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The effect of water vapor pressure on desolvation kinetics of caffeine 4/5-hydrate [☆]

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Abstract

The kinetics of dehydration of caffeine 4/5-hydrate at different relative humidities (RH) was studied at 25° C for two crystal preparations with different crystal sizes. The weight change was evaluated over phosphorus pentoxide and relative humidities of 9, 13, 24, 36 and 43%, using special hygrostats and a below-weight balance. Additionally the samples were stored for 8 months at RH between 0 and 98%. A mechanistic interpretation of the reaction was derived by analyzing the data with numerous kinetic models as well as by microscopic investigations and various thermoanalytical techniques (thermomicroscopy, thermogravimetry, differential scanning calorimetry). The mechanism of the dehydration reaction was found to be very complex, depending on the crystal size and water vapor pressure. Diffusion control as well as nucleation and growth reaction are considered as the fundamental principles of the process. Due to the occurrence of a Smith-Topley effect, a constant loss of water rate of a coarse crystalline batch between 0 and 13% relative humidity takes place. The dehydration rate of small crystals is much more affected by changes in water vapor pressure. Over desiccants, complete transformation to the anhydrate requires about 4 h, a 30th of the time required for the coarse crystals. Caffeine hydrate loses the water of crystallization even at 61% RH (25° C), which should be considered during processing and storing conditions. Beyond that, this paper suggests that a variety of analytical techniques are necessary for sufficient information about the dehydration characteristics of a crystalline hydrate and to avoid misinterpretations of phase transformations in the solid state.

Keywords: Caffeine; Hydrate; Humidity; Dehydration; Kinetics; Thermal analysis; Solid-state reaction

1. Introduction

Many drug substances can form associates with water in different states, and as we have estimated, at least one third of the solid crystalline substances of the European Pharmacopoeia have been reported to form such associates. With about 20% of the substances the hydrate is the official crystal form. The stability and the behaviour of hydrates can vary extremely (Burger, 1973; Byrn, 1982; Kuhnert-Brandstätter and Pröll, 1983; Burger et al., 1988a,b; Burger and Griesser, 1991, 1992) and hydrate formation or desolvation may occur during processing or storage of pharmaceu-

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ticals. Since this phase transition is accompanied by a change in physicochemical properties, it is important to know the conditions under which this reaction takes place, as well as the velocity of the process under a given set of conditions.

Caffeine forms a metastable hydrate with the unusual stoichiometry of 0.8 mol water per mol caffeine (Waters and Beal, 1946; Sutor, 1958; Gerdil and Marsh, 1960, Bothe and Cammenga, 1980, 1981; Suzuki et al., 1985; Pirttimäki and Laine, 1994). This incontestable fact is surprisingly not considered in the pharmacopoeias (US Pharmacopoeia, 1990; Pharmacopoeia Europea, 2nd Edn) since they contain an official monograph of a non-existing monohydrate. Only in a saturated water vapor atmosphere will additional amounts of water be adsorbed at the surface of the 4/5-hydrate which has been denoted as a 5/6-hydrate (Waters and Beal, 1946; Bothe and Cammenga, 1980; Pirttimäki and Laine, 1994). The low stability of caffeine hydrate was already discussed by Oechler (1944) who therefore recommended the use of the anhydrous material. Waters and Beal (1946) found that different samples of the hydrate become anhydrous even at relative humidities of 64% (21° C), but not at the same time (probably the effect of particle size). On the other hand, it has been reported that dehydration of caffeine hydrate takes place only at relative humidities below 50% (Stahl, 1980; Cammenga, 1983). The thermodynamics, thermal dehydration behavior and dehydration kinetics of caffeine hydrate have been extensively studied by Bothe and Cammenga (1980, 1981). The experiments were carried out in a dry nitrogen atmosphere. However, little work has been carried out to study the influence of water vapor pressure on the dehydration behavior of the hydrate. The purpose of this paper concerns the elucidation of the kinetics of desolvation reaction of caffeine 4/5-hydrate, specifically addressing the effect of water vapor. The reaction was studied gravimetrically and the desolvation isotherms were obtained by Karl-Fischer titration. Different kinetic equations as well as microscopic and thermoanalytical observations should help to justify a mechanistic interpretation of the data.

2. Experimental

2.1. Materials

All reagents and solvents were of analytical grade. Caffeine was supplied by Apoka (Austria). One batch which was designated as anhydrous caffeine (coffeinum anhydricum Ph.Eur., K1-896/88) was characterized as the thermodynamic stable modification II (β-form). The second batch, designated as coffeinum monohydricum Ph.Eur. (K1-694/89), was the partially desolvated hydrate with 0.47 mol water per mol caffeine.

Two hydrate batches were prepared from a solution of caffeine in water. To obtain larger crystals of the hydrate (hydrate batch H_A) a saturated solution of caffeine in water of 50° C was slowly cooled in a water bath to room temperature (12 h). The filtered, wet crystals were conditioned at 84% relative humidity to a constant weight. This yields clear, thread-shaped, bent crystals of the pure hydrate with at most 3 mm length and an average diameter of 50 μm. A batch of the hydrate with a smaller particle size (H_B) was crystallized from a saturated solution of caffeine at 80° C. The solution was stirred (magnetic stirrer) during the crystallization process and then treated as hydrate batch H_A. The crystals of hydrate batch H_B are below 100 μm in length and 5–10 μm in diameter. Because of the low stability of the hydrate and to avoid preactivated crystals, the batches were not mortared and sieve fractionated.

