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Additive Effects on the Solvent-Mediated Anhydrate/Hydrate Phase Transformation in a Mixed Solvent

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ABSTRACT: Additives are one of the most influential factors that can affect the polymorphism and solvation state and the morphology of the crystals during crystallization. In this work, the effects of five different additives, sodium lauryl sulfate (SLS), polyethylene glycol 6000 (PEG), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), D-mannitol, on the phase transition from anhydrous (CBZA) to dihydrate (CBZH) carbamazepine in an ethanol−water mixture containing 61 mol % ethanol were studied. A Raman in-line probe was used to obtain the real time transformation rate during the transformation. The mechanism of the additive effects on the phase transition was studied by investigating the influence of the additives on the solubility of CBZA and CBZH and on the cooling crystallization of CBZH. It was observed that HPMC exhibited a strong inhibiting effect on the phase transformation at both 15 and 10 °C. Furthermore, it was found that HPMC selectively increased the solubility of CBZH but had no effect on the CBZA solubility. As a consequence, the solubility difference of CBZA and CBZH decreased dramatically. This resulted in a reduced supersaturation level during the phase transformation. SLS showed a slight promotion effect on the nucleation and crystal growth of CBZH by decreasing the metastable zone width and increasing the size of the final CBZH crystals. The additives had an insignificant effect on the viscosity of the solvent.

1. Introduction

Crystallization is widely used as the central unit operation in the production of a wide range of chemical products.[1] The quality of the crystalline product is mainly determined by the crystal size distribution, median crystal size, crystal shape, purity, and polymorphic or solvation state of the crystals. For a pharmaceutical ingredient, the control of the polymorphs and solvates formation is very important, because different polymorphs and solvates possess different product properties, such as solubility and dissolution rate in a given solvent, density, chemical stability, and morphology.[2] As a result, the phase of the crystalline drug product significantly affects the bioavailability of the final dosage. The polymorph and solvation state of a crystalline product during crystallization is mainly determined by the competitive nucleation and crystal growth of the different polymorphs or solvates and the transformation from the metastable form to the stable form.

Hydrates are the most frequently encountered solvates in the pharmaceutical industry, because aqueous media are often preferred for safety reasons. As an example, mixtures of an organic solvent and water are frequently used in the manufacturing of a pharmaceutical product because the mixed solvents may result in a higher crystal yield for cooling crystallization. This is particularly important when processing a high-value-added species. The appropriate selection and efficient control of the hydration state of the product represents a very important issue in the pharmaceutical product quality control. On one hand, the unexpected hydration of an anhydrate may cause an altered dissolution rate and, therefore, change the bioavailability; on the other hand, the undesired dehydration of a hydrate may result in the labile amorphous form, which may subsequently undergo oxidation.[2] The controlling of the hydration state of the solid product requires an understanding of the thermodynamic relationship of the anhydrate and hydrate and the mechanisms of the phase transition. In principle, the relative stability of an anhydrate/hydrate system depends on the water activity in the surrounding medium and the temperature.[2−6] Many anhydrate/hydrate systems exhibit an enantiotropic relationship. For a given water activity in a surrounding medium (for example, a mixture of water and an organic solvent with a certain composition), there exists a temperature corresponding to the transition point at which the anhydrate and hydrate have equal solubility and stability. If the temperature is higher than the transition point, the anhydrate is the stable form; on the contrary, the hydrate is the stable one if the temperature is lower than the transition point. Any deviation from the transition points will lead to solvent-mediated phase transformation, either from anhydrate to hydrate when the water activity is higher than the transition point water activity or from hydrate to anhydrate if the water activity is lower than the equilibrium value. The solvent-mediated phase transformation between anhydrate and hydrate has been reported for both organic and inorganic compounds.[6−11] The transformation rate between the anhydrate and hydrate can be influenced by many factors, such as solvent, temperature, supersaturation level, mixing conditions, and the presence of additives or impurities.

