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RESEARCH PAPER

Influence of Temperature on Solvent-Mediated Anhydrate-to-Hydrate Transformation Kinetics

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ABSTRACT

Purpose To achieve an in-depth understanding of the underlying mechanism of the acceleration or deceleration effect of temperature on solvent-mediated anhydrate-to-hydrate phase transformation.

Methods The effect of temperature on the phase transformation rate and onset time of two model compounds was investigated using *in situ* Raman spectroscopy. The thermodynamic driving force of the phase transformation (e.g. supersaturation) at different temperatures was determined by measuring the solubility of the anhydrate and the hydrate.

Results Both acceleration and deceleration effects of temperature on the phase transformation were observed. The mechanism of these temperature effects was studied by exploring the influence of temperature on supersaturation level and crystallization kinetics. Increasing temperature usually leads to accelerated phase transformation kinetics, but it simultaneously decreases supersaturation, which has the opposite effect on the kinetics of the phase transformation. The overall effect of temperature on the phase transformation is therefore determined by the combined effects of supersaturation and temperature on the nucleation and crystal growth kinetics of the hydrate.

Conclusions By differentiating and comparing the effects of temperature and supersaturation on the anhydrate-to-hydrate phase transformation, a deeper understanding of the underlying principle of the acceleration and deceleration effects of temperature on the phase transformation has been achieved.

KEY WORDS anhydrate-to-hydrate · crystallization · phase transformation · supersaturation

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INTRODUCTION

Approximately one-third of active pharmaceutical substances (APIs) are capable of forming hydrate. Depending on the desired product performance characteristics of the different solid forms, either the anhydrate or the hydrate form can be selected as the final API dosage form. An undesired phase transformation may cause unexpected changes of the physical and chemical properties of the drug substance in terms of solubility, dissolution rate, hygroscopicity, stability, particle size, and morphology and therefore may significantly affect the quality of the final product (1,2). As a consequence, thorough understanding and control of the anhydrate/hydrate state is required through the whole manufacturing of the drug substance. However, aqueous solutions are frequently used during the drug processing, such as solution crystallization, filtration, granulation, and aqueous film coating. During these processes, a solvent-mediated anhydrate-to-hydrate phase transformation or vice versa might occur depending on the surrounding environment, e.g. water activity and temperature. At given water activity in the surrounding medium, temperature is the most influential variable for the anhydrate/hydrate phase transformation. On the one hand, temperature determines the relative stability of the anhydrate and

hydrate; on the other hand, temperature also strongly affects the kinetics of nucleation and crystal growth of the hydrate, and therefore has a significant influence on the phase transformation rate. Both acceleration and de-acceleration effects of temperature on the solvent-mediated anhydrate-to-hydrate phase transformation have been reported in literature. However, a comprehensive understanding of the underlying principle behind these acceleration and de-acceleration effects has not been achieved.

In principle, the relative stability of the anhydrate/hydrate can be described by the following equilibrium, which has been established by Grant and Higuchi (3):

$$A(solid) + mH_2O \leftrightarrow A \cdot mH_2O(solid)$$

$$K_h = \frac{a[A \cdot mH_2O(solid)]}{a[A(solid)]a[H_2O]^m} \quad (1)$$

where K_h is the equilibrium constant for the process; $a[A \cdot mH_2O(solid)]$, $a[A(solid)]$ and $a[H_2O]$ are the thermodynamic activities of the hydrate, the anhydrate, and water; and m is the number of water moles taken up by one mole of the anhydrate. When $a[H_2O] > \{a[A \cdot mH_2O(solid)]/[a[A(solid)]K_h]\}^{1/m}$, the hydrate is the more stable form. The anhydrous form will be more stable in the inverse situation. If the pure solids of anhydrate and hydrate are taken as the standard states (i.e., with unit activity), then Eq.1 can be simplified as $K_h = a[H_2O]^{-m}$. Since the equilibrium constant K_h is a function of temperature, the relative stability of the anhydrate/hydrate is determined by the water activity and temperature in the surrounding medium. This leads to a significant difference in the behaviour of anhydrate/hydrate and polymorphic systems. At ambient pressure, the transition temperature between two enantiotropically related polymorphs is an inherent thermodynamic property of the system, which is independent of the surrounding medium, such as solvent. On the contrary, the transition temperature between anhydrate/hydrate depends on the water fraction (e.g., water activity) in the solvent; usually, the transition temperature increases with increasing water fraction (4–6) until the maximum transition temperature is approached in pure water. This transition temperature in water is also referred to as the peritectic temperature, which is a fixed invariable for a certain anhydrate-water system.

