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Solubility and stability of anhydrate/hydrate in solvent mixtures

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Abstract

In this paper, the thermodynamics of the anhydrate/dihydrate carbamazepine (CBZA/CBZH) in ethanol–water mixtures was studied by measuring the solubility of anhydrate and dihydrate carbamazepine at 0–60 °C. Both stable form solubility and metastable form solubility were measured, the latter with the assistance of Raman immersion probe. The thermodynamic properties of the anhydrate/dihydrate system, such as the relative stability, and enthalpy and entropy of dissolution, were estimated by plotting the measured solubility data according to the van't Hoff equation. The anhydrate/dihydrate carbamazepine showed an enantiotropic relationship in the studied mixtures and temperature ranges. It was shown that at a certain temperature, there was an equilibrium water activity value at which the anhydrate and dihydrate carbamazepine were in equilibrium. This equilibrium water activity value depends significantly on the temperature. The lower the temperature, the smaller is the water activity value needed to attain equilibrium between anhydrate and dihydrate. The obtained results are useful in determining crystallization parameters to achieve a desired anhydrate or hydrate phase. The approach can be applied to other anhydrate and hydrate systems.

Keywords: Hydrate; Solubility; Metastable solubility; Carbamazepine; Phase transition; Water activity

1. Introduction

Crystallization is widely used in the pharmaceutical and chemical industries for purification, final crystal form selection, or particle size control. In some cases, mixed solvent systems (mixtures of water and an organic solvent) are used in order to get higher crystal yield, especially when processing high-value-added species. The main purpose for the addition of the second solvent is either to reduce the solubility of the solute, or to change the dependence of the solubility on temperature to increase the yield of cooling crystallization. However, the concentration of the second solvent can affect the pseudopolymorphism, polymorphism and morphology of the crystalline product. Consequently, production of the pharmaceutical solid product has to be optimized in terms of final solid form, crystal habit and size distribution, final yield and reproducibility from batch to batch.

Solvates are frequently referred to as pseudopolymorphs, which are defined as the crystals formed by the same substance crystallized with different amounts or types of solvent molecules (Bernstein, 2002). Hydrates are the most common solvates encountered in pharmaceutical compounds, since water and mixtures of water and an organic solvent are frequently used in crystallization processes. A hydrate forms when water molecules are incorporated into the crystal lattice. Hydrates and polymorphs are typically discussed together because of the similarities between the characterization of polymorphs and hydrates. Both polymorphic modifications and various hydration states of a compound have different crystal structures and exhibit different X-ray powder diffraction patterns, thermograms (differential scanning calorimetry or thermal gravimetric analysis), infrared spectra, Raman spectra, etc. The solubility and dissolution rate in a given solvent, density, chemical stability are also different for different polymorphs and crystalline at different hydration states. As a result, the phase of the crystalline drug product significantly affects the bioavailability of the final dosage (Luhtala, 1992; Brittain, 1999; Kobayashi et al., 2000; Murphy et al., 2002). On the other hand, hydrates are not true polymorphs since the chemical composition is not equivalent for anhydrate and hydrate. The difference between the polymorphic systems and anhydrate/hydrate systems is also reflected in the Gibbs free energy analysis. The Gibbs free energy difference ΔG between two polymorphs or anhydrate/hydrate states is proportional to the ratio of the thermodynamic activities a,

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and is approximately proportional to the ratio of the solubilities x in any given solvent.

$$\Delta G = RT \ln\left(\frac{a_2}{a_1}\right) = RT \ln\left(\frac{x_2}{x_1}\right) \quad (1)$$

where the subscripts 1 and 2 denote the different phases (polymorphs or hydration states) of the crystals. For a polymorphic system, the value of the solubility ratio and thus the Gibbs free energy difference is defined by temperature and pressure. Therefore, the relative thermodynamic stability of the polymorphs is independent of the solvent (Brittain, 1999). For an anhydrate/hydrate system, the value of the solubility ratio and Gibbs free energy strongly depends on the water activity in the solvent, and the system is defined by temperature, pressure and water activity in the solvent. The anhydrate/hydrate transition is both solvent and temperature dependent in organic solvent–water mixtures (at ambient pressure). It is essential to understand the thermodynamics of the anhydrate/hydrate system and the mechanisms of the transformation in solvent mixtures in order to control the phase of the crystalline product. The influence of water activity in organic solvent and water mixtures on the hydration state of drug compounds has been reported in the literature (Grant and Higuchi, 1990; Ghosh and Grant, 1995; Zhu et al., 1996; Zhu and Grant, 1996) at room temperature. It was reported that at room temperature (25 °C) there is a certain water activity value at which the anhydrous and hydrate forms are in equilibrium. However, the dependence of the equilibrium water activity on temperature is not fully understood.

