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Determination of hydrate transition temperature using transformation kinetics obtained by Raman spectroscopy

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ABSTRACT

The thermodynamic transition temperature is a key parameter to ascertain when assessing the properties of a crystalline hydrate. The transition temperature is sometimes difficult to determine experimentally due to rapid transformation between the two crystal forms in solution. In this study, a new approach for determining the transition temperature is presented, utilizing the temperature dependence of the transformation kinetics in aqueous slurries, as determined using in-line Raman spectroscopy. The transition temperatures of several hydrate forming compounds, namely theophylline, carbamazepine and caffeine, are presented. In general, good correlations with literature values were found. This method was found to be a simple, fast and reliable approach for the determination of crystal hydrate transition temperatures in aqueous environments.

1. Introduction

Approximately one-third of all drugs can exist as crystalline hydrates and the hydrate is often, although not always, the thermodynamically stable form at room temperature [1]. It is important to control and maintain the desired crystal form of an active pharmaceutical ingredient (API) during primary and secondary manufacturing processes and hence it is critical to elucidate key thermodynamic properties of crystal systems. One important property of anhydrate/hydrate systems is the transition temperature, also known as the stability point, s point, or the quadruple point. This is the temperature at which equilibrium exists between four phases namely the hydrate and anhydrate crystals, the saturated aqueous solution and the vapour phase. Below the transition temperature, the hydrate is the thermodynamically stable form whereas above the transition temperature, the anhydrate is the thermodynamically stable crystal.

Hydrate–anhydrate transformations can occur via two routes. When bulk solvent is present, a solvent mediated transformation from the meta-stable to the stable form can occur [2]. Alternatively, transformation can occur nominally in the solid state under the appropriate conditions of temperature and relative humidity [3]. Solvent mediated transformations typically occur much more rapidly than for solid samples stored at different relative humidities. The transition temperature is a crucial parameter for understanding the potential for a phase change to occur not only during pharmaceutical processing operations involving solvent and/or excursions in temperature/relative humidity conditions, but also when the API or product is stored under various different conditions, for example during accelerated stability testing.

Several different approaches for determining the transition temperature have been employed. The most common approach is by measuring the solubility of the stable form over a range of temperatures. By extrapolating the linear fit of the natural logarithm of the solubility of the stable form versus the reciprocal absolute temperature, the intersection of the regression line of the high-temperature stable form, and the low-temperature stable form, will then correspond to the transition temperature [2]. However, if the temperature range used to determine the solubility is too wide, the linearity of the plot can be compromised, as discussed by Grant et al. [4]. Another approach utilized to determine the transition temperature is intrinsic dissolution rate measurements [5,6]. Essentially, by determining the solubility ratios of the stable and meta-stable forms from knowledge of their individual dissolution rates, and the solubility of the stable form as a function of temperature, the transition temperature can be estimated from the temperature where the solubility ratio is found to be 1. This methodology suffers from similar limitations as solubility method described previously. Bothe et al. [7] maintained a caffeine slurry under temperature-controlled conditions for an extended period of time, before identifying the crystalline phase using differential scanning calorimetry (DSC). Yu [8] has described how the transi-

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tion temperature for polymorphs can be determined from melting temperatures and enthalpies of fusion. Additionally, a method that combines solubility and heat of solution measurements in order to determine the transition temperature has been proposed [9,10]. Finally, Krzyzaniak et al. [11] determined the phase boundaries for the anhydrate and hydrate forms of caffeine as a function of temperature and relative humidity using the transformation kinetics as determined by near infrared spectroscopy. These data were then used to interpolate the transition temperature as the temperature where the anhydrous form was stable at 100% RH, which was found to be similar to the transition temperature derived by Bothe et al. [7] as aforementioned.

Hu et al. [12] recently reported on the determination of the transition temperature of flufenamic acid polymorphs using transformation kinetics data obtained in real time. The objective of this study was to determine the feasibility of using a similar approach to determine the transition temperature hydrate–anhydrate pairs. Five different hydrate forming compounds were investigated. The transition temperature was estimated from the kinetics of the transformation in an aqueous slurry of drug, whereby the transformation was monitored using in-line Raman spectroscopy.