Additives may have significant effects on the polymorphic form[12−13] or hydration state,[8−11,14−15] and the morphology[16−17] of the crystalline product during crystallization. The presence of certain additives may also drastically affect the dissolution of a substance, and the vapor-phase-induced phase transition between anhydrate and hydrate.[18−19] The tailor-made additive effects on the solvent-mediated polymorphic form transformation of an active pharmaceutical ingredient are reported in the literature.[12] Kwon et al. observed that both the morphology and polymorphism of the crystals could be modified by the presence of tailor-made auxiliaries.[13] The excipients, the substances that are usually needed in drug formulations, can also act as additives. The effects of surfactants on the transformation of anhydrous to dihydrate carbamazepine in pure water have been investigated in the literature.[9−11] It was observed in their work that Polysorbate 80 and poloxamer 184 inhibited whereas sodium lauryl sulfate and benzalkonium chloride accelerated

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the phase transition. The promoting effect of sodium lauryl sulfate and sodium taurocholate on the solvent-mediated transformation of carbamazepine in water solution was also reported by Rodriguez-Hornedo and Murphy.[14] Hydroxypropyl methylcellulose was reported as an inhibitor for the phase transition from anhydrate to hydrate[15] and a promoter for the dissolution of anhydrous carbamazepine.[18] Polymers, such as polyethylene glycol and povidone, could increase the solubility and dissolution rate of carbamazepine by preparing a solid dispersion of the drug compound and the polymers.[20] The effects of certain excipients on the kinetics of the vapor-phase-induced hydrate/anhydrate phase transformation were investigated by Salameh and Taylor.[19] It was observed that both mannitol and polyvinylpyrrolidone K12 enhanced the dehydration of the dihydrate carbamazepine, whereas only polyvinylpyrrolidone K12 showed a promoting effect on the hydration process of anhydrous carbamazepine.

In previous work,[5] the relative stability of the anhydrate/dihydrate carbamazepine in ethanol−water mixtures was studied by measuring the solubility of the two forms. It was shown that the relative stability of carbamazepine anhydrate (CBZA) and dihydrate (CBZH) was governed by both water activity in the mixed solvents and the temperature. The solvent-mediated phase transformation kinetics of CBZA to CBZH was investigated at different solvent compositions and temperatures in a successive study.[6] It was concluded that the phase transformation was a two-step process. First, the metastable form, CBZA, was dissolved and the stable form, CBZH, was subsequently crystallized out. The crystallization rate of CBZH was slower than that of the dissolution rate of CBZA, and therefore the latter was the rate-controlling step. It was observed that the induction time decreased and the transformation rate increased with a decrease in temperature and increase in the water fraction in the solvent. In the present work, five different excipients, sodium lauryl sulfate (SLS), polyethylene glycol 6000 (PEG), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and D-mannitol, were selected as additives on the basis of the review of the literature. They have been reported to have an effect on the dissolution of drug compounds and solid-phase or solvent-mediated phase transformation between anhydrate and hydrate. The effects of the additives on the phase transition from CBZA to CBZH in an ethanol−water mixture containing 61 mol % ethanol were studied. A Raman in-line probe was used to obtain the real-time transformation rate during the transformation. The mechanism of the additive effects was revealed by investigating the influence of the additives on the solubility of CBZA and CBZH and the primary nucleation kinetics of CBZH.

2. Experimental Section

Materials. Carbamazepine anhydrous form III was purchased from Hawkings Pharmaceutical and used as received. The additives, sodium lauryl sulfate (SLS), polyethylene glycol 6000 (PEG,), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and D-mannitol, were obtained from the Sigma-Aldrich Chemical Co. Analytical grade ethanol from the Altia Corporation and deionized water were used as solvents. The dihydrate carbamazepine (CBZH) was prepared by cooling crystallization of CBZH from a 61 mol % ethanol aqueous solution, as described in previous works.[5,6] The obtained CBZH solid was identified by Raman spectroscopy. The mixtures of ethanol and water containing 61 mol % ethanol were prepared and used as the solvent in all experiments. The concentrations of the additives are as follows: 0.01 g/100 g of solvent for HPMC, 0.2 g/100 g of solvent for mannitol, and 0.5 g/100 g of solvent for PEG, PVP, and SLS.