Carbamazepine (CBZ), an antiepileptic drug, was selected as the model compound in this work (Fig. 1). Four polymorphorms and a dihydrate as well as other solvates of CBZ have been reported in the literature (Krahn and Mielck, 1987; Rustichelli et al., 2000). Among them, the anhydrous form III, the thermodynamically stable form at room temperature and the dihydrate form are the most commonly encountered forms. The objective of this work is to study the influence of water activity and temperature on the thermodynamics of anhydrate/dihydrate carbamazepine in ethanol–water mixtures. The solubility of the anhydrous form III (CBZA) and the dihydrate (CBZH) in mixed solvents of ethanol–water was measured at certain temperature ranges. The dependence of the relative stability of the anhydrous form III and the dihydrate of CBZ on solvent composition and temperature as well as the thermodynamic properties, such as the enthalpy and entropy of dissolution of CBZA and CBZH, are estimated by plotting the solubility data and temperature using the van't Hoff equation. The equilibrium water activities, at which the solubility and stability of CBZA and CBZH are identical, are evaluated at different temperatures.

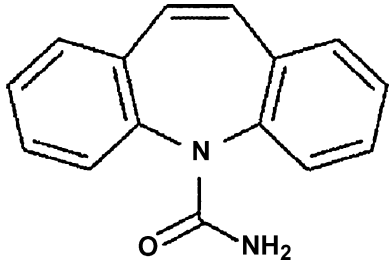

Fig. 1. Structure of carbamazepine.

2. Materials and methods

2.1. Materials

Analytical grade ethanol from Altia Corporation and deionized water were used as solvents. Carbamazepine was used as received from Orion Corporation. Based on the XRPD pattern and DSC trace, it was pure form III (CBZA). The dihydrate form (CBZH) was prepared by cooling crystallization from 61 mol% ethanol aqueous solution. A CBZ solution saturated at 40 °C was prepared by dissolving a certain amount of CBZA in solvent at 45 °C. The solution was quench cooled down to 20 °C, and then it was kept at this temperature for 1 h. The Raman in-line probe was used to monitor the phase of the crystalline during the crystallization. It was observed that only CBZH was crystallized out during the crystallization. The suspension was filtered and the solid was dried at room temperature for 24 h. The obtained CBZH solid was analyzed with an X-ray diffractometer and Raman spectrometer. In order to verify the obtained CBZH crystalline, the XRPD pattern of the CBZH crystallized from the 61 mol% ethanol aqueous solution was compared with figures reported in the literature (Krahn and Mielck, 1987; Luhtala, 1992; Rustichelli et al., 2000). It was observed that the XRPD pattern was identical for the CBZH crystalline.

2.2. Methods

2.2.1. Raman spectroscopy

Raman spectra were collected with a LabRam 300 Raman spectrometer from Horiba Jobin Yvon. The system employed an external cavity stabilized single mode diode laser at 785 nm. The Raman spectroscopy was interfaced with an optical microscope when analyzing powder samples, and an immersion probe sealed with a sapphire window for in-line suspension monitoring. The laser light was focused into the solid or the solid–liquid suspension, using the optical microscope or the immersion probe, respectively. Backscattered Raman light was collected by the interfacial device and transmitted back to the spectroscopy for analysis. The acquisition conditions were optimized so that a spectrum was captured with an exposure time of 5 and 20 s for measurement of dry solid samples and suspension, respectively, with three accumulations.

2.2.2. Powder X-ray diffraction

A Bruker AXS GmbH D8 Advance diffractometer with a Cu Kα radiation source (40 kV, 40 mA) was used to collect powder diffraction patterns at ambient temperature and pressure. The patterns were recorded between 5 and 40° 2θ with steps of 0.05° and a dwelling time of 1 s/step.

2.2.3. Solubility measurement

The solubility of CBZA and CBZH in ethanol–water mixtures was measured gravimetrically. Only CBZA was used as the start solid material. Around 200 g of solvent was kept at a

certain temperature in a 250 ml jacketed vessel equipped with a thermostat and a magnetic mixer. A condenser was used to recover the evaporated solvent. When the temperature was stable, CBZA solid was added gradually until the solid no longer dissolved. Then around 1 g excess CBZA solid was added and the solid–liquid suspension was well mixed for 48 h to achieve equilibrium. Next, the clear solution was taken through a micro filter, and the solid isolated from the suspension was analyzed with Raman spectrometer to identify the form of the solid. With the above-described method, only the solubility of the thermodynamically stable form at the measured conditions (temperature and solvent composition) can be measured, which in the following will be referred to as the stable form solubility. The apparent solubility of CBZA at conditions in which it is in the metastable form was measured by the following method. First, a saturated solution was prepared based on the solubility of CBZH (stable form) at a certain temperature. Then a certain amount of excess CBZA solid was added to the solution. A Raman probe was used to obtain in situ monitoring of the solid form composition. Clear solutions were sampled through a syringe filter until the transformation from CBZA to CBZH was completed.

