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Effects of dehydration temperature on water vapor adsorption and dissolution behavior of carbamazepine

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Abstract

Anhydrous carbamazepine was prepared by heating carbamazepine dihydrate at 60, 80, 100, 120, and 140 °C and used to investigate the effects of dehydration temperature on water vapor adsorption and dissolution behavior. The hydration rate of anhydrous carbamazepine at 75, 83, and 95% relative humidity and 25 °C decreased with increasing heating temperature. From the dissolution study by the rotating disk method, the calculated solubility of anhydrous carbamazepine was about 2.5 times higher than that of the dihydrate. The rate of phase transformation from the anhydrous form into the dihydrate during the dissolution process decreased with an increase in sample preparation temperature. These phenomena were further studied by thermal analysis, specific surface area measurement, density measurement, small-angle X-ray scattering, and wide-angle powder X-ray diffraction. As the heating temperature was raised, the specific surface area was reduced and the density was increased; furthermore, the average of the solid part calculated by the Debye method with small-angle X-ray scattering increased. The anhydrous carbamazepine prepared at lower heating temperatures was found to have a more porous structure and was seen by wide-angle powder X-ray diffraction to comprise both anhydrous forms I and II. © 2002 Published by Elsevier Science B.V.

Keywords: Carbamazepine; Dehydration temperature; Hydration rate; Dissolution rate; Small-angle X-ray scattering

1. Introduction

Numerous drug substances exist in both hydrate and anhydrous forms. As drug substances are often crystallized from an aqueous solvent and contact water vapor in the atmosphere, those having hydrogen bonding sites in the crystal can incorporate stoichiometrically water molecules into the crystal lattice of the drug and form a hydrate. Conversely, the water molecules of a hydrate can be released from its crystal lattice under heating and drying conditions. Most of the hydrate-anhydrous form transformation is reversible and is influenced by temperature, relative humidity, particle size, and surface area. It is possible for the transformation to occur under

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ambient conditions during drug processing, transportation, and storage. Evaluations of the hydration and dehydration behavior of drug substances are important for the development of stable formulations, because, the physicochemical, mechanical, and biological properties of the hydrate form may differ significantly from those of the corresponding anhydrous form (Kobayashi et al., 2000). Thus, it is necessary to clarify the hydrate-anhydrous form transformation behavior of drugs and select the most stable form.

There are many cases of drug substance hydrates, including the well-known ampicillin trihydrate, caffeine monohydrate, and theophylline monohydrate. In our previous study (Ono et al., 2001), we found that theophylline anhydrous forms prepared by heating the monohydrate at various temperatures exhibited different hydration behaviors depending on the heating temperature. It remained to be clarified whether this phenomenon would be observed in other drug substances.

Carbamazepine is a widely used antiepileptic drug that reportedly has four anhydrous forms and one dihydrate form. Three anhydrous polymorphic forms have been identified by the X-ray diffraction method: monoclinic form (Himes et al., 1981; Reboul et al., 1981), trigonal form (Lowes et al., 1987), and triclinic form (Ceolin et al., 1997). Different nomenclatures for these anhydrous forms were described by several authors (Behme and Brooke, 1991; Edwards et al., 2001). The nomenclature described by Rustichelli et al. (2000) was used in this study. The anhydrous form obtained by heating dihydrate was the triclinic form called form I. Whereas, the anhydrous form obtained by dehydration under reduced pressure was form II (Krahn and Mielck, 1987; Rustichelli et al., 2000) and that by dehydration under dry nitrogen flow was the amorphous form (Li et al., 2000). The anhydrous forms and dihydrate form of carbamazepine were studied for their solubility and bioavailability (Kahela et al., 1983; Kobayashi et al., 2000), and the hygroscopicity and moisture adsorption isotherms of the anhydrous forms were investigated (Kaneniwa et al., 1984, 1987; Young and Suryanarayanan, 1991). Moreover, the dehydration profile of the dihydrate form was reported (McMahon et al., 1996; Han and Suryanarayanan, 1998). Although, there have been a large number of studies on the carbamazepine anhydrous forms and hydrate, the physicochemical properties of the anhydrous forms obtained under different drying conditions have not yet been clarified. In many cases, the process of drying a drug substance is performed in the final manufacturing stage; thus, the physicochemical properties of drug substances are influenced significantly by the conditions of this process. In this study, we chose carbamazepine as the model drug and investigated the effects of dehydration temperatures on the water vapor adsorption behavior and the dissolution rate of its anhydrous forms prepared by different heating temperatures.