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 operating at 150 mW. The Raman spectrometer was interfaced with an optical microscope in the case of analyzing solid mixtures and an immersion probe sealed with a sapphire window in the case of in-line suspension monitoring. The laser light was focused into the solid or the slurry, using an optical microscope or an immersion optic, 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 45 s for measurement of the solid and suspension respectively, with two accumulations. The calibration of the Raman spectra was accomplished using a univariable method by correlating the height of the characteristic peaks to the composition of the mixtures. The dry powder mixtures of CBZA and CBZH were use to generate the calibrating spectra.[21−23] The description of the calibration method can be found elsewhere.[6]

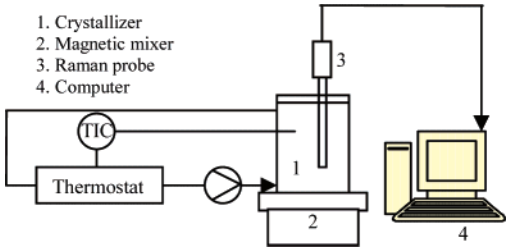

Figure 1. Setup of the in-line phase transformation monitoring system.

Figure 2. Hermetic metal box equipped with magnetic mixer and thermostat for solubility measurements.

In-line Monitoring of Phase Transformation. The experiment was conducted in a 250 mL jacketed glass crystallizer equipped with a magnetic mixer and thermostat (Figure 1). The mixing intensity was kept constant for all operations by keeping the agitation speed of the magnetic bar at 400 rpm. The CBZ solution was prepared by dissolving a certain amount of CBZA solid in solvent, with or without additives, depending on the solubility of CBZH at a given temperature. After 1 h of dissolving at 5 °C higher than the saturation temperature, the solution was cooled to the saturation temperature in 30 min, and the transformation was initiated 10 min after the saturation temperature was achieved by adding a certain amount of CBZA solid, 3 g/100 g of solvent, to the clear solution. The Raman probe was inserted into the crystallizer to obtain in-line monitoring of the solid form composition.

Additive Effects on the Solubility of CBZA and CBZH. The solubility of CBZA and CBZH in the mixed solvent with and without the additives was measured gravimetrically with the isothermal method. CBZA was used as the initial solid material, unless otherwise specified. The solvents were prepared first by dissolving the additives in the water−ethanol mixture. Excess CBZA solid and solvents were mixed in 20 mL bottles, which were then kept in a hermetic metal box full of water. The temperature of the water bath was controlled by a thermostat (shown in Figure 2), to keep all the solid−liquid suspension at a fixed temperature. A magnetic mixer was used to provide sufficient mixing in all of the bottles. After keeping the suspension at the fixed temperature for 72 h to attain solid−liquid equilibrium, we took around 15 mL of clear solution through a 0.2 μm pore size syringe filter. The solid isolated from the suspension was analyzed with a Raman spectrometer to identify the form of the solid. The solution samples were evaporated in an oven at 100 °C, which is much higher than the

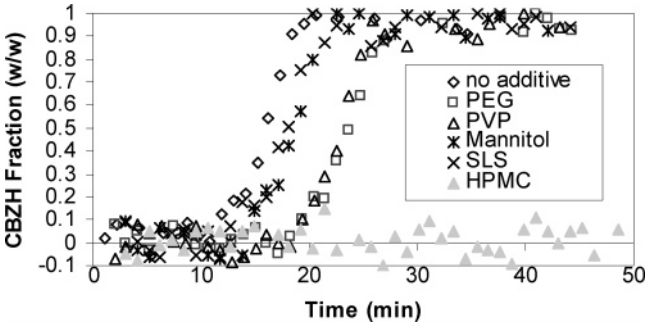

Figure 3. CBZH fraction in the solid phase during phase transformation at 10 °C.

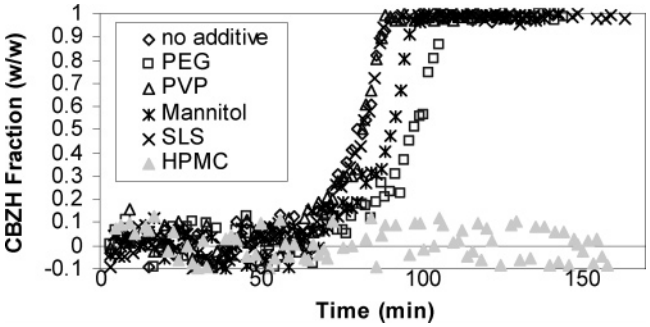

Figure 4. CBZH fraction in the solid phase during phase transformation at 15 °C.

dehydration temperature of CBZH. No weight loss of the solid was observed after it was dried in an oven for 24 h. The dry solid from the oven was analyzed with a Raman spectrometer; the characteristic peak for CBZH at 383 cm^{-1} was not seen. Therefore, the dry solid was confirmed to be the anhydrous form of carbamazepine.