2.2. Thermomicroscopy

Thermomicroscopic investigations were carried out with a polarizing microscope (Reichert, Vienna, Austria) fitted with a Kofler hot-stage (Reichert, Vienna, Austria). For microscopic observations up to 1000 × (immersion oil) a Micro-Star microscope (Reichert-Jung) was used.

2.3. DSC

DSC thermograms were recorded with a 7 Series/UNIX DSC-7 Lab system (Perkin-Elmer), calibrated with pure benzophenone (m.p. 48.0° C) and caffeine (m.p. 236.2° C). About 2–6 mg of sample was weighed into aluminium pans. The pans were either used without cover or sealed with a cover, which was perforated by a needle. High-pressure cups (Perkin Elmer) were used for closed condition studies. The samples were heated under a stream of nitrogen (30 ml min^{-1}).

2.4. *Thermogravimetry*

A TGA 7 thermogravimetric system (Perkin-Elmer, Norwalk, CT, USA) was used for thermogravimetry. Samples (2–6 mg) were placed into 50 μl platin pans. In addition, some runs were performed with samples enclosed in aluminium pans with perforated cover. The determinations were carried out under a nitrogen purge (balance purge, 50 ml min^{-1}; sample purge, 25 ml min^{-1}).

2.5. *Kinetic studies*

The mass change of the different samples was determined using special glass hygrostats (semimicro-hygrostat, SMH), which were manufactured after the model of Schepky (1982) with slight variations. A glass hygrostat (Fig. 1) consists of four different parts: (a) a 250 ml conical-shoulder bottle (wide neck, brown-glass); (b) a mounted glass tube with a ground standard taper joint (T_1, 34/24) and a 19/26 taper (T_2, about 10 mm shortened); (c) a 19 mm ground-glass stopper with a short hook at the top and a 40 mm long hook on the bottom; and (d) the sample holder, consisting of a cylindrical vessel (30 mm in diameter, 10 mm high), a glass bow and glass loop which hangs upward into the lower hook of part c. Saturated salt solutions (SSS) at the bottom of the bottle (close to the sample) are used to adjust different relative humidities. For weighing the sample (about 300 mg), part c is lifted slightly and suspended in the loop of a wire which is mounted on a below-weighing balance (AT 250 semimicro balance, Mettler Instrumente AG, Greifensee, Switzerland). The loss of water curve was estimated from about 10–30 weighings. The values in the range of 5–95% fractional dehydration (expressed as fractional composition α, with values from 0 to 1) were used for the calculation of kinetic parameters.

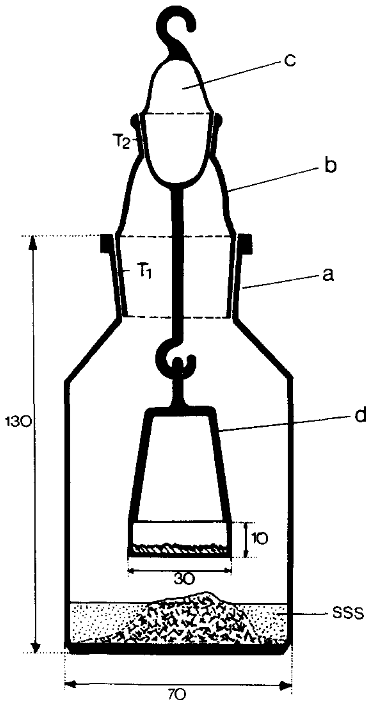

Fig. 1. Semimicro-hygrostate for gravimetric sorption-desorption studies.

2.6. *Preparation of the climatic conditions*

The water vapor sorption and desorption isotherms were determined by storing the samples in desiccators over silica gel or saturated salt solutions at 25° C. The measurement and control of relative humidity were carried out by a calibrated Durotherm® hygrometer (G. Lufft, Stuttgart, Germany). The conditions in % relative humidity (RH) obtained for each humidity chamber are listed in Table 1.

2.7. *Determination of the water content*

The water content was determined by Karl Fischer titration, using pyridine-free reagents and dead stop method (Karl Fischer-Titrator E 551 and Multidosimat 645, Methrom AG, Herisau, Switzerland). The standard samples for calibra-

Table 1
Saturated salt solutions and determined relative humidity conditions at 25° C

Salt solution	RH (%)
Potassium hydroxide	9
Lithium chloride	13
Potassium acetate	24
Calcium chloride	30
Sodium thiocyanate	36
Potassium carbonate	43
Potassium thiocyanate	46
Magnesium nitrate	53
Ammonium nitrate	61
Sodium chloride	74
Potassium chloride	84
Potassium nitrate	92
Potassium sulfate	97

tion were analytical grade dipotassium tartrate dihydrate and oxalic acid dihydrate. The water contents are expressed as percent water related to the anhydrous substance.

3. Results and discussion

3.1. *Desorption isotherms*

The water content of the two hydrate batches, stored in desiccators at different relative humidities, was determined after 30 days and 8 months. The resulting isotherms (Fig. 2) show that the dehydration rate of the larger crystals (H_A) is significantly lower than that of the smaller one (H_B). At 53% relative humidity, H_A is not affected within 1 month but during 8 months the water content decreases to 0.25 mol water per mol caffeine, and even at 61% RH a loss of water took place. After 8 months, at 61% RH, H_B is dehydrated to a water content of less than 20% of its original one. Therefore, it is obvious that caffeine hydrate is not stable under ambient storage conditions. The average water content of the hydrate samples stored between 75 and 98% RH measured by the titrimetric method (21 determinations) is 0.807 mol water per mol caffeine and underlines the existence of a 4/5-hydrate.