2. Materials and methods

2.1. Materials

Five different model compounds were used for this study. The starting materials were nitrofurantoin anhydrous (Sigma–Aldrich, Inc., St. Louis, MO, USA), theophylline anhydrous (Ruger Chemical Co., Inc., Irvington, NJ, USA), caffeine anhydrous (Knoll AG, Ludwigshafen, Germany), sulfaguanidine monohydrate (Sigma–Aldrich, Inc., St. Louis, MO, USA), and carbamazepine anhydrous (Hawkins, Inc., Minneapolis, MN, USA). Hydrate materials were recrystallized from water or by exposure to 100% relative humidity (RH), while anhydrous materials were produced by placing the material in an oven at 105 °C for at least one hour, with the exception of nitrofurantoin anhydrous, which was used as received. The physical form of the starting material was verified using Raman spectroscopy. Double-distilled water was used for all experiments.

2.2. Methods

Raman spectra were collected using a RXN1 System (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) with a 1/4 in. immersion optic sampling device with 785-nm excitation. For theophylline and caffeine, spectra were collected every 5 s or 30 s, for 50:50 (mol/mol) anhydrate–hydrate mixtures and experiments seeded with 5% of the stable form, respectively. Spectra were collected every 30 s for carbamazepine and nitrofurantoin systems, and every 3 s for sulfaguanidine slurries.

In order to attempt to determine the transition temperature of the five model compounds, the transformation kinetics was monitored in aqueous slurries using in-line Raman spectroscopy. The various systems were analyzed as at different temperatures ranging from 15 °C to 85 °C in 10 °C intervals. Experiments were carried out by preparing a powder blend consisting of 95% of the meta-stable form (meta-stable at the experimental temperature of interest) with 5% of the stable form followed by addition of the powder to water equilibrated at the experimental temperature in a jacketed vessel. The temperature of the slurry was monitored throughout the experiment using a thermocouple. A syringe pump was used to add small amounts of water if necessary to compensate for water evaporation during long experiments at elevated temperatures. A second set of experiments was performed around the transition temperature at intervals of 2 °C. For these experiments a 50:50 powder blend of the hydrate and anhydrate was used. This ratio ensured that transformation would be observed, regardless of whether the temperature was above or below the transition temperature.

2.3. Software

HoloGRAMS software (version 4.0, Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) was used to control the Raman spectrometer. Sigma Plot (version 8.02, SSPS, Inc., Chicago, IL, USA) was used for curve fitting and graph plotting.

3. Results and discussion

Experiments were performed in two stages. For the first stage, single determinations of transformation kinetics were performed over a large temperature range. These experiments provided information about the general range of the transition temperature for each model compound and were carried out with 5% (w/w) seeds of the stable form, eliminating the need to wait for spontaneous nucleation of the stable form to occur. A 5% (w/w) level of seeds was chosen because a larger quantity of seeds was found to result in too rapid a transformation profile at temperatures significantly above or below the transition temperature. In Fig. 1b and c the spectral changes observed during such experiments are shown for theophylline at 25 °C and 75 °C, respectively. For comparison, the spectra of pure theophylline anhydrous and monohydrate are shown in Fig. 1a. At temperatures below the transition temperature, the spectral features of the monohydrate form become more prominent as time progresses, since it is the most stable form, as shown in Fig. 1b. Above the transition temperature, the anhydrate is the most stable form and following conversion of the monohydrate, spectral features of the anhydrous form will prevail, which is shown in Fig. 1c. It should also be noted that, due to the appreciable aqueous solubility of theophylline, particularly at elevated temperatures, spectral features of theophylline in solution will also be present.

Based on these initial screening experiments, the transition temperature of caffeine was found to be in the range of 45–55 °C, theophylline was found to be in the range 55–65 °C and the transition temperature of carbamazepine was believed to be in the range 55–75 °C. No transition temperatures could be determined for sulfaguanidine or nitrofurantoin using this experimental procedure.

Once the general region of the transition temperature had been established for three of the model compounds, similar experiments were performed in triplicate employing smaller temperature intervals over this temperature range to facilitate a more accurate determination of the transition temperature. However, since the transformation kinetics around the transition temperature are much slower than at temperatures far away from it, a 50:50 mixture of the meta-stable and stable form was used. The transformation profiles for theophylline from such experiments are shown in Fig. 2a and b. These results are representative of results obtained for the other model compounds.