Viscosity Measurement. The kinematic viscosity of the solvent with and without additives was determined using a capillary viscometer at room temperature.

Additive Effects on the Cooling Crystallization of CBZH. Cooling crystallizations of CBZH were performed in the system shown in Figure 1. CBZ solution saturated at 35 °C was used as the initial solution. A mixture of a certain amount of CBZ solid and solvent, with or without additives, was heated to 40 °C within 25 min and kept at 40 °C for 35 min to obtain thorough dissolution of the solute. After that, the solution was cooled from 40 to 15 °C at a cooling rate of 25 °C/h. A Raman in-line probe was used to monitor the solid phase during the crystallization.

3. Results and Discussion

Additive Effects on the Solvent-Mediated Transformation from CBZA to CBZH. As has been shown in the previous study,[5] the relative stability of CBZA and CBZH in ethanol−water mixtures was influenced by both solvent composition and temperature. For a certain solvent composition, there exists transition temperatures at which CBZA and CBZH have equivalent solubility and are therefore in equilibrium. The transition temperature of CBZA/CBZH in the solvent containing 61 mol % ethanol was 24.7 °C. This means that at temperatures lower than this transition point, the solvent-mediated transformation from CBZA to CBZH will occur. It was found in previous work[6] that the transformation rate increased with a decrease in temperature. This is because the solubility difference between CBZA and CBZH was increased when the temperature was lowered. This resulted in a higher supersaturation level and thus a higher transformation rate. The additive effects on the solvent-mediated transformation were studied at two different temperatures, 10 and 15 °C. The CBZH fraction in the solid phase measured with an in-line Raman probe is shown in Figures 3 and 4. It can be observed that HPMC was the most influential additive, which significantly retarded the phase transition at both temperatures. The two suspensions with HPMC were kept for 3 days at the experimental temperature, and the phase of the solid in the suspensions was checked with a Raman spectrometer. It was observed that after 3 days, the phase transition was finished in the suspension at 10 °C, whereas for the suspension at 15 °C, the CBZA remained unchanged even after 3 days.

Compared with HPMC, all the other additives showed only slight effects on the phase-transformation kinetics. PEG slightly inhibited the phase transition at both temperatures. PVP showed a small retarding effect at 10 °C, but this effect became negligible at 15 °C. SLS has been reported as a phase transformation promoter in the literature;[11,14] however, its effect

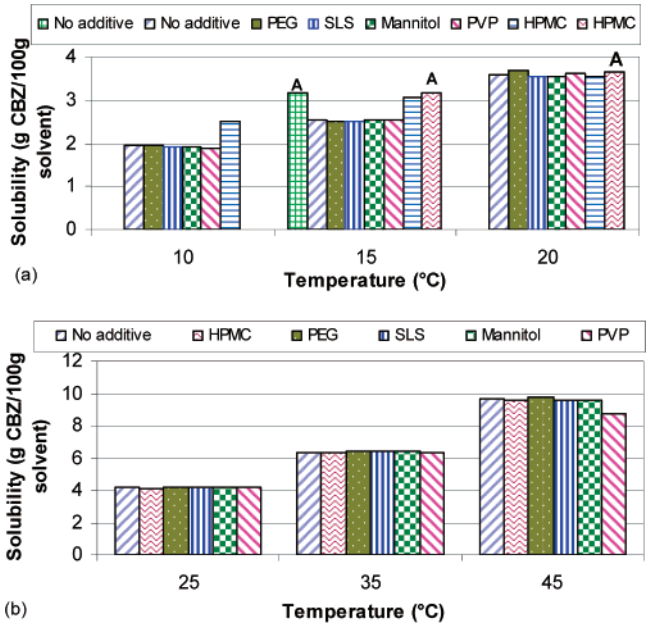

Figure 5. Additive effects on the solubility of CBZH and CBZA: (a) "A" denotes the solid in equilibrium when the saturated solution was CBZA, all other columns represent the solubility of CBZH; (b) all columns represent the solubility of CBZA.

in this study was not significant. This is probably because an ethanol−water mixture was used as the solvent in this work instead of water. The solubility and the morphology of the CBZH crystals in pure water are dramatically different from that in ethanol−water mixtures. Luhtala[11] reported that SLS increased the solubility of CBZH in pure water and broadened the CBZH needlelike crystals into platelike shapes. It was observed in the previous study[6] that the addition of ethanol as a cosolvent also increased the CBZH solubility and modified the crystal morphology in a similar way. This probably implies that the solvent effect on the solubility and crystallization of CBZH in ethanol−water mixtures was overwhelming compared with the effect of SLS.