Equation 1 denotes the relative stability of the anhydrate/hydrate and therefore identifies the direction of the phase transformation (anhydrate-to-hydrate or hydrate-to-anhydrate); however, it does not explain the mechanism and kinetics of the transformation process. Cardew and Davey (7,8) have interpreted the solvent-mediated phase transformation as a two-step process. First, the metastable form is dissolved, which results in a supersaturated solution with respect to the stable form; second, the nucleation and crystal growth of the stable form is driven out by the supersaturation. Depending on the relative kinetics of the dissolution and the crystallization steps, the transformation process can be either dissolution controlled or crystallization controlled. All factors that may affect the kinetics of the dissolution and crystallization process will exert an effect on the phase transformation rate. It has been observed that the rate of the anhydrate-to-hydrate transformation can either decrease or increase with increasing temperature in aqueous solution (9). However, the underlying mechanism of this observation has not been well understood yet due to the complex nature of the phase transformation process. On one hand, the increasing temperature may lead to a decreased solubility difference between the anhydrate and the hydrate, which slows down the transformation; on the other hand, increasing temperature also causes increased nucleation and crystal growth rate, accelerating the transformation. The competition of these effects will determine the overall effect of temperature on the transformation process.

The objective of the present work is therefore to investigate the underlying mechanism of the effect of temperature on the solvent-mediated anhydrate-to-hydrate transformation. Two model compounds, carbamazepine and piroxicam (Fig. 1), were used to demonstrate the different phase transformation mechanisms driven by temperature change. With increasing temperature, the phase transformation profiles of carbamazepine and piroxicam changed in a very different way. The overall transformation rate of anhydrous carbamazepine decreased with increasing temperature, following a tendency that also has been observed for some other well-known hydrate-forming drug substances, such as theophylline and caffeine (9). However, the overall phase transformation rate of piroxicam can either increase or decrease with increasing temperature. This different phase transformation behavior was interpreted through the effect of temperature on both the thermodynamic driving force of the process and the kinetics of the sub-processes, such as the dissolution of anhydrate and the nucleation and crystal growth of the hydrate. The competition between the thermodynamic and kinetic factors during the phase transformation is considered as the key element which determines the rate of the whole transformation process.

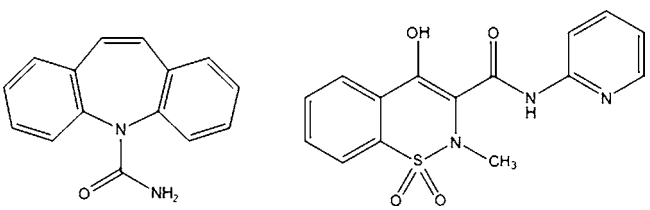

Fig. 1 Chemical structure of carbamazepine (*left*) and piroxicam (*right*).

MATERIALS AND METHODS

Materials

Analytical-grade ethanol from Altia Corp. (Finland) and deionized water were used as solvents. Carbamazepine and piroxicam were used as received from Orion Corp. (Finland) and Hawkins Pharmaceutical Group (Minneapolis, USA), respectively. The solid form of the raw materials was analyzed using X-ray powder diffraction. Carbamazepine is capable of forming four polymorphs and one dihydrate form (10,11), and the purchased carbamazepine powder was identified as the anhydrous form III (CBMZPN01 (12)). Three polymorphs and one monohydrate form of piroxicam have been reported in the literature (13,14). The obtained piroxicam was identified as the anhydrous form I (BIYSEH02 (15)). The dihydrate carbamazepine crystals were prepared by cooling crystallization from 61 mol% ethanol aqueous solution, as described in the previous work (16). The pure piroxicam monohydrate was prepared by suspending anhydrate (10 g) in ion-exchanged water (500 ml) under magnetic stirring at 70°C. The suspension was kept dark, and after 3 h the yellow suspension was filtered and dried overnight at ambient conditions. The obtained carbamazepine dihydrate and piroxicam monohydrate demonstrate identical X-ray powder diffraction (XRPD) patterns as that published in Cambridge Crystallographic Data Centre (CCDC refcode FEFNOT (17) and CIDYAP01 (15), respectively).

Raman Spectroscopy

The phase transformation of piroxicam and carbamazepine was investigated using a dispersive Raman spectrometer with a fiber optic probe (laser spot size 90 μm, focal length 5 mm; InPhotonics, Norwood, MA), a diode laser (wavelength 785 nm; Starbright 785 S, Torsana Laser Technologies, Denmark) and a thermoelectrically cooled 2DMPP charge coupled device (CCD) (1024×64) detector (Control Development, Inc., South Bend, IN, USA). Spectra were collected using 20 s integration time and 6 consecutive scans for carbamazepine, and 1 s integration time and 16 consecutive scans for piroxicam.

The calibration of the Raman spectra for the monitoring of the phase transformation of carbamazepine and piroxicam has been described in a previous publication (18).

Solubility Measurements

The solubility of carbamazepine anhydrate (CBZA) and dihydrate (CBZH) in ethanol-water mixtures were measured gravimetrically. Only CBZA was used as the starting solid material. The method has been described elsewhere (16).