Once the transformation profiles around the transition temperature had been established, the profiles were fitted to an empirical exponential equation (1) in order to extract the transformation rate constant.

$$X = X_0 + \frac{A}{1 + e^{-(t - t_{mid}/b)}} \quad (1)$$

where X and X_0 are the actual and initial amount of stable form, respectively. A is related to the change in the amount, and t_{mid} is the time to the midpoint of the transformation. The rate of the transformation (b) can be empirically related to the transformation rate

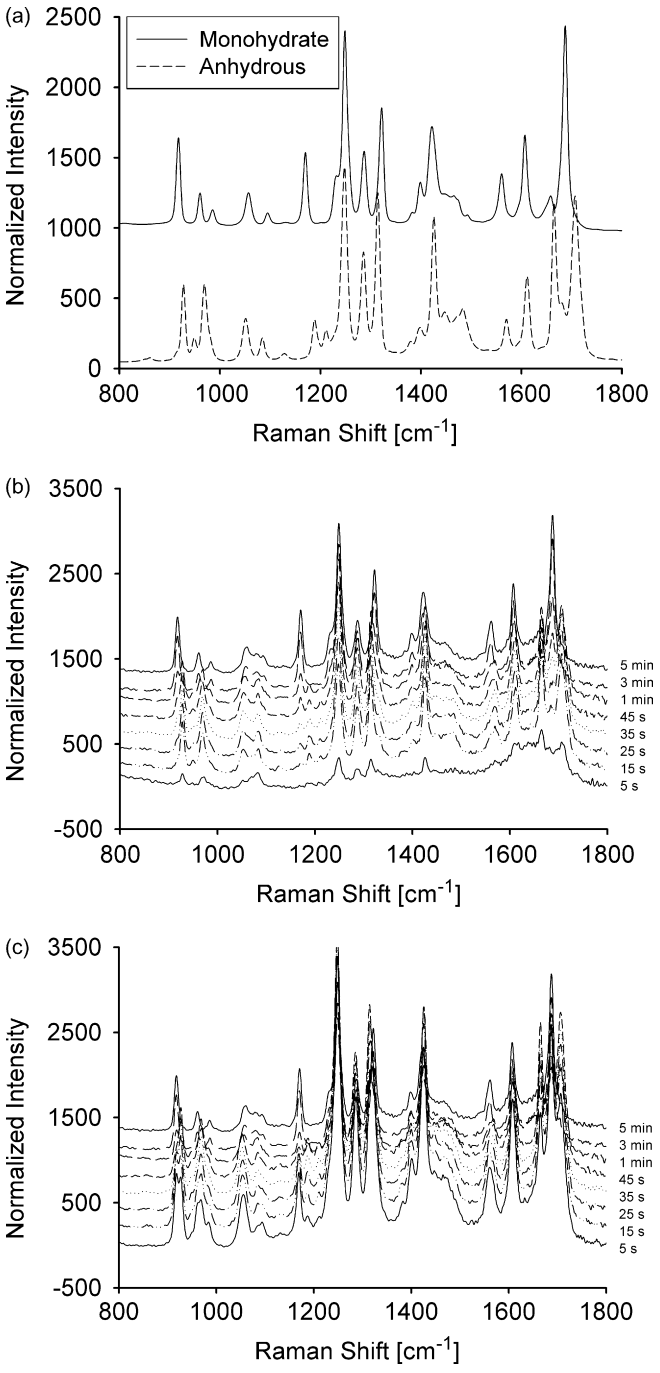


Fig. 1. Spectral changes observed during slurry transformation of theophylline. (a) Raman spectra of theophylline anhydrous and its monohydrate form. (b) Spectra obtained at various time points from a slurry experiment with theophylline at 25 °C. (c) Spectra obtained at various time points from a slurry experiment with theophylline at 75 °C.