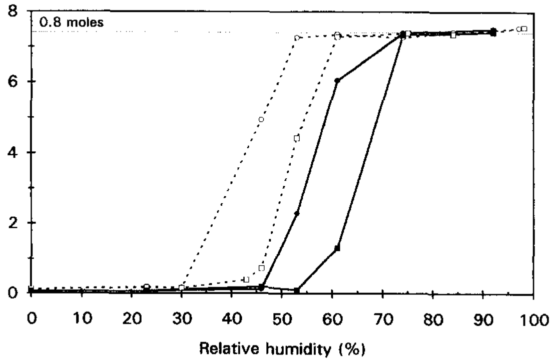

Fig. 2. Desorption isotherms of caffeine hydrate at 25° C; batch H_A (coarse crystals) after 30 days (○) and 8 months (●); batch H_B (small crystals) after 30 days (□) and 8 months (■).

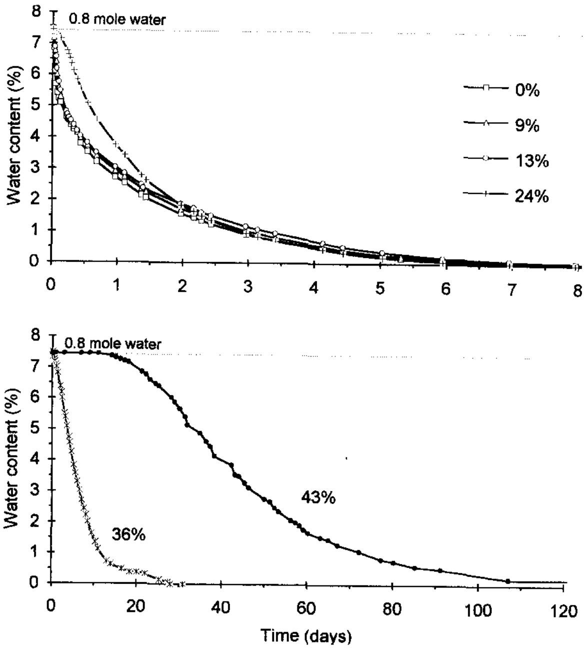

Fig. 3. Weight loss vs time plots of caffeine hydrate (batch H_A, coarse crystals) at different relative humidities.

3.2. *Weight loss curves at different water vapor pressures*

The dehydration kinetics of the two hydrate batches was determined at 0, 9, 13, 24, 36 and 43% relative humidity. The weight loss vs time curves (Fig. 3) of H_A (bigger crystals) at 0, 9, 13 and 24% are of the decelerating type but at higher relative humidities they become sigmoidal

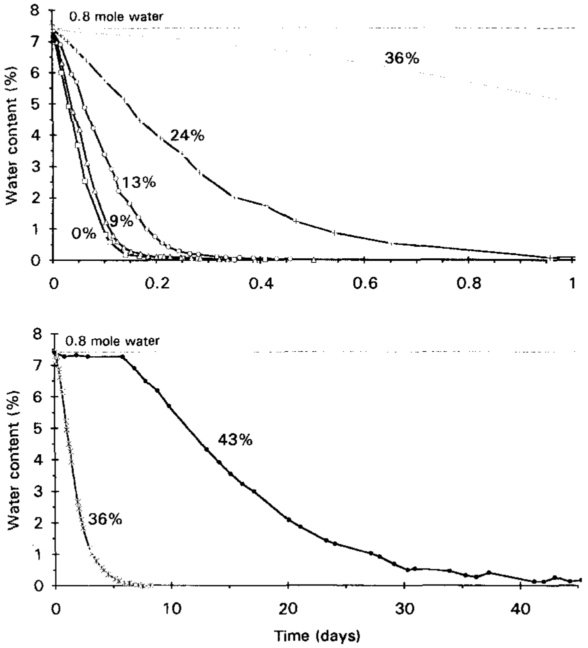

Fig. 4. Weight loss vs time plots of caffeine hydrate (batch H_B, small crystals) at different relative humidities.

in shape. At relative humidities of 0–13%, the dehydration rate of H_A is already equal. The initial rate of the 24% RH curve is much slower, but after 2 days the water content of all samples stored between 0 and 24% RH reached about the same values. At higher water vapor pressures, in particular at 43% RH, the dehydration curves show an initial period and a delay at the end of the reaction. The dehydration rate of H_B (smaller crystals, Fig. 4) is distinctly faster than that of H_A and within roughly 4 h the crystals become anhydrous at very low water vapor pressures (0–13% RH). The weight loss curves are similar in shape and become sigmoidal at 36 and 43% RH. The average water content of all gravimetric measurements is 0.803 mol water per mol caffeine.

The dehydration curves were analyzed by using various kinds of solid state kinetic model equations which are quoted in many reviews and papers (e.g., Sharp et al., 1966; Brown et al., 1980a; Hemminger and Cammenga, 1989), and which are expressed by the general integrated rate equation (Eq. 1):

$$g(\alpha) = k \cdot t \qquad (1)$$

where k is the rate constant, t denotes the reaction time and $g(\alpha)$ is a function of the reaction mechanism. A plot of the appropriate $g(\alpha)$ function vs t should give a straight line with slope k. The models of particular interest in this work are listed in Table 2. The mechanistic representations of these models have been widely applied in the interpretation of dehydration reactions, and in many studied systems there is experimental evidence of their existence.

At the relative humidities of 0–13%, the dehydration curves of H_A are best represented by the three-dimensional diffusion mechanism (Jander equation, D3) but at 24% RH the decay follows the first-order rate equation (F1). The sigmoidal curves (36 and 43% RH), up to a reaction extent of $\alpha = 0.90$, are best described by the Avrami-Erofeev model (A4), the contracting volume equation (R3) or the first-order reaction model (F1). A4 and R3 also give the best linearization of the dehydration curves of batch H_B under all the water vapor pressure conditions.