Additive Effects on the Solubility of CBZA and CBZH. The solubility of CBZA and CBZH was measured with and without additives from 15 to 45 °C, as shown in Figure 5. As the transition temperature was 24.7 °C for the solvent containing 61 mol % ethanol, the phase transition from CBZA to CBZH was expected to happen during the solubility measurement at temperatures lower than 24.7 °C. It was observed that at 10 °C, the solid phase was CBZH for all samples. However, as HPMC was a strong inhibitor for the phase transition from CBZA to CBZH, special attention was paid to ensure that the CBZH solid was really in equilibrium with the solution at 10

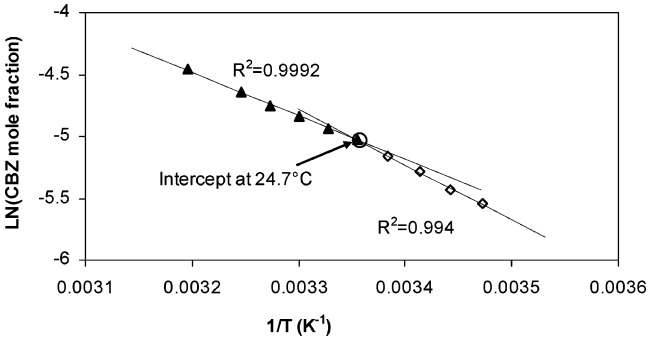

Figure 6. Solubility of CBZA (solid symbols) and CBZH (open symbols) in ethanol−water mixtures containing 61 mol % ethanol.

°C. Five samples were prepared by mixing excess CBZA solid and solvent with HPMC in 20 mL bottles, and the samples were then kept in the hermetic metal box. After that, the temperature of the water bath was decreased from room temperature to 10 °C with a thermostat. The suspensions were filtered at 3, 8, 24, 48, and 72 h, respectively. It was observed that the CBZA solid was transformed to CBZH after 3 h. This is probably because the solubility measurement experiment was started at room temperature. It took around 15 min for the thermostat to decrease the temperature of the water bath from room temperature to 10 °C. The dissolution of CBZA during this cooling time caused a relatively high supersaturation in the liquid phase compared with that in the phase transformation experiment. As a consequence, CBZH crystallized out when the temperature reached 10 °C. It is clear that HPMC increased the solubility of CBZH significantly.

For the solubility measurement at 15 °C, the presence of HPMC prevented the phase transition from CBZA to CBZH during the 3 days. Thus the solubility of CBZA at 15 °C was obtained with HPMC. To know the effect of HPMC on the solubility of both CBZA and CBZH at 15 °C, we carried out two additional measurements to obtain the CBZA solubility without any additive and the CBZH solubility with HPMC. First, the apparent solubility of CBZA was determined by keeping the CBZA solid with the solvent, without additive, at 15 °C for 40 min. The suspension was then filtered and the solid was confirmed by a Raman spectroscopy to be still CBZA, and the clear solution was evaporated in an oven at 100 °C to obtain the solubility of CBZA, as shown by the green bar in Figure 5a. Comparing the green and the wine red bar (both marked with "A") in Figure 5a at 15 °C, it can be seen that HPMC has no effect on the solubility of CBZA at 15 °C. The solubility of CBZH with HPMC was measured by suspending excess CBZH crystals in the solvent for 3 days. The final solid was also analyzed with a Raman spectrometer, which was confirmed to be unchanged form CBZH. The promoting effect of HPMC on CBZH solubility was obvious at 15 °C. In other words, HPMC decreased the solubility difference between CBZA and CBZH, due to the fact that it selectively increased the solubility of CBZH but had no effect on the solubility of CBZA. As it has been discussed above, the solubility difference between the two forms determines the supersaturation level during the solvent-mediated phase transformation, which is the driving force of the metastable form dissolution and the stable form crystallization. The presence of HPMC decreased the supersaturation level