3. Results and discussion

3.1. Identification of solid form with XRPD and Raman spectra

The raw material CBZA and the prepared CBZH solid were analyzed with an X-ray diffractometer and Raman spectrometer. The X-ray diffraction patterns and Raman spectra of CBZA and CBZH are shown in Figs. 2 and 3. The morphology of the crystals is shown in the images in Fig. 4, which were taken with a Jeol JSM-5800 scanning electron microscope. The anhydrous and dihydrate forms clearly exhibit different morphologies.

3.2. Stable form solubility and thermodynamic property

The stable form solubility was measured in five solvent mixtures with different ethanol–water fractions. The experimental data are listed in Table 1. It was observed that the solubility of CBZ in pure ethanol was much higher than that in pure water.

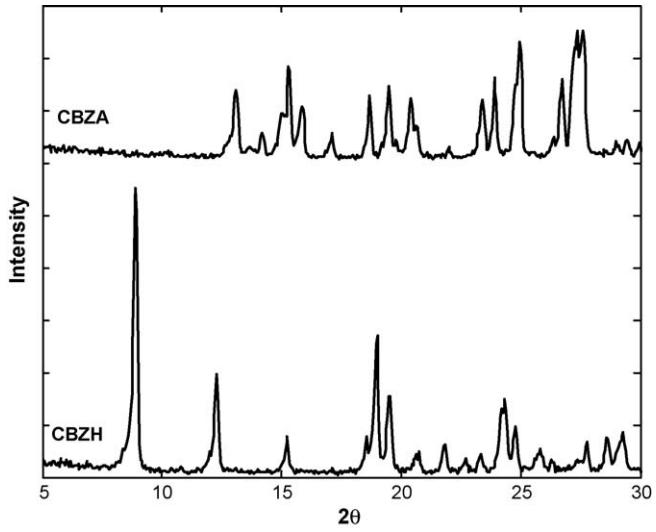

Fig. 2. X-ray diffraction patterns of anhydrous (CBZA) and dihydrate (CBZH) of carbamazepine.

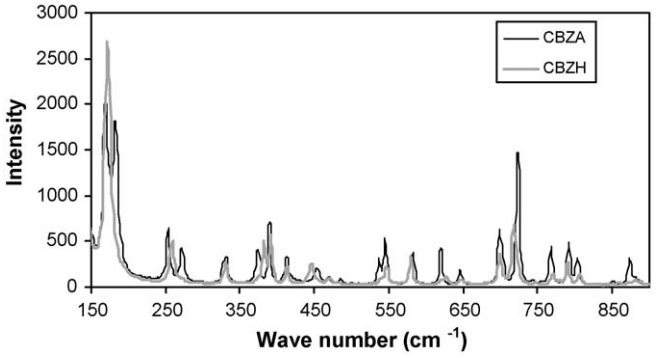

Fig. 3. Raman spectra of CBZA and CBZH crystalline.

At a certain temperature, CBZ solubility exhibits a maximum value in an ethanol–water mixture having a certain composition (Fig. 5). As shown in Fig. 6, the dependence of CBZ solubility on temperature changed significantly in mixed solvent compared with that in pure ethanol. The yield of the crystallization process can be significantly increased if mixed solvent with 54 mol% ethanol is used instead of pure ethanol.

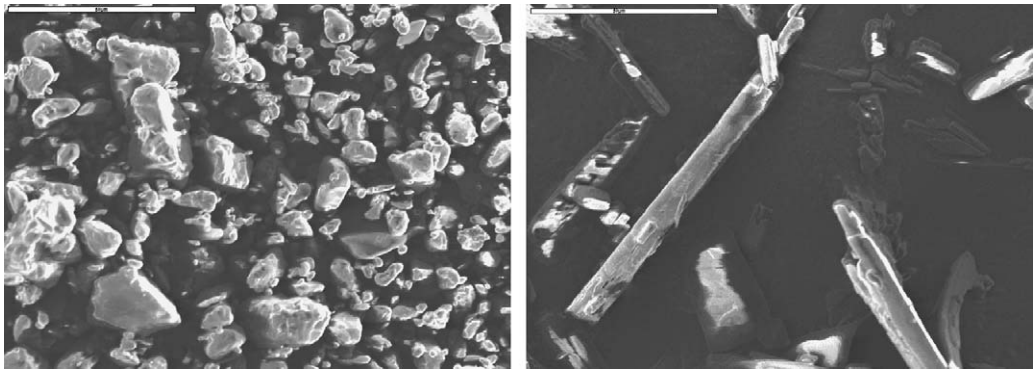

Fig. 4. SEM pictures of CBZA (left), and CBZH (right). The white bar represents 50 μm.