Table 2
Common kinetic equations for solid-state reactions of particular interest in this study

$g(\alpha)$	Symbol	Rate-controlling process
$(1-\alpha)\cdot\ln(1-\alpha)+\alpha$	D2	two-dimensional diffusion
$[1-(1-\alpha)^{1/3}]^2$	D3	three-dimensional diffusion (Jander)
$1-(2/3)\cdot\alpha-(1-\alpha)^{2/3}$	D4	three-dimensional diffusion (Ginstling-Brounshtein)
$2\cdot[1-(1-\alpha)^{1/2}]$	R2	two-dimensional phase boundary reaction
$3\cdot[1-(1-\alpha)^{1/3}]$	R3	three-dimensional phase boundary reaction
$-\ln(1-\alpha)$	F1	first-order reaction
$[-\ln(1-\alpha)]^{1/4}$	A4	constant random formation of nuclei and three-dimensional, growth, boundary control (Avrami-Erofeev equation)

Table 3
Parameters for the biphasic first-order model (Eq. 2) of the dehydration curves of the caffeine hydrate batches (H_A, H_B) at different relative humidities

RH (%)	H_A					H_B				
q	A	K_a (day^{-1})	B	K_b (day^{-1})	t_i (days)	A	K_a (day^{-1})	B	K_b (day^{-1})	t_i (days)
0	0.65	0.574	0.31	14.861	0	1.83	28.000	−0.83	69.130	0
9	0.66	0.535	0.34	0.970	0	3.94	28.554	−2.97	39.674	0
13	0.66	0.486	0.34	0.797	0	5.32	18.043	−4.36	22.884	0
24	1.00	0.704	0.00	0.000	0	1.44	4.589	−0.45	11.450	0
36	1.84	0.221	−0.85	0.463	0	1.98	0.822	−0.99	1.705	0
43	2.37	0.043	−1.35	0.066	14	1.32	0.109	−0.34	0.323	6

Alternatively, we used a biphasic first-order model for the entire dehydration process expressed as:

$$1 - \alpha = \{A \cdot e^{-k_a \cdot (t - t_i)}\} + \{B \cdot e^{-k_b \cdot (t - t_i)}\} \qquad (2)$$

where $1 - \alpha$ is the fractional amount of hydrate, t the time of reaction and t_i the lag time period until the start of reaction. A and k_a are the intercept and slope of the terminal part, and B and k_b the intercept and slope of the initial part of the reaction, respectively. This composed exponential function has been widely used not only for pharmacokinetic models (Ritschel, 1980) and dissolution studies (Burger, 1981) but also for solid-state degradations (Chong, 1992). The results obtained by feathering are listed in Table 3 and the data are plotted in Fig. 5. The dehydration rate of H_A up to 13% RH is faster at the initial part of the reaction and decreases with increasing reaction time. At 24% RH the reac-

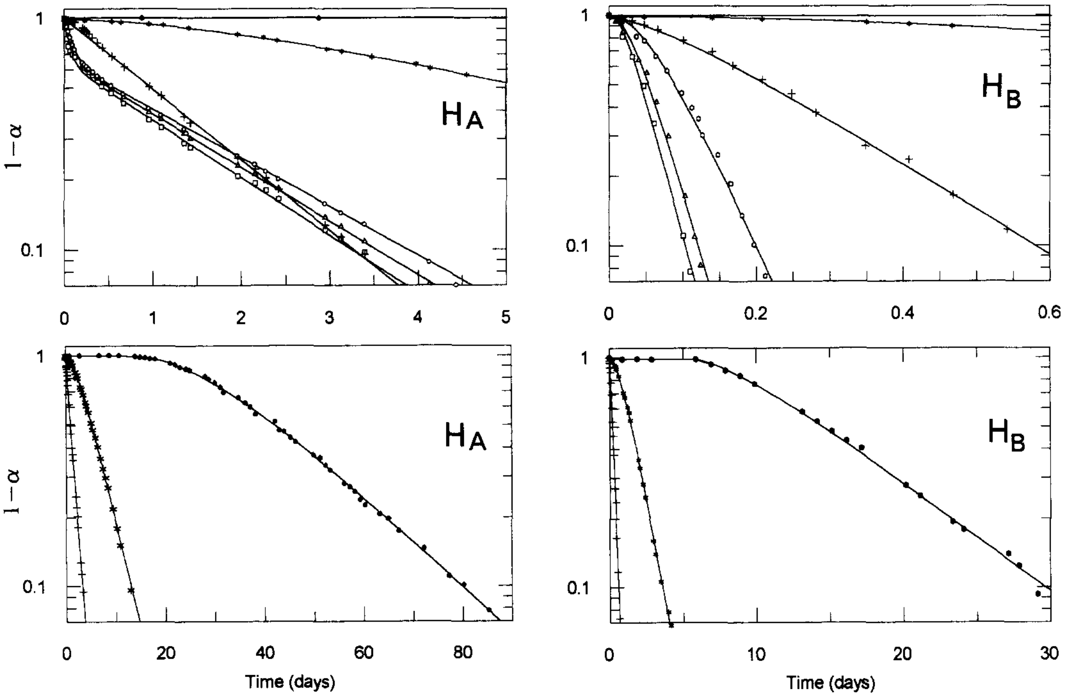

Fig. 5. Plot of logarithmic fractional amount of caffeine hydrate (batch H_A and batch H_B) vs time at 0% (□), 9% (△), 13% (○), 24% (+), 36% (⋆) and 43% (●) relative humidity with calculated curves.

tion is an almost straightforward first-order process and at higher RH values an accelerating phase occurs with a lag phase at 43% RH. All curves of the hydrate batch H_B show an initial acceleration phase.