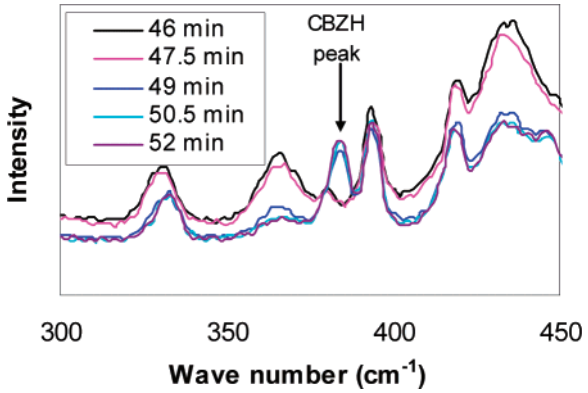

Figure 7. Raman spectra taken before and after the nucleation of CBZH during cooling crystallization without additives.

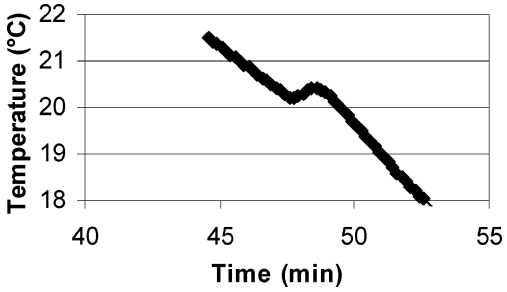

Figure 8. Determination of the nucleation onset from the temperature profile for CBZH cooling crystallization without additives.

and thus retarded the phase transformation. The inhibiting of the phase transformation from CBZA to CBZH caused by HPMC was due to the thermodynamic effect rather than the kinetic effect. It should be emphasized here that the changing of the solubility difference between the anhydrate and hydrate form due to the additives resulted in the altering of the supersaturation level during the phase transformation, and therefore the phase transformation rate was affected. The promotion or reduction effect of the additives on the solubility of the anhydrate and/or hydrate does not always lead to the changing of the phase transformation kinetics. Mohan et al.[8] have performed a study on the effect of various electrolytes and nonelectrolyte on the solvent-mediated phase transformation of anhydrous L-phenylalanine to the hydrate form in pure water. The authors observed that ammonium sulfate inhibited the phase transformation, and this inhibiting effect was attributed to the reduction of the anhydrous L-phenylalanine solubility due to ammonium sulfate. It was also observed in their work that the presence of aluminum sulfate and potassium aluminum sulfate dodecahydrate significantly increased the solubility of anhydrous L-phenylalanine; however, no effect on the phase transformation kinetics of L-phenylalanine was observed for these two additives. Because the effect of the additives on the solubility of L-phenylalanine hydrate was not reported in the literature, the effect of these additives on the solubility difference between the anhydrate and hydrate form of L-phenylalanine was unknown.

At 20 °C, the phase transition from CBZA to CBZH also occurred except when HPMC was used. The solubility of CBZH with HPMC was measured using a method similar to that used

Table 1. Kinematic Viscosity of the Solvent with and without Additives

additive concentration	no additive	HPMC (0.01 g/100 g of solvent)	PEG (0.5 g/100 g of solvent)	PVP (0.5 g/100 g of solvent)	SLS (0.5 g/100 g of solvent)	mannitol (0.2 g/100 g of solvent)
viscosity (mm^2/s)	2.17	2.34	2.37	2.26	2.21	2.21

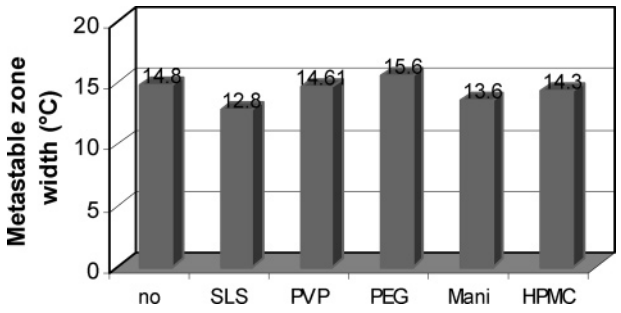

Figure 9. Additive effects on the metastable zone width; cooling rate = 25 °C/h.