The solubility of piroxicam anhydrate (PXA) and monohydrate (PXH) in water at different temperatures was measured with a UV spectrometer (absorbance at 360 nm). A series of standard piroxicam-water solutions was prepared and analyzed with a UV spectrometer to generate the calibration model. Excess PXH was kept in 200 ml of water in a flask immersed in a water bath at the examined temperature for 48 h. Magnetic stirring was used to provide the mixing of the suspension. Five mL clear solution was taken through a syringe filter, and after dilution, it was analyzed with a UV spectrometer. The solid phase was also sampled and analyzed with XRPD to confirm that no transformation from PXH to PXA occurs. The apparent solubility of the PXA, which is the metastable form under the conditions used in the present work, was measured by a similar method for the measurement of the apparent solubility of CBZA. Excess PXA was suspended in water at the examined temperature. Clear solutions and solids were both sampled at 10, 20, 30, and 60 min. The clear solutions were analyzed with a UV spectrometer, and the solid samples were analyzed with XRPD. The solution concentration before the phase transformation started was considered as the apparent solubility of PXA.

Monitoring of Phase Transformations

The anhydrate-to-hydrate phase transformation experiments of carbamazepine were conducted in a 150 ml glass vessel immersed in a temperature-controlled water bath. A overhead mixer was used to provide the mixing of the suspension, and the mixing intensity was kept constant for all operations by keeping the agitation speed at 120 rpm. One-hundred-twenty milliliters of ethanol-water mixture containing 61 mol% ethanol was kept in the vessel under mixing; after the solvent temperature reached the target temperature, 6 g CBZA powder was added to the solvent. A Raman probe was fixed above the suspension to perform online monitoring of the solid form composition. The phase transformation experiments of carbamazepine were carried out at four different temperatures ranging from 8°C to 14.5°C, and all experiments were repeated in triplicates.

The phase transformation experiments of piroxicam were performed in duplicates at five different temperatures ranging from 40°C to 80°C. For each conversion experiment, PXA (1500 mg) was dispersed in water (5 ml) while stirring at 450 rpm. A small amount of sample (approximately 5 mg) was withdrawn every 5 min and dried on two layers of filter paper to remove excess water. The piroxicam slurry on the filtration paper surface was then scraped off with a spatula and transferred into three aluminum sample cups consecutively (about 1 mg sample per cup). The Raman spectra were recorded immediately after filling the sample cups. The phase transformation

experiments were followed until PXA was completely converted to PXH.

Fitting and Calculations of the Kinetic Data

All the conversion data were fitted to Eq. 2, using a four-parameter non-linear least squares routine (written in-house using Matlab 2009a/2009b, The MathWorks, Natick MA, USA). A Gauss-Newton algorithm (19,20) was chosen for simplicity of implementation and performed adequately.

$$X = X_o + \frac{\alpha}{1 + e^{-\beta(t-t_{50})}} \quad (2)$$

Confidence bands were calculated according to the method reported by Jennrich and Ralston (19). Lag times were calculated as the intersection between two lines defined using the fraction of converted compound and the calculated tangent (obtained from the fitted model) at t= 0 min and t=t_{50}, respectively. The conversion rate constant was calculated according to Eq. 3.

$$K = \ln 2 * \beta \quad (3)$$

RESULTS

Thermodynamic Driving Force of Solvent-Mediated Anhydrate-to-Hydrate Phase Transformation

At ambient pressure, the relative stability of anhydrate/hydrate is determined by the temperature and water activity in the surrounding medium. For any aqueous solution with a certain water activity (e.g., water fraction), there exists a corresponding transition temperature T_r, at which the anhydrate and the hydrate have equal Gibbs free energy and therefore equal stability. The transition temperature between anhydrate and hydrate in a solvent with certain water activity can be obtained by measuring the solubility of both forms and then plotting the natural logarithm of the solubility against the reciprocal absolute temperature. The transition temperature can then be identified as the interception of the solubility lines (21,22). Another approach to assess the transition temperature is by means of the transformation kinetics data (9). For this method, the phase transformation rate constant is extracted from the *in situ* measured transformation profiles. Then the transformation rate constant is plotted against the temperature at which the phase transformation has happened. The transition temperature is determined as the temperature at which the phase transformation rate is zero. Wikström *et al.* (9) has utilized this approach for determining the transition temperature of three pharmaceutical compounds. All the values found from this approach have showed good agreement with those published earlier.

The transition temperature of CBZ in ethanol-water mixture determined by the solubility method from the earlier report is shown in Fig. 2 (solid symbols). The lowest transition temperature is 14.3°C obtained at 0.31 mole fraction of water and increases with increasing water fraction in the solvent mixture. This increasing trend of transition temperature, when plotted together with the transition temperature of CBZ in water (64.5°C at 1 mole fraction of water reported by Wikström *et al.* (9)), shows a good agreement (Fig. 2, open symbol).