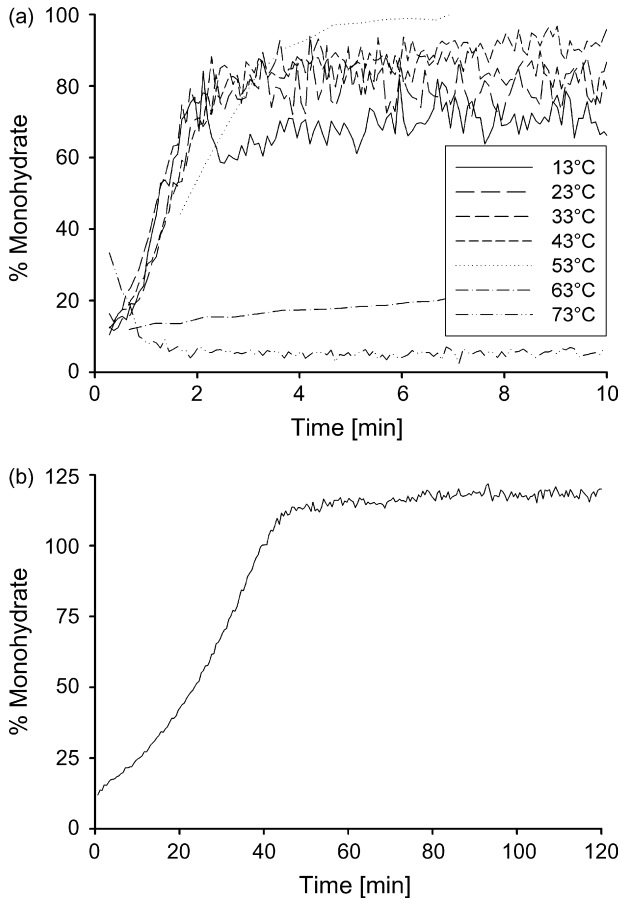


Fig. 2. Transformation profiles of theophylline seeded with 5% of the stable form at each temperature. (a) Transformation profiles from various experiments conducted above and below the transition temperature. (b) Transformation profile at 63 °C. The experiment at 63 °C is close to the actual transition temperature; hence the transformation kinetics is very slow at this temperature.

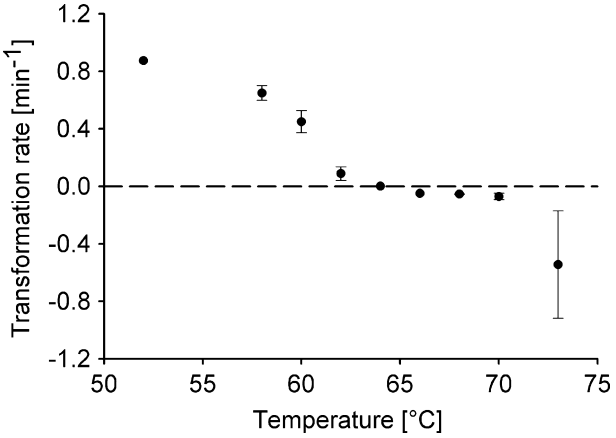


Fig. 3. Transformation rate constant for the carbamazepine anhydrous/dihydrate system as a function of temperature around the transition temperature.

constant (k) of a first order reaction according to Eq. (2):

$$k = \frac{\ln 2}{b} \quad (2)$$

The rate constant was then plotted against temperature (T). This is shown for CBZ in Fig. 3. The transition temperature is determined as the temperature at which the transformation rate is zero. Based on these results the transition temperature for CBZ was determined to be 64.5 ± 1.4 °C. The error in this estimation was determined from the variability of the kinetic measurements obtained from triplicate kinetics determination at each temperature around the transition temperature. For carbamazepine, the transition temperature reported in the literature is 100 °C [13]. This value was obtained by extrapolating intrinsic dissolution rate values obtained at different temperatures. The results presented above clearly shows that the transition temperature is below 100 °C.

The results for CAF are shown in Fig. 4. These results indicate a transition temperature of about 49.3 ± 0.3 °C. For caffeine, transition temperatures between 44 °C and 86 °C have been reported

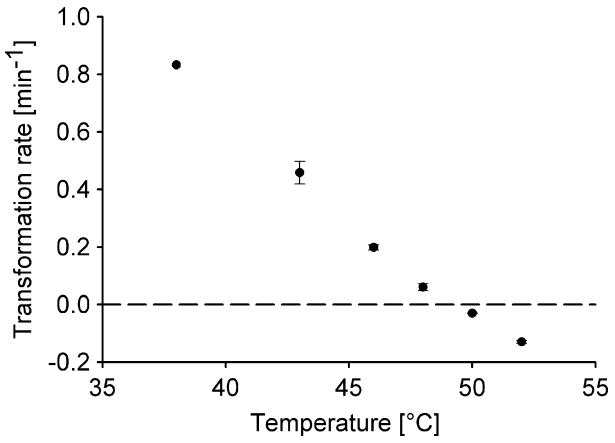


Fig. 4. Transformation rate constant for the caffeine anhydrous/hydrate system as a function of temperature around the transition temperature.