at 15 °C. It is noticeable that all additives have a negligible effect on the solubility of CBZH. It is obvious that the promotion effect of HPMC on the CBZH solubility depends on the temperature. The CBZH solubility was increased by 27.6 and 21.2% at 10 and 15 °C, respectively. When the temperature was at 20 °C, this promoting effect was not visible at all. To understand this behavior, the dependency of the solubility difference of CBZA and CBZH on temperature and solvent composition that has been reported in previous work[5−6] has to be recalled. As shown in Figure 6, for the solvent containing 61 mol % ethanol, CBZH exhibits a lower solubility than CBZA at temperatures lower than the transition point (24.7 °C). The solubility difference between CBZA and CBZH was greater when the temperature was decreasing. The promotion effect of HPMC was also intensified with decreasing temperature. When the temperature was increased toward the transition point, the solubility difference between CBZA and CBZH was reduced, and so was the promotion effect of HPMC. This observation indicated that regardless of the significant promotion effect of HPMC on the solubility of CBZH, the relative stability of CBZA and CBZH is still governed by the water activity in the solution and the temperature. The transition point of CBZA and CBZH in the solvent containing 39 mol % water remained unchanged at 24.7 °C. This conclusion is also supported by the solubility data shown in Figure 5a; the solubility of CBZH was still