Table 1
Solubility of carbamazepine in ethanol–water mixtures

68.9 mol% ethanol		61.0 mol% ethanol		54.0 mol% ethanol		47.7 mol% ethanol		35.1 mol% ethanol	
T (K)	g CBZ/100 g solvent	T (K)	g CBZ/100 g solvent	T (K)	g CBZ/100 g solvent	T (K)	g CBZ/100 g solvent	T (K)	g CBZ/100 g solvent
273.0	1.47(H)	288.0	2.65(H)	288.0	2.07(H)	288.0	1.69(H)	303.0	2.47(H)
277.7	1.93(H)	290.5	2.94(H)	292.9	2.77(H)	292.9	2.28(H)	308.0	3.35(H)
283.0	2.41(H)	292.9	3.42(H)	295.5	3.15(H)	298.0	3.01(H)	313.0	4.67(H)
285.5	2.78(H)	295.5	3.90(H)	298.0	3.66(H)	300.5	3.52(H)	318.0	6.36(H)
288.0	3.11(A)	298.0	4.47(A)	300.5	4.19(H)	303.0	4.01(H)	323.0	8.27(A)
292.9	3.71(A)	300.5	4.83(A)	303.0	4.98(H)	305.5	4.76(H)	328.0	10.58(A)
298.0	4.42(A)	303.0	5.38(A)	308.0	6.27(A)	308.0	5.56(H)	332.9	13.31(A)
303.0	5.27(A)	305.5	5.86(A)	313.0	7.76(A)	316.0	8.27(A)		
308.0	6.32(A)	308.0	6.52(A)	318.0	9.51(A)	321.0	10.24(A)		
		313.0	7.85(A)			326.0	12.43(A)		
						331.0	15.66(A)		
T_r = 14.3 °C		T_r = 24.7 °C		T_r = 33.1 °C		T_r = 41.0 °C		T_r = 46.6 °C	

H and A in the bracket denote the phase of the equilibrium solid as anhydrate and dihydrate, respectively; T_r is the transition temperature.

For an ideal solution, the solubility of the solute can be predicted from the van't Hoff equation as follows (Prausnitz et al., 1999; Mullin, 2001):

$$\ln x = -\frac{\Delta H_f}{RT} + \frac{\Delta H_f}{RT_f} = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R}t \quad (2)$$

where x is the mole fraction of solute in the solution, T_f the fusion temperature and ΔH_f and ΔS_f are the molal enthalpy and entropy of fusion, respectively.

In practice, very few solutions can be considered as ideal solution. If the solution exhibits non-ideal behavior, the solvent effect must be allowed for, which means the enthalpy and entropy of mixing must be taken into account by replacing ΔH_f with ΔH_d (enthalpy of dissolution) and ΔS_f with ΔS_d (entropy of dissolution) (Beiny and Mullin, 1987).

$$\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (3)$$

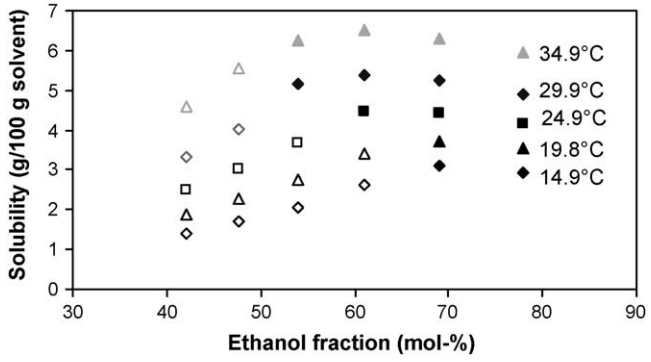

Fig. 5. Solubility of CBZA (solid symbols) and CBZH (open symbols) in ethanol–water mixtures at various temperatures.