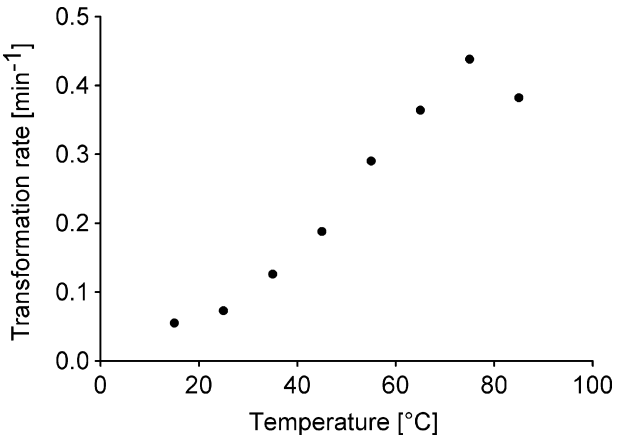


Fig. 6. Transformation rate constant for the nitrofurantoin anhydrous/monohydrate system as a function of temperature over a wide range of temperatures.

[7,11,14–16], for example, Bothe et al. reported a value of 51.5 ± 0.7 °C determined using differential scanning calorimetry. Their result is in good agreement with the results obtained using the approach described herein.

For theophylline, the rate constant plot (Fig. 5a) is somewhat different when compared with the previous two examples. There is a much steeper relationship between the rate constant and temperature close to the transition temperature. In (Fig. 5b) the relationship between the rate constant and temperature is shown over an expanded scale for this system. Using the narrower range of temperature, a transition temperature of 63.4 ± 0.4 °C is obtained. The transition temperature of theophylline has been previously reported to be around that obtained in this study, i.e. 63.8 ± 1.3 °C by Fokkens et al. [17] and 67.0 ± 0.2 °C by Bruns et al. [18].

For sulfaguanidine and nitrofurantoin, no transition temperature could be determined. In the case of sulfaguanidine, the transformation rate was so quick that it was not possible to analyze the kinetics reliably. Typically the transformation time was less than 15 s. Additionally, at higher temperatures, the solution spectrum interfered with quantitation of the amount of transformed solid. The transition temperature of nitrofurantoin has been reported as 134 °C [19]. Hence, it would theoretically be impossible to determine the transition temperature using the experimental set-up described herein, since the boiling point of water is 100 °C. In confirmation of the high transformation temperature for NF, it was found that a sample of the hydrate slurried in boiling water remained as the hydrate. The relationship between the transformation rate and temperature for NF is shown in Fig. 6.

The methodology described in this work provides a quick and accurate approach for determining the transition temperature of crystalline hydrates in aqueous solution (Table 1). In addition, the transition temperature is determined directly under relevant processing conditions for a drug substance. While this method appears to be a good approach to determine the transition temperature for some compounds, two out of the five model substances studied were problematic. For very soluble drug substances, the solution

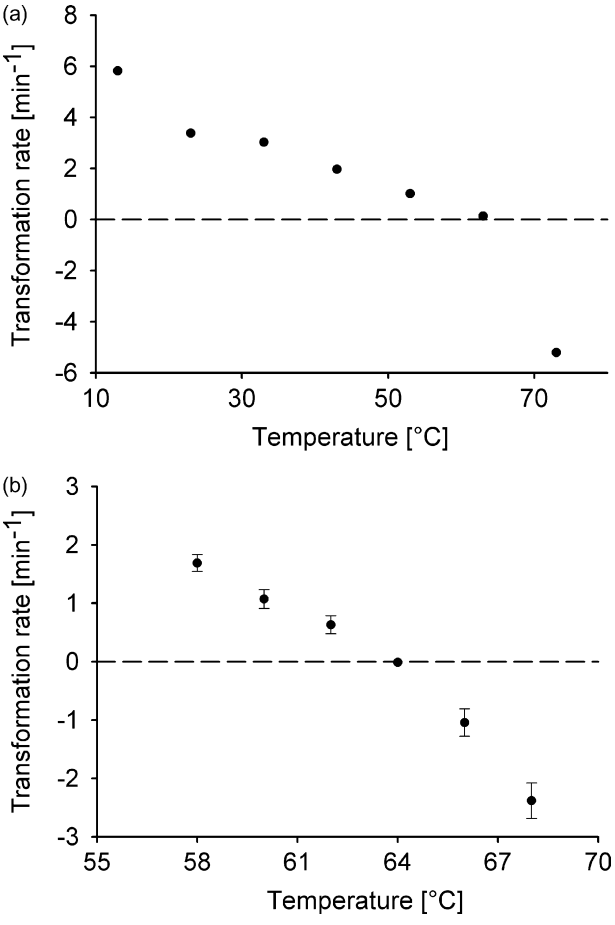


Fig. 5. Transformation rate constant for the theophylline anhydrous/monohydrate system as a function of temperature. (a) Screening experiment covering a wide range of temperatures; (b) prediction experiments around the transition temperature.