For most pharmaceutical compounds, similar to CBZ, their transition temperature in a certain solvent, for instance water, can be determined by both methods. Once the transition temperature is determined, the relative stability of the two forms can be established. For example, if CBZA crystals are brought into contact with an ethanol-water mixture containing 39 mol% of water at temperatures lower than T_r=24.7°C (Fig. 3 and Table 1), the dissolution of CBZA will lead to a solution saturated with respect to CBZA while supersaturated with respect to CBZH.

However, it has to be noted that there are exceptions where the transition temperature of a compound in water cannot be determined using both of these methods. Such anhydrate/hydrate systems usually have a transition temperature in water higher than the boiling point of water (23). Such systems, although rarely encountered, do need full attention. One example is piroxicam. The solubility of PXA and PXH is shown in Fig. 4 and Table 1. The transition temperature cannot be defined, but the solubility

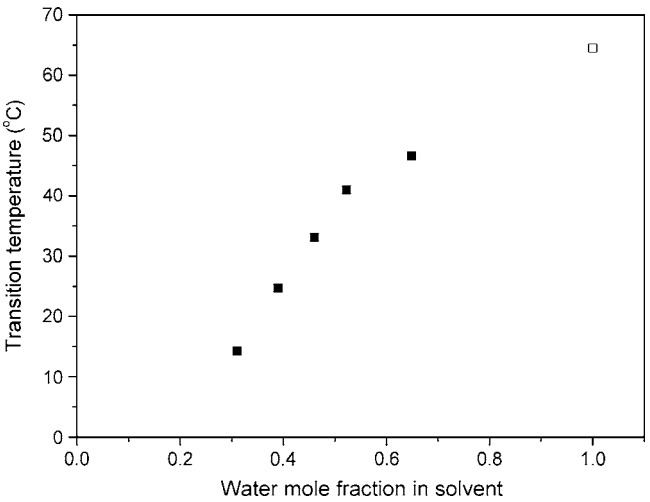

Fig. 2 Transition temperature of anhydrous and dihydrate carbamazepine as a function of water fraction in ethanol–water mixtures (solid symbols: obtained from solubility data; open symbol: obtained from transformation kinetics data (9)).

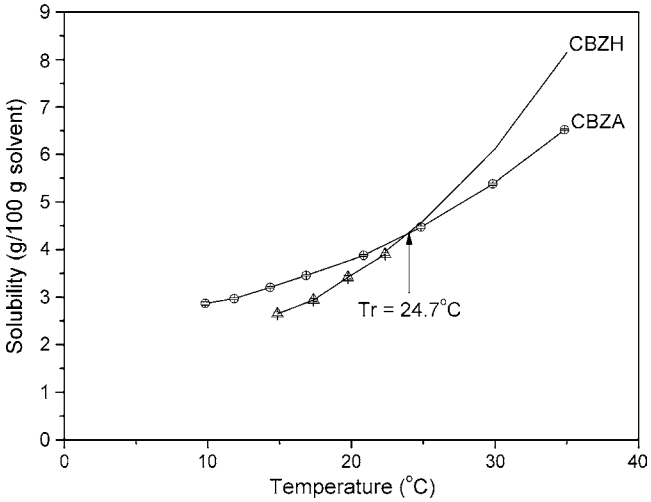

Fig. 3 Solubility of carbamazepine anhydrate (CBZA) and dihydrate (CBZH) in ethanol–water mixture containing 39 mol% of water.

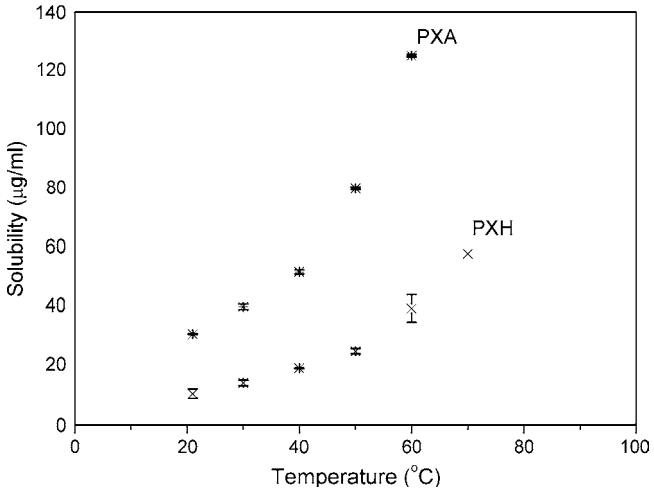

Fig. 4 Solubility of piroxicam anhydrate (PXA) and monohydrate (PXH) in water.

of PXA is much higher than that of PXH over the whole temperature range, indicating that, in theory, the transformation from PXA to PXH can happen throughout the whole temperature range (from 20°C to 80°C). For such a system, one possible way to estimate the anhydrate/hydrate transition temperature is the method suggested by Gu and Grant by using the heats of solution and solubility data (24).