3.3. Microscopy

Byrn and Lin (1976) noticed that caffeine hydrate dehydrates faster when the ends of the needles are cut off. Scanning electron micrographs of dehydrated crystals (Bothe and Cammenga, 1981; Suzuki et al., 1985) show that needle-shaped crystallites of the anhydrous phase are oriented parallel to the long axis forming channel-like cavities. This arrangement is consistent with the crystallographic studies of Sutor (1958) and Gerdil and Marsh (1960), who found that the chains of water molecules are arranged along this axis.

From microscopic observations of the coarse hydrate batch (H_A), which were withdrawn at different reaction extents, it was observed that at first the crystals become opaque from the ends and ruptures due to the formation of polycrystalline product phase (pseudomorphosis). This reaction proceeds along the long direction of the crystals but the front becomes very irregular during progressive movement and the rate seems to slow down with increasing distance to the end of the crystal. Simultaneously, anhydrous phase appears at a few random positions of the crystal surface. The growth rate of these centres perpendicular to the c-axis is rather low in contrast to that along this direction, and the crystals are more and more covered with anhydrous phase. Thus, it seems that crystal faces react non-simultaneously, and we have to consider a more complicated topochemical reaction (Prodan, 1984).

3.4. Thermal analysis

To compare the results of the desorption studies in the more or less static atmosphere over a desiccant with the dynamic atmosphere in a dry nitrogen stream and to establish the temperature dependence of the process, isothermal thermogravimetric measurements of the coarse crystals (H_A) between 34 and 80° C were carried out. Up to 70° C, the curves are best represented by the equations for three-dimensional diffusion, in particular the Jander equation (D3), with correlation coefficients greater than 0.999. At 80° C, Eq. R3 and A4 give the best fit, indicating the dominance of the nucleation process at higher temperatures. From the Arrhenius relation (Fig. 6) we have calculated an activation energy of $E_A = 105.5 \pm 2.1$ (95% c.i.) kJ mol^{-1}.

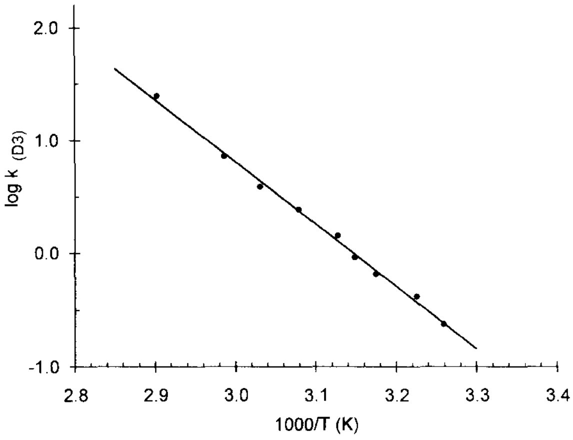

Fig. 6. Arrhenius plot of isothermal dehydration reactions of caffeine hydrate (batch H_A). The values of k were calculated with the Jander equation (D3). The 80° C value (+) was not used for calculation of the Arrhenius parameters.

Bothe and Cammenga (1981) found that dehydration of caffeine hydrate at low water vapor pressures is a topochemical reaction, starting at the crystal surface and following the contracting volume mechanism (R3). They studied single crystals and crystals of smaller dimensions (similar to our hydrate batch H_A) with different thermogravimetric methods. The calculated activation energy of 94 ± 3 kJ mol^{-1} is somewhat lower than our value. Later, applying temperature-resolved diffractometry, Epple and Cammenga (1992) suggested a multiple reaction with a nucleation period up to an extent of reaction of 0.6 ($E_A = 76$ kJ mol^{-1}) followed by a three-dimensional diffusion mechanism (D3) with an activation energy of 111 kJ mol^{-1}. However, the atmospheric conditions (ambient) and particle size (ground crystals) of the second study are rather

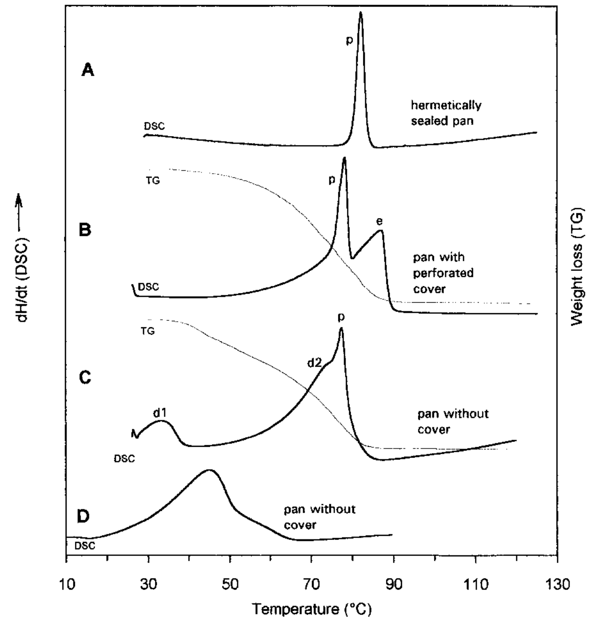

Fig. 7. DSC and thermogravimetric (TG) curves of caffeine hydrate under different vapor pressure conditions. Curves A–C, batch H_A (coarse crystals); curve D, batch H_B (small crystals); heating rate, 2.5 K min^{-1}.

different and suggest the great influence of the experimental and sample conditions on dehydration behavior.