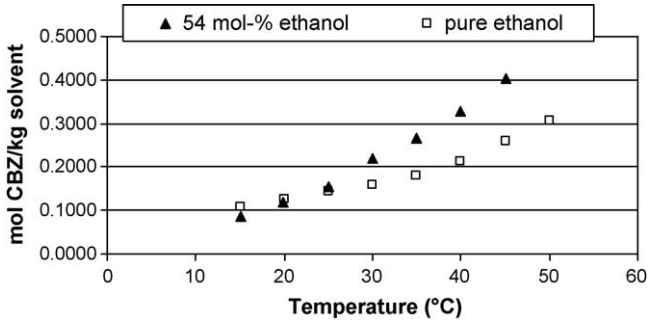

Fig. 6. Solubility of CBZ in pure ethanol and ethanol–water mixture.

The solubility of CBZH and CBZA are plotted on a semi-logarithmic scale against the reciprocal of the absolute temperature for specified solvent systems in Fig. 7. The enthalpy and entropy of dissolution of both forms were obtained from the slope and the interception with y-axis of the resulting trend line. As shown in Fig. 8, the enthalpy and entropy of dissolution of both CBZA and CBZH increased with the increasing water fraction in the solvent. The enthalpy and entropy of dissolution of CBZH are higher than that of CBZA. A similar result has been reported by Luk and Rousseau (2005) for the anhydrate and monohydrate of L-serine in water–methanol mixtures. They observed that the enthalpy and entropy of dissolution of L-serine decreased with increasing water fraction in the solvent, as the solubility of L-serine in water was much higher than that in methanol.

The relative stability of CBZA and CBZH can be obtained from Fig. 7. The system exhibits enantiotropic behavior. For a certain solvent composition, the thermodynamically stable form must have a lower solubility than the metastable form. The interception of the extrapolation of the solubility of the two forms represents the point where the solubility of CBZA and CBZH are identical; in other words, the CBZA and CBZH are in equilibrium, and thus it is referred to as the transition temperature in the specified solvent system. CBZA is the stable form at temperatures higher than the transition point; CBZH is the stable one if the temperature is lower than the transition point.

3.3. Metastable form solubility

The solubility of the metastable form is usually very difficult to determine in anhydrate/hydrate systems, since the transformation happens very quickly in most cases. The Raman in-line