Kinetics of the Solvent-Mediated Anhydrate-to-Hydrate Phase Transformation

As discussed in the previous section, the solvent-mediated anhydrate-to-hydrate transformation is driven by thermodynamic factors, e.g., the solubility difference between the anhydrate and the hydrate. This means that whether the transformation from anhydrate to hydrate will happen is determined by the relative thermodynamic stability of the anhydrate and hydrate. However, if the transformation happens, the rate of the metastable anhydrate transformation to the stable hydrate is governed by both the thermodynamic driving force (i.e. the supersaturation level with respect to the hydrate) of the phase transformation and kinetic factors, for instance the kinetics of dissolution of the anhydrate, and the nucleation and growth kinetics of the hydrate. Both the thermodynamic driving force and the kinetic factors may be affected by temperature. According to the authors' knowledge, for all the published work so far, the limiting step of the phase transformation is the nucleation and growth of the hydrate crystals (4,25,26). This also includes the compounds studied in the present work, carbamazepine and piroxicam. It has been observed that the concentration of carbamazepine or piroxicam in solution rapidly increased to a maximum and remained there until the phase transformation was almost finished. This observation confirmed that the crystallization step is the rate-controlling step for the phase transformation of

Table I Solubility of Carbamazepine Anhydrate (CBZA) and Sihydrate (CBZH) in Ethanol-Water Mixture Containing 39 mol% of Water, and Solubility of Piroxicam Anhydrate (PXA) and Monohydrate (PXH) in Water

Carbamazepine				Piroxicam		
T (°C)	CBZA (g/100 g solvent)	T (°C)	CBZH (g/100 g solvent)	T (°C)	PXA (g/100 g solvent)	PXH (g/100 g solvent)
9.82	2.86	14.85	2.65	21	30.8	10.6
11.83	2.97	17.35	2.94	30	40.0	14.2
14.34	3.21	19.75	3.42	40	51.9	19.2
16.85	3.46	22.35	3.90	50	80.3	25.0
20.85	3.88			60	125.3	39.5
24.85	4.47			70		58
29.85	5.38					
34.85	6.52					

both carbamazepine and piroxicam. The phase transformation from CBZA to CBZH was performed in the ethanol-water mixture containing 61 mol% of ethanol at different temperatures ranging from 8°C to 14.5°C (Fig. 5a). The phase transformation from PXA to PXH was conducted in water at temperatures from 21°C to 80°C. However, due to the long time elapsed before the PXH was nucleated at temperatures lower than 40°C, only the transformation profiles obtained at higher temperatures (40–80°C) are shown in Fig. 5b. The transformation profiles obtained from the Raman spectra were fitted to Eq. 2 in order to ascertain the transformation rate constant.

The measured transformation profiles and the fitted curves are shown in Fig. 5. The phase transformation profiles can be characterized by two factors: the lag time t_{lag}, which is defined as the time elapsed between the starting of the anhydrate dissolution and the formation of the hydrate, and the phase transformation rate constant K. The detailed calculation methods are described in the Materials and Methods section. Table 2 lists the t_{lag} and K obtained at different temperatures for carbamazepine and piroxicam.