To gain more insight into such effects, we studied the dehydration reaction of caffeine hydrate by DSC at different vapor pressure conditions, produced by varying the tightness of the sample pans (Fig. 7). When the hydrate is heated up in gas-tight containers (Fig. 7, curve A), a sharp endotherm (p) occurs at 80° C, which can be attributed to the peritectic decomposition process of the hydrate (Suzuki et al., 1985). In sample pans with a perforated cover (B), slow dehydration starts at about 50° C, followed by the sharp peritectic decomposition (p) and a broad endothermic process (evaporation of water, e). The corresponding TG curve does not show separate steps under these conditions. The DSC curve (C) of the hydrate, recorded in an open sample pan, shows an endothermic peak (d1) at the start of the run and a wide endothermic reaction (d2) starting at about 50° C which is coupled with the peritectic decomposition peak (p). The first endotherm is accompanied by a distinct step (about 1% weight loss) in the corresponding TG curve. As shown in Fig. 7 (curve D), in an open pan the complete dehydration process of the hydrate batch with smaller crystal size (H_B) already starts at about 20° C. The first DSC peak in curve C (Fig. 7) may therefore be attributed to the dehydration of the amount of particles with very small dimensions in the H_A batch. This suggestion is in accordance with that of Bothe (1980), who obtained two step curves of caffeine crystals not uniform in size by dynamic TG experiments. Similar DSC curves have also been obtained by Suzuki et al. (1985) under open conditions. They, however, attributed the two peaks to the dehydration and subsequent evaporation of water. From the microscopic observations we noticed that the ends (or cracks) of the crystals react very soon, but dehydration along the length direction then decreases markedly. Thus, we must take into account that also large crystals are partly involved in the early dehydration step (d1). The desorption of surface-bound ‘free water’ at d1 can be ruled out in this study since the used hydrate batches were well conditioned. Moreover, the existence of a lag time period at 43% RH (Fig. 3) clearly demonstrates the absence of free water.

Fig. 8 shows the DSC curves of H_A recorded in open pans, at different heating rates. The reaction (d1) at the start has been explained above. The dehydration step d2 is more temperature-dependent but rather slow. If the temperature rises above about 75° C before dehydration is complete at d2, the fast peritectic decomposition (p) occurs, which is not dependent on the vapor pressure conditions.

3.5. Mechanistic interpretations

From these results it is obvious that the dehydration mechanism of caffeine hydrate is not a straightforward process. The rate of water removal is sensitive to particle size, and with increasing vapor pressure a change of the reaction mechanism occurs. The microscopic observations point out that there exist differences in reactivity of the crystal faces and, moreover, the particle size of the used hydrate batches is not uniform. All these factors can cause problems in kinetic

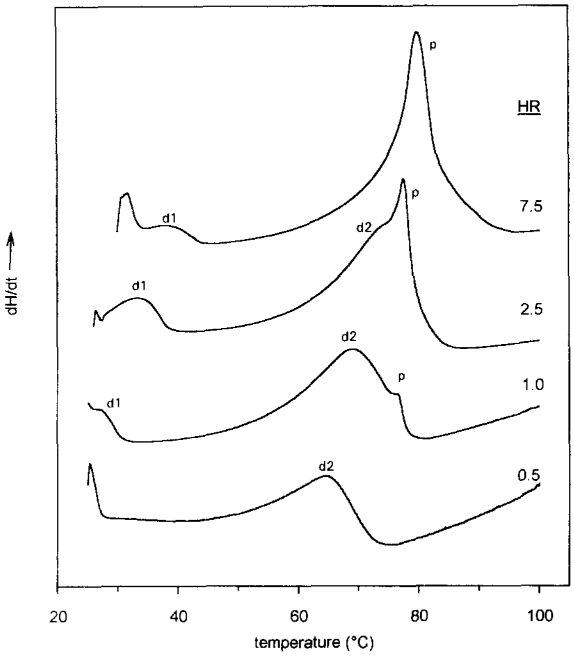

Fig. 8. DSC curves of caffeine hydrate (coarse crystals, H_A) at different heating rates (HR) under open conditions (coverless sample pan).

studies (Hancock and Sharp, 1972; Brown et al., 1980a; Ray, 1990). Hence, it is very questionable to find strict agreement with one of the theoretical kinetic models for solid-state reactions.

The decomposition of a hydrate originates at the surface of the crystals, which is activated due to the low water vapor pressure of the surrounding atmosphere. Dehydration reactions are reversible, but the reverse reaction is diminished with decreasing water vapor pressures. In general, the rate control for water release in dehydration reactions of crystalline hydrates is mostly ascribed either to diffusion or interface processes (Brown et al., 1980b). Galwey (1992) recently discussed possible elementary processes participating in dehydrations of solids, and he concluded that diffusion and interface controls together contribute towards the release of water.

