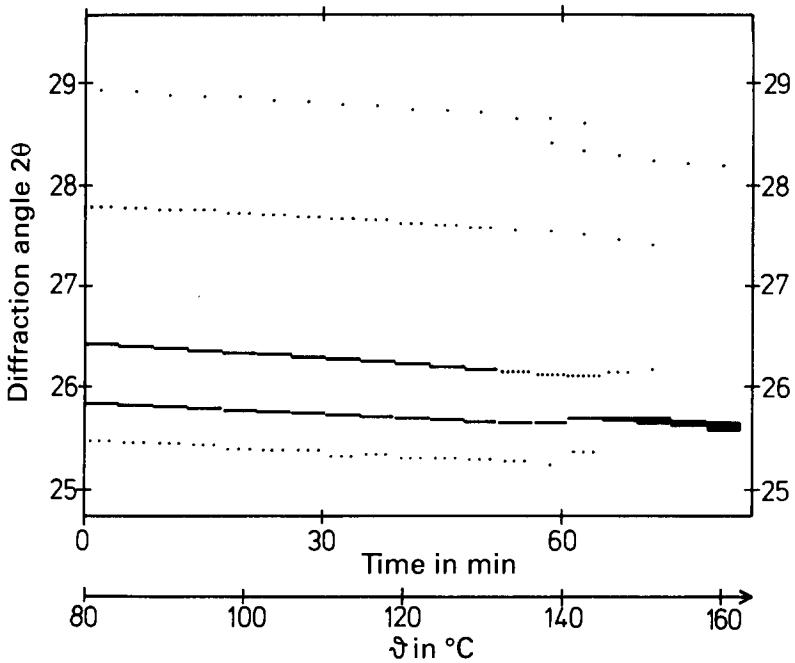

Fig. 5. Film-analogous plot of the diffraction data shown in Fig. 4. The whole temperature range 80–165°C is displayed. The line width is approximately proportional to the logarithm of the corresponding peak intensity (=height). In contrast to Fig. 4, the smaller peaks are more clearly visible in this representation.

is directly proportional to the molar fraction of the corresponding phase [7]. Unfortunately, the structures of the low- and high-temperature phase are very similar; therefore the X-ray diffractograms are not very different. Many peaks overlap and cannot be easily separated, even by peak-fitting routines. For this reason, the three strong peaks in the angular range 25–26.5° 2θ were not evaluated. As a suitable reference peak we chose the one of the β-phase at 27.8° 2θ (at 80°C; 28.4° 2θ at room temperature).

A sample of β-caffeine was transformed into α-caffeine by heating to 160°C. It was then rapidly cooled (at about 3 K min^{-1}, free cooling) to 100°C. This temperature was held constant for 22 h, and powder diffractograms were continuously recorded. The results are displayed in Fig. 6 as the extent of reaction versus time. At the top of the figure the sample temperature is plotted. The extent of reaction was calculated as the ratio of the intensity of the reference peak at 27.8° 2θ (angle at 80°C) at time t to its intensity at $t = \infty$ (pure β-phase). Therefore

$$a = I(t)/I(t = \infty) \tag{1}$$

At the end of the experiment, the extent of reaction reaches 1. The peak intensity at this time is equal to that of the pure β-phase we used to prepare the α-phase. It