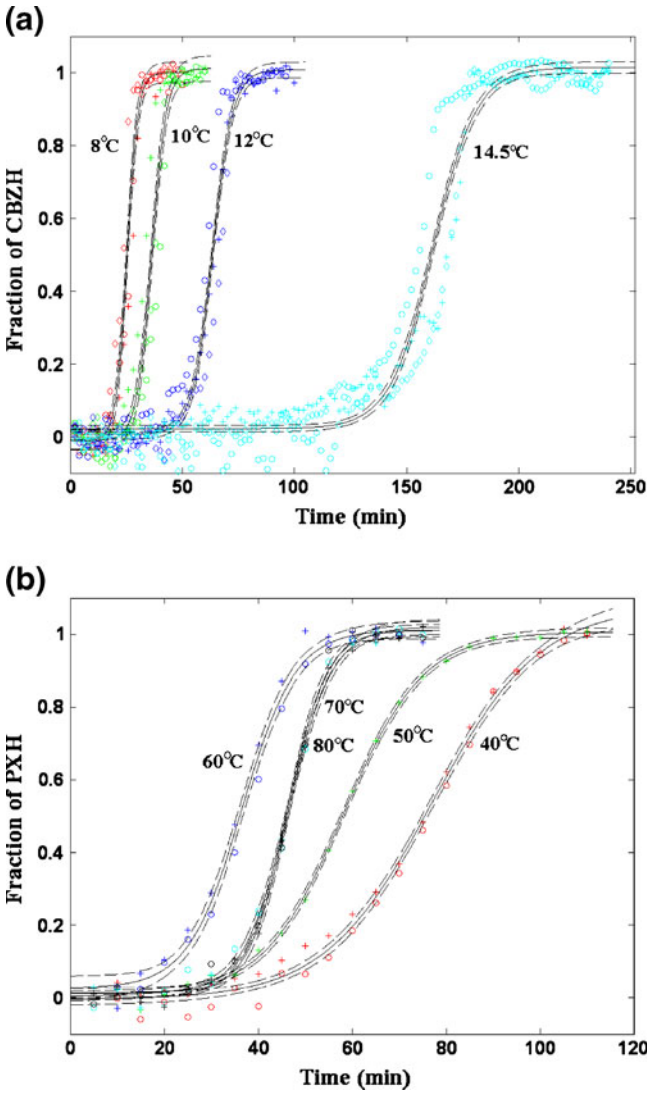

Fig. 5 Fitted conversion profile of carbamazepine (**a**), and of piroxicam (**b**) with 95% confidence intervals.

It can be seen from Fig. 5a that with increasing temperature from 8°C to 14.5°C, the transformation rate from CBZA to CBZH followed the same decreasing trend for the whole temperature range, as denoted by an increased lag time t_{lag} and a decreased transformation rate constant K. For the phase transformation from PXA to PXH, interestingly, there was a turning point in the lag time t_{lag} with increasing temperature. When the temperature increased from 40°C to 60°C, the lag time t_{lag} kept decreasing while the transformation rate constant was increasing. However, when the temperature increased further to 70 and 80°C, the transformation rate constant K was still increasing, but the lag time t_{lag} started to decrease. In order to explore the underlying principle of the changes in the transformation profiles with increasing temperature, the influence of temperature on the thermodynamic driving force of the transformation process and on the kinetics of the nucleation and crystal growth of the hydrates were examined.

DISCUSSION

The phase transformation experiments presented in this work were performed in suspensions, in which the hydrate crystallized out when the anhydrate partly dissolved in the solvent. In other words, the anhydrate and the hydrate were coexisting during the transformation until all anhydrate had been dissolved. As discussed above, the dissolution of CBZA and PXA was fast, which means that the concentration measured in solution was equivalent to the apparent solubility of the respective anhydrate CBZA or PXA. Therefore, the supersaturation at which the nucleation of the hydrate happens can be calculated as

$$S = \frac{C_A^*}{C_H^*} \tag{4}$$

where C^* represents solubility and the subscripts A and H denote the anhydrate and hydrate forms. The supersaturation S at which the phase transformations were happening is shown in Fig. 6 and Table 3. It is clear that the supersaturation with respect to CBZH was decreasing with increasing temperature, which implies a decrease in the thermodynamic driving force for the phase transfor-

Table 2 The Lag Time t_{lag} and Phase Transformation Rate Constant K Extracted from the Phase Transformation Profiles of Carbamazepine and Piroxicam

Carbamazepine			Piroxicam		
T (°C)	t_{lag} (min)	K (min^{-1})	T (°C)	t_{lag} (min)	K (min^{-1})
8	21	0.28625 ± 0.00215	40	54	0.06043 ± 0.00003
10	30	0.20748 ± 0.00112	50	41	0.08129 ± 0.00002
12	54	0.15272 ± 0.00024	60	25	0.12093 ± 0.00023
14.5	142	0.07178 ± 0.00003	70	37	0.14400 ± 0.00015
			80	38	0.16722 ± 0.00019

mation process. As a result, the phase transformation of CBZA to CBZH became slower, as indicated by the increasing lag time t_{lag} and the decreasing transformation rate constant K (see Fig. 5a and Table 2). Such influence of increasing temperature on the lag time and rate constant of the transformation has been commonly observed for other substances, such as theophylline and caffeine (9).

However, for compounds like piroxicam, change of the supersaturation with respect to PXH was more complicated. When temperature increased from 20°C to 40°C, the supersaturation decreased slightly, but with a further increase of temperature to 50°C, the supersaturation started to increase. Clearly, the phase transformation profiles of PXA to PXH shown in Fig. 5b cannot be explained solely by changes in the supersaturation with increasing temperature as shown in Fig. 6.

The increase of temperature also influences the kinetics of the nucleation and crystal growth of the hydrate. The rate of nucleation usually can be characterized by the induction time t_{ind}, which is defined as the time elapsed between the creation of supersaturation and the formation of a new solid phase (27). As observed in the present study, the dissolution of the anhydrates was fast, and the creation of supersaturation was rapid. The lag time t_{lag} shown in the transformation profiles in Fig. 5 and Table 2 was mainly due to the induction time of the hydrate nucleation. The rate of nucleation can be considered to be inversely proportional to the induction time as follows (27,28):

$$J = \frac{1}{t_{ind}} = A' \exp\left[\frac{-F\delta^3 V^2 \phi}{(kT)^3 \ln^2(\frac{C}{C^*})}\right] \quad (5)$$