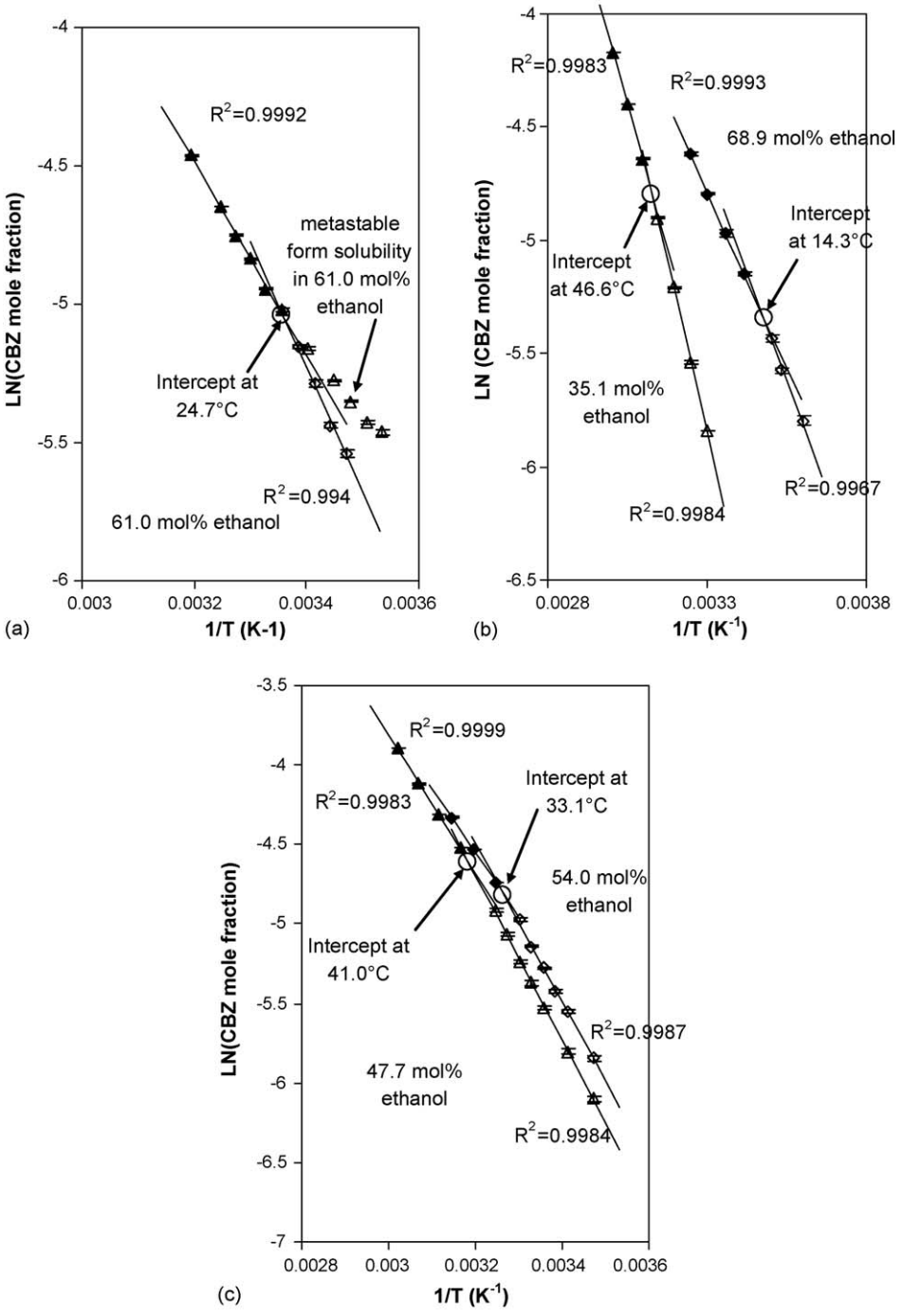

Fig. 7. Solubility of carbamazepine in ethanol–water mixtures. (Solid symbols represent CBZA solubility, open symbols represent CBZH solubility, metastable solubility of CBZA in 61.0 mol% ethanol solvent is shown in (a). The error bars are shown in the figure, with upper and lower limit of the error bar defined as $\ln(x + \text{std}) - \ln(x)$ and $\ln(x) - \ln(x - \text{std})$, respectively. x is the solubility in mole fraction and std is the standard deviation.).

probe offers a facility for metastable form solubility measurement. In this work, in addition to the stable form solubility, the metastable form solubility of CBZA was also measured in the solvent mixture containing 61 mol% ethanol. Figs. 9 and 10 show one measurement result, the concentration of CBZ in the solution and the evolution of the Raman spectra, respectively. The transformation of CBZA to CBZH can be clearly observed from the Raman shift. The average of the points where the concentration was stable before the phase transition started was considered as the metastable form solubility. The data are shown in Fig. 7(a). The metastable form solubility was not in the extrapolation of the stable form solubility curve, and the further it is from the transition point, the greater the deviation between the stable form solubility extrapolation line and the metastable form solubility. It has been reported that the unexpected high metastable solubility could be caused by a greater density of

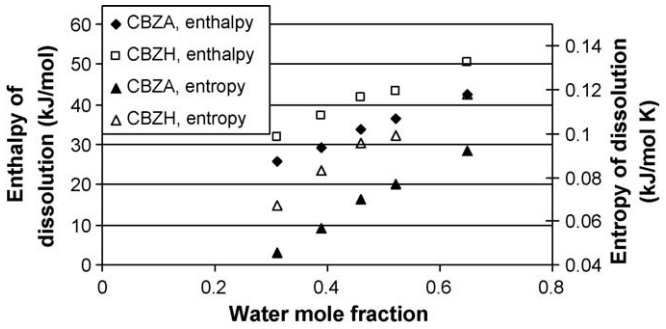

Fig. 8. Enthalpy and entropy of dissolution of CBZA and CBZH.

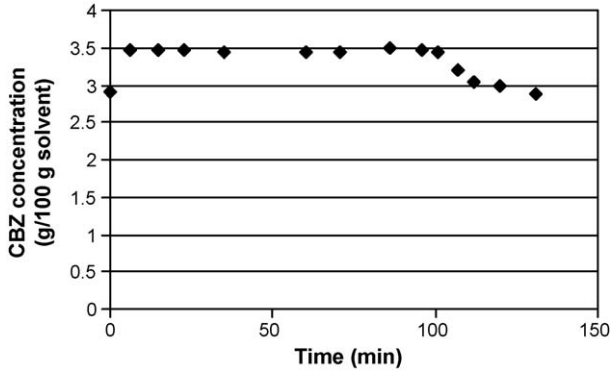

Fig. 9. Concentration of CBZ in the solution during the measurement of the metastable form solubility of CBZA.

crystal defects rather than by polymorphism (Brittain, 1999). However, the effect of crystal defects on solubility seems to be very small since the concentration reached a certain value and then remained constant at that value for quite a long time. The deviation between the metastable solubility and the extrapolation of the stable form solubility of CBZA implies that the dissolution enthalpy and entropy of CBZA in ethanol–water mixtures where CBZA is the stable form differ from those where CBZA is the metastable form.