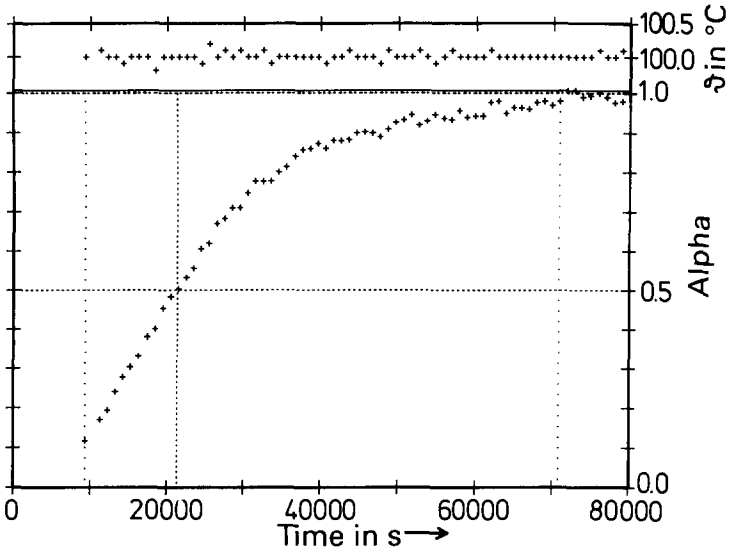

Fig. 6. Monitoring the transformation of the high-temperature phase α-caffeine into the low-temperature phase β-caffeine by X-ray diffractometry. A freshly prepared sample of α-caffeine was rapidly cooled from 160°C to 100°C and held for 22 h at this temperature. The reaction extent was determined from the intensity of the reference peak of the β-phase at 27.8° 2θ (angle at 80°C). At the top of the graph the sample temperature ϑ is shown; in the lower part the calculated reaction extent α vs. the reaction time t is displayed.

is obvious that there is an induction time of about 5000 s before the transformation starts. We tried to fit the data points falling between the dotted lines at $t = 9500$ s and $t = 71\,000$ s in Fig. 6 to the common kinetic models for solid–state reactions [11–14]. A good fit could be obtained for an Avrami–Erofeev mechanism A_n in Eq. (2) with $n = 1.56$ ($r = 0.9863$).

A_n mechanism:

$$d\alpha/dt = k(T)(1-\alpha)[-\ln(1-\alpha)]^{(n-1)/n} \quad (2)$$

If an induction time of 8650 s is subtracted, a better fit to a first-order reaction F_1 is obtained ($r = 0.9875$). The first-order reaction in Eq. (3) is a special case of the Avrami–Erofeev model, where n is equal to 1.

F_1-mechanism:

$$d\alpha/dt = k(T)(1-\alpha) \quad (3)$$

These results suggest that the reaction is nucleation controlled, at least in the early stages. This is supported by earlier experiments of Diedrich [5] on the kinetics of back-transformation during storing and grinding. The above predicted maximum in the reaction rate (or minimum in the half-life time $t(\alpha = 0.5)$) was found by additional isothermal TXRD experiments at a temperature of approximately 90–95°C [15].

4. Conclusions

The phase transformation of anhydrous caffeine was studied by emanation thermal analysis (ETA) and by time- and temperature-resolved X-ray powder diffractometry (TXRD). The transformation of the low-temperature phase α-caffeine into the high-temperature phase β-caffeine could be clearly detected with both methods. The sample morphology changes during the phase transformation; namely, the porosity increases and this can be attributed to the formation of cracks, grain boundaries and micropores. This was shown by ETA and SEM.

The back-transformation of the supercooled α-phase into the β-phase is kinetically restrained. The very low reaction rate makes it difficult to study this transformation with dynamic techniques such as DSC. However, it could be quantitatively followed by isothermal X-ray powder diffractometry at higher temperatures. This demonstrates the application potential of this method for the investigation of slow processes, where dynamic methods such as DSC can no longer be employed. The evaluation of the reaction extent versus time data suggests a nucleation-controlled transformation.

The conclusions, from the standpoint of the pharmaceutical application of caffeine can be summarized as follows:

(1) The high-temperature phase α-caffeine is better suited if a fast metabolical resorption is desired. The rough surface and the higher energy content should promote faster dissolution. It is metastable below the transition temperature.

(2) The back-transformation of α-caffeine into β-caffeine is very slow. However, it may well take place during a "normal" tablet life of months to years.

(3) A nucleation-controlled transformation mechanism makes the stability of a sample of α-caffeine below 141°C very sensitive to its pre-history. Mechanical or thermal shocks, for example, during a rapid quenching of the melt or the freshly prepared α-phase, would promote the formation of nuclei, which in turn would enhance the reaction rate. Extended experiments of the influence of the cooling rate, the particle size and the mechanical treatment of a sample would be necessary to elucidate this effect quantitatively.

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