A striking result of our observation is the constant dehydration rate of hydrate batch H_A between 0 and 13% and the slight rate increase at 24% RH. This behavior may be attributed to the so-called Smith-Topley effect (S-T), which has been frequently reported in hydrate decompositions (Topley and Smith, 1935; Brown et al., 1980b). The S-T behavior is represented by a more or less sharp maximum of the dehydration rate as the partial pressure of water increases. This effect has only been observed for dehydration reactions, although there exist various mechanistic interpretations (Brown et al., 1980b). The most probable reason for the S-T effect in caffeine hydrate dehydration appears to be the catalytic effect of the water vapor to the reorganization of the dehydrated phase. Due to the escape of the loosely bound water molecules in the crystal lattice a vacancy structure is produced on the surface of the hydrate crystals. This intermediate structure is unstable and recrystallization (nucleation and growth) to the anhydrous product occurs. In this way a phase boundary is formed which gradually moves inside the crystal (preferentially along the *c*-axis). The water molecules liberated from the hydrate lattice must diffuse through this interface layer and the growing product layer. A progressive growth of the initial polydisperse microcrystallites to crystalline particles in the product layer results in a porous aggregate. Since the extent of the product phase recrystallization is generally strongly influenced by the water vapor pressure conditions, it can be assumed that the nucleation rate at low vapor pressures is particularly slow. Conversely, the pressure gradient and the water evaporation rate are high at low vapor pressures. Thus it can be concluded that the mass transfer (diffusion) of the water molecules through the unrecrystallized product layer of the large crystals plays the dominant role and may therefore be discussed as the rate-limiting process at very low vapor pressures (Galwey, 1992). Indeed, the best fit of the dehydration curves of H_A at the relative humidities 0 to 13% has been observed for the three-dimensional diffusion process (Jander equation, D3). The D3 mechanism was also supported by the results obtained for isothermal thermogravimetry of H_A (dynamic, dry atmosphere). Considering the shape of the crystals we should expect a two-dimensional diffusion reaction (D2) which nevertheless gives a significantly poorer fit. However, the geometry of the reaction advance is not proportional to the shape of the crystals, since the reaction along the *c*-axis proceeds more rapidly than perpendicular to this direction. With increasing vapor pressure, the nucleation and growth of the anhydrous product phase is promoted and because of the production of a very porous product layer the resistance of the water molecule migration decreases. On the other hand, the rate of hydrate decomposition decreases because of the reverse reaction caused by atmospheric water molecules. In this way, nucleation and growth gradually become the rate-determining step instead of diffusion control with increasing relative humidity.

3.6. *Effect of crystal size*

The most dramatic differences in the dehydration rate between the hydrate batches H_A and H_B were observed at RH values below 10%. Over a desiccant, batch H_B (small crystals) loses all the crystal water in about 4 h (Fig. 4). The coarse crystalline hydrate (H_A) still contains about two-thirds of the original water content at this time (Fig. 3) and the complete dehydration lasts about 5 days (factor 30). At 43% RH, the time required for complete dehydration of H_A (120 days) is only about 3-times that of H_B. The reaction characteristic of the two batches is quite different at RH conditions up to 24%, but comparable at 36 and 43% RH. This is largely due to the dominance of diffusional control in case of large crystals and very low water vapor pressures and the increasing role of nucleation and growth of the anhydrous phase when the water vapor pressure, the surface area and the amount of high reacting zones of the hydrate (crystal ends and cracks) increase. However, the dehydration rate of caffeine hydrate is very sensitive to crystal size.

4. Conclusions

The dehydration process of caffeine hydrate is very complex, consisting of consecutive processes which are greatly dependent on vapor pressure conditions, temperature and crystal dimensions. Both diffusive migration of water molecules and the nucleation and growth behavior of the anhydrous phase are assumed as the predominating processes in dehydration kinetics of this hydrate. The results of the present work demonstrate the particular influence of water vapor pressure and crystal size on the kinetic characteristics of dehydration reactions. Hydrates are most frequently characterized by thermoanalytical techniques (DSC, TG), but less attention is usually paid to the prevailing atmospheric conditions (dynamic dry atmosphere, self generated atmosphere, enhanced gas pressure under closed conditions) and the effects based on particle size distribution. However, knowledge of the influence of water vapor and sample characteristics on dehydration reactions is essential for the interpretation of thermoanalytical results and for sufficient characterization of metastable hydrates. Moreover, this study supports the view that different processes can control the loss of water of crystalline hydrates and that common kinetic models do not necessarily define a certain mechanism. Finally, it should be emphasized that the caffeine 4/5-hydrate, which besides is still referred to as a monohydrate in most handbooks and pharmacopoeias, is an official, extremely unstable crystal form and if the use of the pure hydrate is considered, it is necessary to condition and to store the fresh crystallized hydrate at about 75% relative humidity. This fact has already been known for 50 years (Oechler, 1944) but has not been considered adequately up to now. However, this is remarkable, particularly in connection with further details concerning the polymorphism of caffeine (to be published).

References

Bothe, H. and Cammenga, H.K., Composition, properties, stability and thermal dehydration of crystalline caffeine hydrate. *Thermochim. Acta*, 40 (1980) 29–39.

Bothe, H. and Cammenga, H.K., Kinetic study of the topotactic dehydration of caffeine hydrate studied by different experimental techniques. *Z. Phys. Chem.*, 127 (1981) 193–206.

Bothe, H., Dissertation, Braunschweig, p. 83 (1980).

Brown, W.E., Dollimore, D. and Galwey, A.K., Reactions in the solid state. In Bamford, C.H. and Tipper, C.F.H. (Eds), *Comprehensive Chemical Kinetics*, Vol. 22, Elsevier, Amsterdam, 1980a, pp. 41–113.

Brown, W.E., Dollimore, D. and Galwey, A.K., Reactions in the solid state. In Bamford, C.H. and Tipper, C.F.H. (Eds), *Comprehensive Chemical Kinetics*, Vol. 22, Elsevier, Amsterdam, 1980b, pp. 115–135.

Burger, A., Das Auflösungsverhalten von Sulfanilamid in Wasser. *Pharm. Ind.*, 35 (1973) 626–633.