where F is the shape factor ratio of the nuclei, ϕ is the wetting angle, δ is surface tension, k is Boltzman's constant, T is solution temperature, and V is molecule volume. Although Eq. 5 clarified the various factors that affect the rate of nucleation, it is not feasible to calculate the nucleation rate using Eq. 5. The wetting angle and the surface tension are difficult to be measured with an adequate accuracy. Since the nucleation of the hydrate started in a suspension where the anhydrate crystals were present, many properties of the anhydrate, such as the size distribution, specific surface area, and crystallinity, may significantly affect the nucleation rate of the hydrate. Furthermore, the nucleation kinetics of the hydrate also strongly depends on the hydrodynamics of the system. Therefore, in the present work, the authors' focus is on the understanding of the influence of temperature on the phase transformation through its effect on the nucleation kinetics and also through its impact on the driving force of the phase transformation. For that purpose, the physical

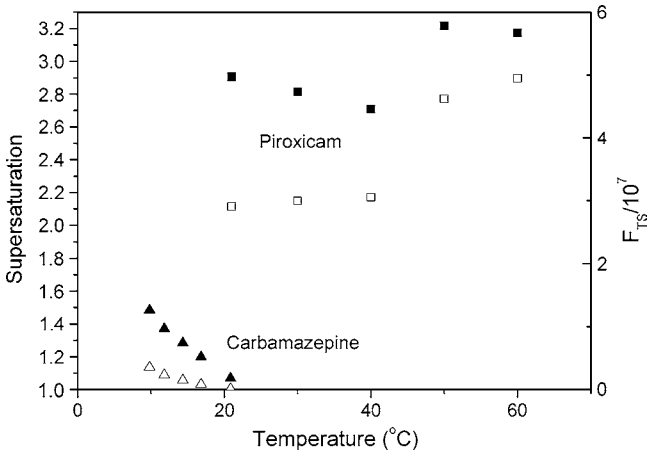

Fig. 6 Supersaturation with respect to carbamazepine dihydrate (CBZH) and piroxicam monohydrate (PXH), (*solid symbols*), and temperature-supersaturation combined effects variable F_{TS} (*open symbols*) as a function of temperature for the solvent-mediated transformations studied in this work.

Table 3 Supersaturation with Respect to Carbamazepine Dihydrate (CBZH) and Piroxicam Monohydrate (PXH), and Temperature-Supersaturation Combined Effects Variable F_{TS} as a Function of Temperature for the Solvent-Mediated Transformations

Carbamazepine			Piroxicam		
T (°C)	S	FTS × 10^{-7}	T (°C)	S	FTS × 10^{-7}
9.82	1.48	0.35	21	2.91	2.91
11.83	1.37	0.23	30	2.82	3.00
14.34	1.28	0.15	40	2.70	3.05
16.85	1.20	0.08	50	3.21	4.61
20.85	1.07	0.01	60	3.17	4.94

properties of the anhydrate and the operation conditions of the experiments were kept unchanged for the phase transformation experiments of carbamazepine and piroxicam, respectively. A variable F_{TS} that reflects the combined effects of temperature and supersaturation on nucleation according to Eq. 5 is defined as

$$F_{TS} = T^3(\ln\frac{C}{C^*})^2 \quad (6)$$

The combined variable F_{TS} and supersaturation level with respect to carbamazepine dihydrate (CBZH) and piroxicam monohydrate (PXH), as a function of temperature for the solvent-mediated transformations, are shown in Fig. 6 and Table 3. For a given compound crystallizing from a given solution, the nucleation rate increases with increasing temperature and increasing supersaturation ratio C/C^*. For the solvent-mediated phase transformation of CBZA to CBZH, the temperature increase will promote the nucleation rate according to Eq. 5; however, the increase in temperature can also lead to decreased supersaturation, which will lead to a reduced nucleation rate. Therefore, the overall effect of temperature on the nucleation rate and thus on the phase transformation is determined by the combined effects of temperature and supersaturation. It can be observed from Fig. 6 that the combined effect variable F_{TS} is also decreasing with increasing temperature, which suggested that the nucleation rate of CBZH was decreasing with increasing temperature. This prediction is consistent with the phase transformation experiments, results shown in Fig. 5a, where an increase in the temperature from 8°C to 14.5°C led to a decreased nucleation rate as denoted by the increased lag time t_{lag}.