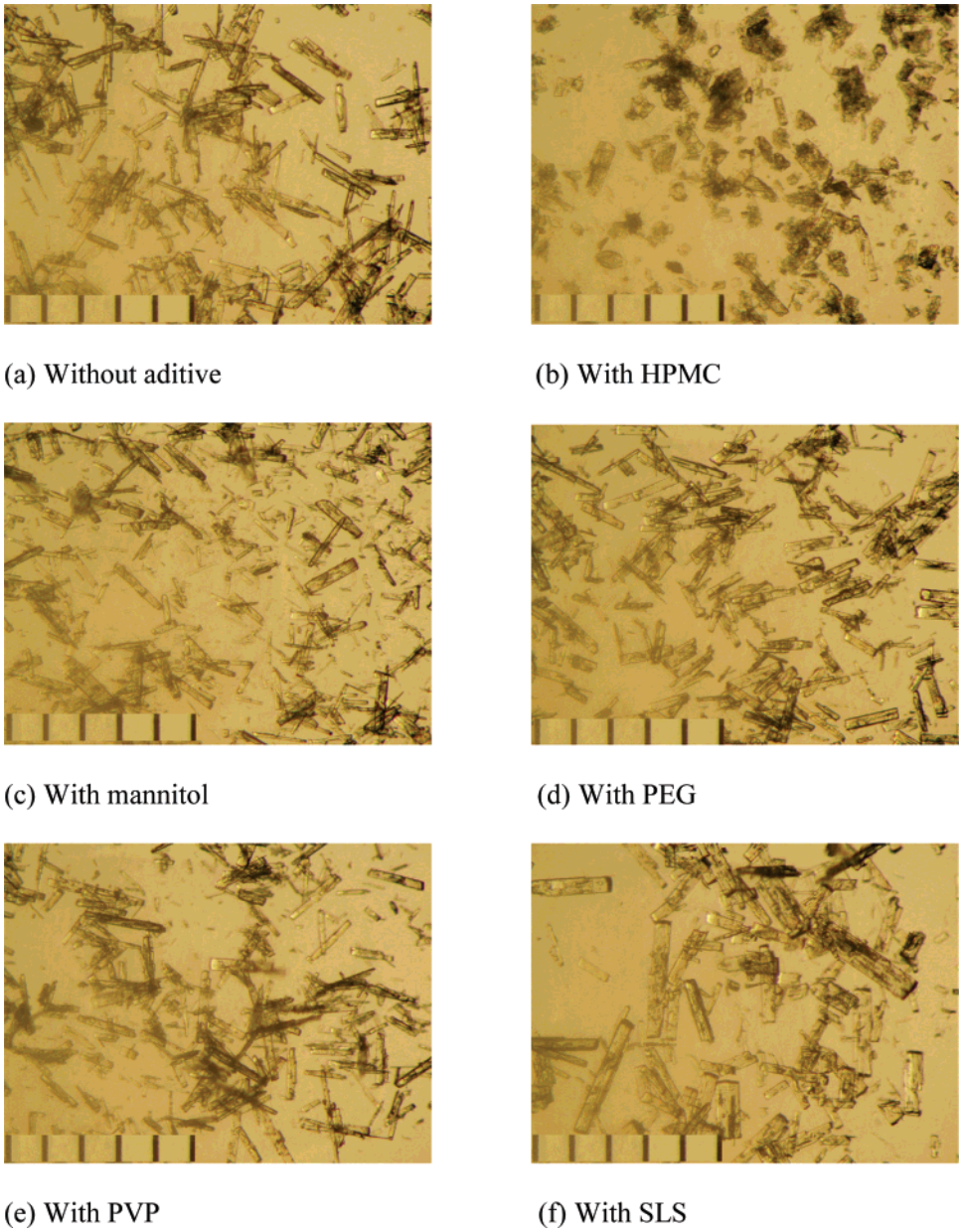

Figure 10. CBZH crystals produced by cooling crystallization with and without additives (the grid bar represents 500 μm).

slightly lower than that of CBZA at 15 and 20 °C when HPMC was present, indicating that CBZH was the thermodynamic stable form. Further understanding of the promotion effect of HPMC on the solubility of CBZH at lower temperatures might require information on the structural details of CBZ in ethanol−water solution and the interactions of the CBZ molecules with the solvents and additive molecules.

The additive effects on the solubility of CBZA were investigated also at temperatures of 25 , 35, and 45 °C. The effects of all additives were not significant, except at 45 °C, at which PVP showed a solubility decreasing influence. As there was no effect observed for PVP at all other temperatures, this decreasing effect at 45 °C cannot be explained in this study.

Additive Effects on Solution Viscosity, Primary Nucleation, and Crystal Growth of CBZH. The viscosity of the solvent with and without additives is shown in Table 1. PEG and HPMC caused a slight increase in the solvent viscosity. The increased viscosity may have caused a lower mass-transfer rate in the solution. The additive effects on the nucleation were studied by detecting the nucleation temperature of CBZH with and without additives. The onset of the primary nucleation can be clearly observed from the in-line Raman spectra. The spectra taken before and after the nucleation are shown in Figure 7. It can be seen that the nucleation of CBZH caused a sudden increase in the characteristic peak of CBZH at 383 cm^{-1}. However, because the measurement time of one spectrum was 1.5 min, this caused difficulties in determining the exact moment when the nucleation started. The exothermic nucleation can sometimes result in an unusual change in the temperature in the crystallizer. Therefore, a temperature profile in the crystallizer measured with a Pt-100 probe at 10 s intervals was used to detect the nucleation temperature. The corresponding temperature profile of Figure 7 is shown in Figure 8, where the nucleation moment can be clearly seen from a sudden increase in the temperature. The metastable zone widths, defined as the saturation temperature 35 °C minus the nucleation temperature, with and without additives, are shown in Figure 9. It can be observed that only SLS exhibited a slight promotion effect and that the other additives showed insignificant effects on the nucleation of CBZH. The morphology of the CBZH crystals produced by the cooling crystallizations is shown in Figure 10. HPMC modified the crystal morphology by increasing the width of the CBZH crystals and decreasing the crystal size. Larger crystals were formed with the presence of SLS, probably suggesting that SLS promoted the crystal growth of CBZH, which is in agreement with the promotion effect on nucleation shown in Figure 9.

4. Conclusions

The effects of five different additives on the solvent-mediated phase transformation from anhydrous to hydrate carbamazepine have been studied. HPMC was proved to be a strong inhibitor for the phase transformation. The mechanism of the inhibiting effect was studied by investigating the effect of HPMC on the solubility of CBZA and CBZH, and on the cooling crystallization of CBZH. It was shown that HPMC selectively increased the solubility of CBZH, whereas it had no effect on CBZA solubility. As a consequence, HPMC decreased the solubility difference of CBZA, and CBZH therefore decreased the driving force of the solvent-mediated phase transformation. HPMC also modified the morphology of the CBZH crystals during cooling crystallization. SLS showed a slight promoting effect on the nucleation and crystal growth of CBZH during cooling crystallizations. PEG, PVP, and mannitol showed an insignificant effect on the phase transformation of CBZA to CBZH.

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