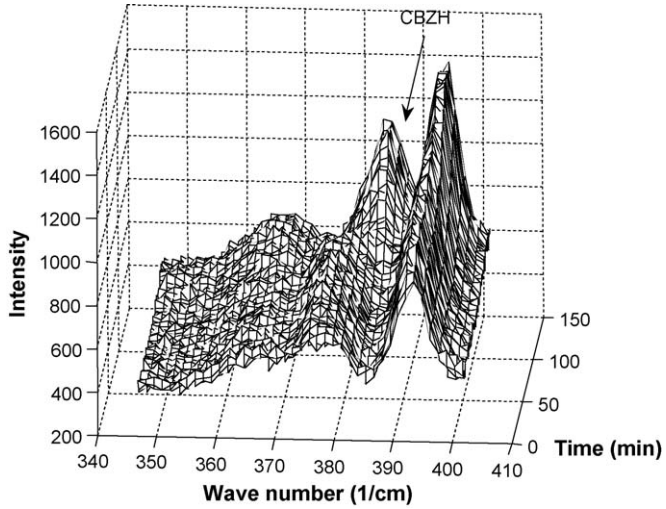

Fig. 10. Raman spectra during the measurement of metastable form solubility.

3.4. Correlation of water activity and solid phase stability

Grant and Higuchi (1990) have established the following relationship to describe the equilibrium between a hydrate and an anhydrate:

$$\mathrm{A(solid)} + m\mathrm{H_2O} \leftrightarrow \mathrm{A}\cdot m\mathrm{H_2O(solid)}$$

$$K_\mathrm{h} = \frac{a\,[\mathrm{A}\cdot m\mathrm{H_2O(solid)}]}{a\,[\mathrm{A(solid)}]\,a[\mathrm{H_2O}]^m} \quad (4)$$

where K_h is the equilibrium constant for the process, and $a[\mathrm{A}\cdot m\mathrm{H_2O(solid)}]$, $a[\mathrm{A(solid)}]$ and $a[\mathrm{H_2O}]$ are the thermodynamic activities of the hydrate, the anhydrate and water. m is the number of water moles taken up by one mole of the anhydrate. When $a[\mathrm{H_2O}] > [a[\mathrm{A}\cdot m\mathrm{H_2O(solid)}]/a[\mathrm{A(solid)}]K_\mathrm{h}]^{1/m}$, 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 unity activity), then Eq. (4) can be simplified as: $K_\mathrm{h} = a[\mathrm{H_2O}]^{-m}$. Thus, the hydration state of a hydrate depends on the water activity in the surrounding medium. Zhu et al. (1996) have studied the influence of water activity in organic solvent and water mixtures on the anhydrate/monohydrate phase of theophylline at 25 °C. They found that solvent composition corresponding to $a[\mathrm{H_2O}] = 0.25$ was the transition point; if the water activity is higher than 0.25, the monohydrate was the stable form, and the anhydrate was more stable if water activity was lower than 0.25. The effect of temperature was not taken into account in the above description.

A crystalline hydrate is a two-component system and is specified with three parameters: temperature, pressure and water activity. Thus, it is important to study the way the temperature affects the hydration equilibrium of anhydrate/hydrate in mixed solvent. In the above section, the transition points of CBZA to CBZH, which represent the conditions in terms of solvent composition and temperature where CBZA and CBZH are in equilibrium, were obtained from the intercept of the solubility curves shown in Fig. 7. The molar fraction solubility of CBZ in the studied temperature range is in the range of 0.3–2 mol%, so it is assumed that the water activity in the ternary system is not affected by the dissolved CBZ. The water activity in ethanol–water mixtures has been evaluated at various tempera-

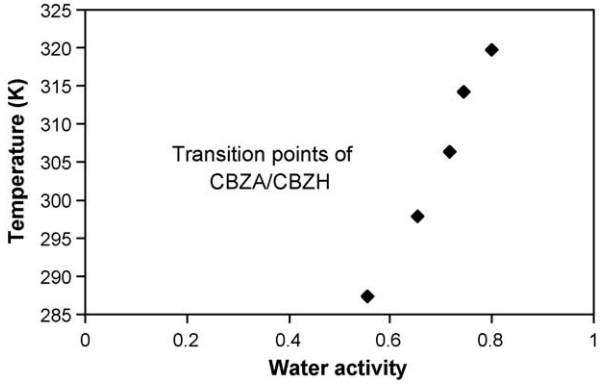

Fig. 11. Transition points of CBZA and CBZH in ethanol–water mixtures.

tures (10, 15, 20, 25, 30 and 50 °C) in the literature (D'Avila and Silva, 1970; Pemberton and Mash, 1978). The water activity corresponding to the transition point in terms of water/ethanol mole fraction and temperature can be obtained from the ethanol–water binary mixture data. The result is shown in Fig. 11. The smaller the water activity, the lower the temperature needed to attain the equilibrium between CBZA and CBZH.