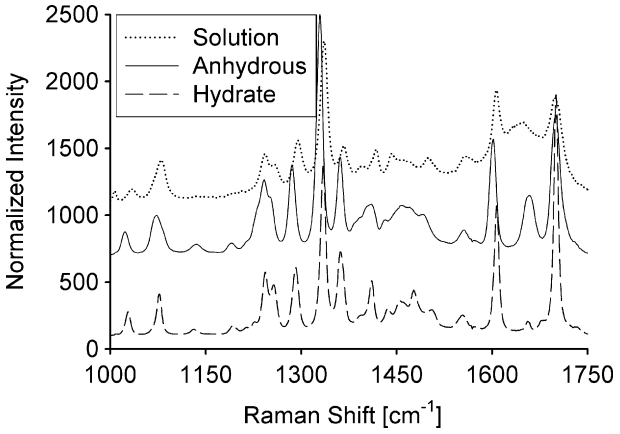
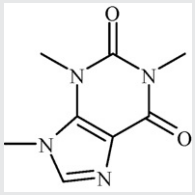
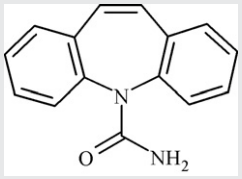
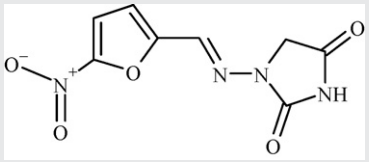
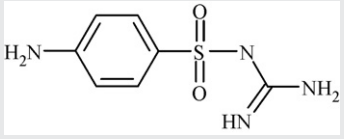
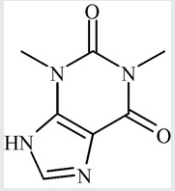


Fig. 7. Raman spectra of caffeine anhydrous, caffeine hydrate and caffeine in solution.

Table 1
Summary of model compounds, experimental results and available literature data.

Material [CAS#]	Molecular structure	MW [Da]	mp [°C]	T_t [°C]	T_t (lit.) [°C]	Refs
Caffeine (CAF) [58-08-2]		194.19	238	49.3 ± 0.3	51.5	[7]
Carbamazepine (CBZ) [298-46-4]		236.28	193	64.5 ± 1.4	100	[13]
Nitrofurantoin (NF) [67-20-9]		238.16	268	–	134	[19]
Sulfaguanidine (SFG) [57-67-0]		214.25	188–192	–	–	–
Theophylline (TP) [58-55-4]		180.17	270–274	63.4 ± 0.4	63.8, 67.0	[17,18]

mp, melting point of anhydrous form; T_t, hydrate/anhydrate transition temperature.

spectrum may interfere with the quantitation of the two forms. This is exemplified with CAF in Fig. 7. While the solution spectrum was significant for both CAF and TP, quantitation was still possible. For SFG, rapid transformation, significant spectral interference from the high solution concentration and a seemingly high transition temperature made elucidation of the transition temperature impossible using this experimental set-up. Similar problems were found for NF where the transition temperature appears to be higher than 100 °C, hence the determination of its transition temperature was impossible without significant modifications of the experimental set-up.

4. Conclusions

Transformation kinetics from slurry experiments has been successfully employed to establish the transition temperature of a hydrate–anhydrate system. Transition temperatures of such systems are inherently problematic to obtain, since the anhydrate is meta-stable at lower temperatures in aqueous solutions. Commonly employed techniques may result in inaccurate determinations of the transition temperature for this reason. By utilizing Raman spectroscopy to establish the transition temperature based on the transformation kinetics, the transition temperature is directly determined in the system of interest. Raman spectroscopy could be used to accurately determine the transformation kinetics up to 85 °C. Above this temperature, a more advanced experimental set-up would need to be employed in order to combat water evaporation. Hence, this approach is not valid for systems were the transition temperature is close to 100 °C, without modifications to the experimental set-up. In summary, the transition temperature could be established for three of the five model compounds studied, namely caffeine, carbamazepine and theophylline. Finally, with detailed knowledge of the transition temperature, the solubility-temperature relationship for the stable form and the solubility ratio between the two forms at one temperature, a van't Hoff plot can be constructed, which can provide important information about the system.

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