Burger, A., Zur Wirkstofffreigabe aus pflanzenextrakthaltigen Dragees: 2. Linearisierung der Auflösungskurven der Drageekerne. *Sci. Pharm.*, 49 (1981) 482–495.

Burger, A. and Griesser, U.J., The polymorphic drug substances of the european pharmacopoeia: 7. Physical stability, hygroscopicity and solubility of succinylsulfathiazole crystal forms. *Eur. J. Pharm. Biopharm.*, 37 (1991) 118–124.

Burger, A. and Griesser, U.J., Zur Kinetik der Wasserabgabe von Arzneistoff-Hydraten. *Sci. Pharm.*, 60 (1992) 226.

Burger, A., Ratz, A.W. and Zölß, G., Polymorphie und Pseudopolymorphie von Celiprololhydrochlorid. *Acta Pharm. Technol.*, 34 (1988a) 147–151.

Burger, A., Sturm, S. and Bolitschek-Dialer, R.D., Polymorphie und Pseudopolymorphie von Sulfametrol. Löslichkeit und Tablettierverhalten. *Pharm. Ind.*, 50 (1988b) 1396–1405.

Byrn, S.R., Loss of solvent of crystallization. *Solid State Chemistry of Drugs*, Academic Press, New York, 1982, pp. 149–188.

Byrn, S.R. and Lin, C.T., The effect of crystal packing and defects on desolvation of hydrate crystals of caffeine and L-(−)-1,4-cyclohexadiene-1-alanine. *J. Am. Chem. Soc.*, 98 (1976) 4004–4005.

Cammenga, H.K., Coffein, Theophyllin und Theobromin: Physikalisch-chemische Untersuchungen für Lebensmitteltechnologie und Pharmazie. *41. Berichtsband des Forschungskreises für Ernährungsindustrie*, Hannover, 1983, pp. 97–141.

Chong, M.W., Kinetics of degradation of Levothyroxine in aqueous solution and in solid state. *Pharm. Res.*, 9 (1992) 131–137.

Epple, M. and Cammenga, H.K., Investigation of solid-state reactions and solid-solid phase-transformations with time-resolved and temperature-resolved X-ray powder diffractometry. *Ber. Bunsenges. Phys. Chem.*, 96 (1992) 1774–1778.

Galwey, A.K., Some recent studies of the mechanism of dehydration reactions of solids. *J. Thermal Anal.*, 38 (1992) 99–110.

Gerdil, R. and Marsh, R.E., On the arrangement of water molecules in the crystal structure of caffeine. *Acta Crystallogr. C*, 13 (1960) 166–167.

Hancock, J.D. and Sharp, J.H., Method of comparing solid-state kinetic data and its application to the decomposition of kaolinite, brucite and $BaCO_3$. *J. Am. Ceram. Soc.*, 55 (1972) 74–77.

Hemminger, W.F. and Cammenga, H.K., Kinetik. *Methoden der Thermischen Analyse*, Springer, Berlin, 1989, pp. 246–267.

Kuhnert-Brandstätter, M. and Pröll, F., Thermische Analyse von Hydraten organischer Verbindungen: I and II. *Mikrochim. Acta*, II (1983) 463–467; and *Mikrochim. Acta*, III (1983) 287–300.

Oechler, F., Über Coffein und Zitronensäure. *Pharm. Zentralhalle Dtschl.* 85 (1944) 1–5.

Pirttimäki, J. and Laine, E., The transformation of anhydrate and hydrate forms of caffeine at 100% RH and 0% RH. *Eur. J. Pharm. Sci.*, 1 (1994) 203–208.

Prodan, E.A., Localization phenomena of topochemical reactions. *J. Thermal Anal.*, 29 (1984) 941–948.

Ray, H.S., Some factors that lead to uncertainities in kinetic studies in metallurgy. *J. Thermal Anal.*, 36 (1990) 743–764.

Ritschel, W.A., *Handbook of Basic Pharmacokinetics*, 2nd Edn, Hamilton Press, Hamilton, 1980, pp. 208–218.

Schepky, G., Ein Hygrostat mit einfacher und störungsarmer Probenauswaage. *Acta Pharm. Technol.*, 28 (1982) 87–88.

Sharp, J.H., Brindley, G.W. and Achar, B.N.N., Numerical data for some commonly used solid state reaction equations. *J. Am. Ceram. Soc.*, 49 (1966) 379–382.

Stahl, P.H., *Feuchtigkeit und Trocknen in der pharmazeutischen Technologie*, Dr. Dietrich Steinkopff Verlag, Darmstadt, 1980, pp. 45–46.

Sutor, D.J., The structures of the pyrimidines and purines: VII. The crystal structure of caffeine. *Acta Crystallogr. C*, 11 (1958) 453–458.

Suzuki, E., Shirotani, K., Tsuda, Y. and Sekiguchi, K., Studies on methods of particle size reduction of medicinal compounds: XXIII. Water content and dehydration behavior of crystalline caffeine hydrate. *Chem. Pharm. Bull.*, 33 (1985) 5028–5035.

Topley, B. and Smith, M.L., Kinetics of salt-hydrate dissociations: $MnC_2O_4, 2H_2O = MnC_2O_4 + 2\,H_2O$. *J. Chem. Soc.*, (1935) 321–325.

Waters, K.L. and Beal, G.D., Notes of the water content of crystalline caffeine. *J. Am. Pharm. Assoc. Sci.*, 35 (1946) 12–14.

US Pharmacopoeia XXII, The National Formulary XVII, US Pharmacopoeial Convention, Rockville, MD, 1990, p. 204.