4. Conclusions

In this work, the solubility of CBZA and CBZH in ethanol–water mixtures was measured at a certain temperature range. The enthalpy and entropy of dissolution of both forms and the thermodynamic relative stability of CBZA and CBZH were defined by correlating the solubility data and temperature with the van't Hoff equation. It was shown that the hydrate state of a CBZA/CBZH system in water–ethanol mixtures depends on both water activity (mainly determined by the water–ethanol fraction) and temperature. At a given temperature, there is a certain water activity value corresponding to the equilibrium between the anhydrous and hydrate form. This equilibrium water activity value increases with increase of temperature. The methodology is useful in determining the operation parameters for crystallization of compounds that are capable of forming hydrates.

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References

Beiny, D.H.M., Mullin, J.W., 1987. Solubility of higher normal alkanes in *m*-xylene. J. Chem. Eng. Data 32, 9–10.

Bernstein, J., 2002. Polymorphism in Molecular Crystals. Oxford University Press, Oxford.

Brittain, H.G., 1999. Polymorphism in Pharmaceutical Solids. Marcel Dekker Inc., New York.

D'Avila, S.G., Silva, R.S.F., 1970. Isothermal vapor–liquid equilibrium data by total pressure method. J. Chem. Eng. Data 15, 421–424.

Ghosh, S., Grant, D.J.W., 1995. Determination of the solubilities of crystalline solids in solvent media that induce phase changes: solubilities of 1,2-dialkyl-3-hydroxy-4-pyridones and their formic acid solvates in formic acid and water. Int. J. Pharm. 114, 185–196.

Grant, D.J.W., Higuchi, T., 1990. Solubility Behavior of Organic Compounds. John Wiley, New York.

Kobayashi, Y., Ito, S., Itai, S., Yamamoto, K., 2000. Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. Int. J. Pharm. 193, 137–146.

Krahn, F.U., Mielck, J.B., 1987. Relations between several polymorphic forms and the dihydrate of carbamazepine. Pharm. Acta Helv. 62, 247–254.

Luhtala, S., 1992. Effect of sodium lauryl sulphate and polysorbate 80 on crystal growth and aqueous solubility of carbamazepine. Acta Pharm. Nord. 4, 85–90.

Luk, J.C., Rousseau, R.W., 2005. Solubility and pseudo-polymorphic transition of L-serine in water-methanol systems. In: Proceedings of 16th International Symposium on Industrial Crystallization, Dresden, Germany, 11th–14th September 2005. VDI-Gesellschaft Verfahrenstechnik und Chemieingenieurwesen, pp. 199–204, VDI-Berichte Nr. 1901.1.

Mullin, J.W., 2001. Crystallization, fourth ed. Butterworth-Heinemann, Oxford.

Murphy, D., Rodriguez-Cintron, F., Langevin, B., Kelly, R.C., Rodriguez-Hornedo, N., 2002. Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder. Int. J. Pharm. 246, 121–134.

Pemberton, R.C., Mash, C.J., 1978. Thermodynamic properties of aqueous non-electrolyte mixtures II. Vapour pressures and excess Gibbs energies for water + ethanol at 303.15 to 363.15 K determined by an accurate static method. J. Chem. Thermodyn. 10, 867–888.

Prausnitz, J.M., Lichtenthaler, R.N., Azevedo, E.G., 1999. Molecular Thermodynamics of Fluid-Phase Equilibrium, third ed. Prentice Hall Inc., New Jersey.

Rustichelli, C., Gamberini, G., Ferioli, V., Gamberini, M.C., Ficarra, R., Tommasini, S., 2000. Solid-state study of polymorphic drugs: carbamazepine. J. Pharm. Biomed. Anal. 23, 41–54.

Zhu, H., Yuen, C., Grant, D.J.W., 1996. Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 1: Theophylline. Int. J. Pharm. 135, 151–160.

Zhu, H., Grant, D.J.W., 1996. Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 2: Ampicillin. Int. J. Pharm. 139, 33–43.