As expected, the overall effect of temperature on the phase transformation of PXA to PXH is much more complicated than that of CBZA to CBZH. When the temperature increased from 21°C to 30 and 40°C, the supersaturation slightly decreased; however, the combined effect factor F_{TS} slightly increased. The significant decrease of the lag time t_{lag} (results obtained at 21°C and 30°C are not shown in Fig. 5b and Table 2) indicated that the nucleation rate was increasing, which confirmed that the temperature effect on the nucleation rate of PXH was dominating compared to the effect of supersaturation, as predicted by the combined effect factor F_{TS} shown in Fig. 6. Further increasing the temperature to 50 and 60°C led to increased supersaturation, and therefore significantly increased F_{TS}, which resulted in an accelerated nucleation rate of the hydrate. Thus, the lag time continued to decrease with increasing temperature. However, the dominating effect of temperature on the nucleation rate of PXH seemed to be diminishing when the temperature increased to 70 and 80°C. The lag time t_{lag} started to increase with temperature from 60°C to 70 and 80°C. This observation probably suggested that the increasing temperature in this range caused a decrease in the supersaturation, and also the dominating factor that governs the nucleation kinetics changed from temperature to supersaturation. As a consequence, the nucleation rate of PXH decreased, and, therefore, the lag time increased.

After nucleation, the formed hydrate nuclei will continue to grow into large crystals. The growth of crystals in supersaturated solutions is a complex multi-step process. Two of these steps are considered to be the most significant for crystal growth. First, the growth units are transported from bulk solution to the crystal surface by diffusion and convection; second, the units are incorporated into the crystal lattice through an integration reaction (28). Depending on the system, flow conditions, and supersaturation, either the diffusion process or the integration process can be the rate-controlling process. In practice, it is difficult to classify a system into diffusion-limited or integration-limited groups. The following simple equation is often used to describe crystal growth (27,28):

$$\dot{m} = k_g(\Delta C)^g \quad (7)$$

where $\dot{m}$ is the mass rate of crystal growth, k_g is a constant, $\Delta C = C - C^*$ is the supersaturation, and C* is the solubility. In most cases, the crystal growth rate is limited by bulk diffusion and surface integration, and thus the exponent g in Eq. 7 is in the range $1 < g < 2$. The constant k_g in Eq. 7 is a function of temperature and usually increases with increasing temperature, due to the fact that higher temperature can promote both mass diffusion in the bulk solution and integration on the crystal surface. The crystal growth rate will increase with increasing temperature or supersaturation.

During the solvent-mediated anhydrate-to-hydrate phase transformation, the transformation rate constant K is mainly determined by the growth rate of the hydrate crystals. For the phase transformation of CBZA to CBZH, increasing temperature caused a decreased supersaturation level; therefore, the effect of temperature and supersaturation on the crystal growth of CBZH were competing. The increasing temperature promoted crystal growth, while the decrease in supersaturation was reducing the crystal growth rate. The decrease of the transformation constant K with increasing temperature demonstrated that the supersaturation played a dominant role for this process. However, the acceleration effect of temperature on the transformation rate of PXA to PXH was much more dominating. It can be seen from Fig. 5 and Table 2 that the transformation rate constant increased with increasing temperature (from 40°C to 80°C). As discussed in the previous section, the key factor

that governed the nucleation rate of PXH changed from temperature to supersaturation when the temperature increased from 40°C to 60°C. A similar change of the key factor was not observed for the transformation rate constant. This observation suggested that the phase transformation rate constant of PXA to PXH was mainly determined by the crystal growth rate of PXH, for which temperature exerted a much stronger influence than supersaturation.

CONCLUSION

Solvent-mediated anhydrate-to-hydrate phase transformation is a complex process, which is driven out by the thermodynamic driving force and consists of two steps: dissolution of the anhydrate and crystallization of the hydrate. For most compounds investigated so far, including the two examples shown in the present work, crystallization of the hydrate was the rate-controlling step, and, therefore, the change of the whole transformation rate with increasing temperature was due to the effect of temperature on the nucleation and growth of the hydrate crystals. In most cases, increasing temperature leads to decreased supersaturation level (thermodynamic driving force) and thus decreased nucleation and crystal growth rate. The phase transformation of CBZA to CBZH at different temperatures illustrated such dominating effect of supersaturation. However, one has to be aware that increased temperature itself also accelerates the nucleation and growth kinetics of the hydrate crystals, which may overcome the diminishing effect caused by the decreasing in supersaturation level. One specific example presented in this study is piroxicam. The effect of temperature on nucleation kinetics was dominating within the temperature range 40–60°C, and thus increasing temperature from 40°C to 60°C led to an increased nucleation rate. When the temperature further increased from 60°C to 80°C, the dominating factor changed from temperature to the supersaturation, and increasing of temperature from 60°C to 80°C caused a decrease in nucleation rate probably due to the decreased superaturation. The combined-effects variable F_{TS} defined in the present work reflects the overall effects of temperature and supersaturation on the hydrate nucleation and, thus, can be used to briefly predict how the phase transformation rate is affected by the changing of temperature. The results of the present work revealed the complex nature of solvent-mediated anhydrate-to-hydrate phase transformation and also highlighted the importance of understanding the underlying principle of the acceleration and de-acceleration effects of temperature on the solvent-mediated anhydrate-to-hydrate phase transformation processes.

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