The investigations and the hydrate-anhydrous form transformation of a pseudo-polymorphic form were characterized by using a powder X-ray diffraction method, thermal analysis, infrared spectroscopy, near-infrared spectroscopy, Raman spectroscopy (McMahon et al., 1996), and solid-state nuclear magnetic resonance (Kimura et al., 1999; Gandhi et al., 2000). Recently, it was reported that the small-angle X-ray scattering method was useful for pore structure analysis (Suzuki et al., 2001). To clarify the reasons why the hydration behavior of anhydrous forms prepared at various temperatures differed from each other, the properties of the anhydrous forms were analyzed by thermal analysis, the wide-angle powder X-ray diffraction method, and the small-angle X-ray scattering method.

2. Materials and methods

2.1. Materials

Carbamazepine (Tokyo Kasei, Japan) was of reagent grade. Carbamazepine dihydrate was recrystallized from a 50% water–ethanol solution. The precipitated crystals were filtrated and dried on a filter paper at room temperature. Carbamazepine anhydrous forms were prepared from the dihydrate form by heating at 60, 80, 100, 120, and 140 °C for 2 h. The anhydrous forms were stored in a desiccator over silica gel.

2.2. Methods

2.2.1. Water vapor adsorption behavior

Accurately weighted samples of anhydrous form were stored in individual desiccators maintained at the relative humidities (RHs) of 75, 83, and 93% at 25 °C. The relative humidities were prepared by using saturated-salt aqueous solutions of sodium chloride, potassium bromide, and potassium nitrate, respectively. The weight changes of the samples were monitored for 3 months.

2.2.2. Dissolution study by the dispersed amount method

The dissolution profiles of the dihydrate and anhydrous forms prepared by heating at various temperatures were measured in distilled water at 25 °C. An excess amount (about five times the saturated concentration of dihydrate) of sample was added to 50 ml of distilled water and vigorously stirred by a magnetic stirrer. Samples of the solution were withdrawn with a syringe at definite time intervals. The solution was passed through a membrane filter (0.45 μm) and then diluted with distilled water appropriately. The concentration of carbamazepine in solution was measured with an ultraviolet spectrophotometer UV230 (Hitachi, Japan) at a wavelength of 285 nm.

2.2.3. Intrinsic dissolution rate study by the rotating disk method

The intrinsic dissolution rates of the dihydrate and anhydrous forms were measured by the rotating disk method (Nogami et al., 1966). A disk of 13 mm diameter was prepared by compressing 400 mg of sample at 200 kg/cm^2 for 5 min. It was confirmed by powder X-ray diffraction analysis that the solid-solid transformation did not occur during preparation of the disk.

The disk was rotated at 100 rpm in 50 ml distilled water at 25 °C. The sample solution was circulated into a flow cell by a peristaltic pump and the concentration of carbamazepine in solution was measured with an ultraviolet spectrophotometer UV230 (Hitachi, Japan) at a wavelength of 285 nm.

2.2.4. Wide-angle powder X-ray diffraction

The powder X-ray diffraction patterns of the samples were obtained by using an X'Pert-MPD PW 3050 diffractometer (Phillips, The Netherlands). Powder samples were presented in the glass holder cavity. The operating conditions were as follows: target, Cu; filter, Ni; voltage, 35 kV; current, 20 mA; receiving slit, 0.2 mm; and scanning speed, 0.025° 2θ per s.

2.2.5. Thermal analysis

Differential scanning calorimetry (DSC) was performed on the SSC/5200 DSC 220 (Seiko Instruments, Japan). The instrument was calibrated with indium and tin. The operating conditions in the open-aluminum pan system were as follows: sample weight, 5 mg; heating rate, 10 and 40 °C/min; and nitrogen gas flow rate, 100 ml/min.

Thermogravimetric analysis (TG) was performed on the SSC/5200 TG/DTA 220 (Seiko Instruments, Japan). The operating conditions in the open-aluminum pan system were as follows: sample weight, 5 mg; heating rate, 10 °C/min; and nitrogen gas flow rate, 200 ml/min.

2.2.6. Density measurement

Apparent density was determined with a helium-air pycnometer, Multivolume Pycnometer 1305 (Shimadzu, Japan).

2.2.7. Specific surface area

Specific surface area was determined by the low temperature krypton adsorption method. The data were obtained with a micrometritics ASAP 2010 (Shimadzu, Japan). The specific surface areas were calculated by the BET method.

2.2.8. Small-angle X-ray scattering

The X-ray small-angle scattering patterns were obtained with an X-ray diffractometer, RINT-2500 (Rigaku, Japan). Powder samples were loaded into quartz glass capillary tubes of 1.0 mm diameter. Scattering due to the apparatus and air was corrected by the subtraction of a measurement with only the capillary tube. The operating conditions were as follows: target, Cu; filter, Ni; voltage, 50 kV; current, 150 mA; scanning range, $2\theta = 0.010–0.300°$ in steps of 0.002°; width of first

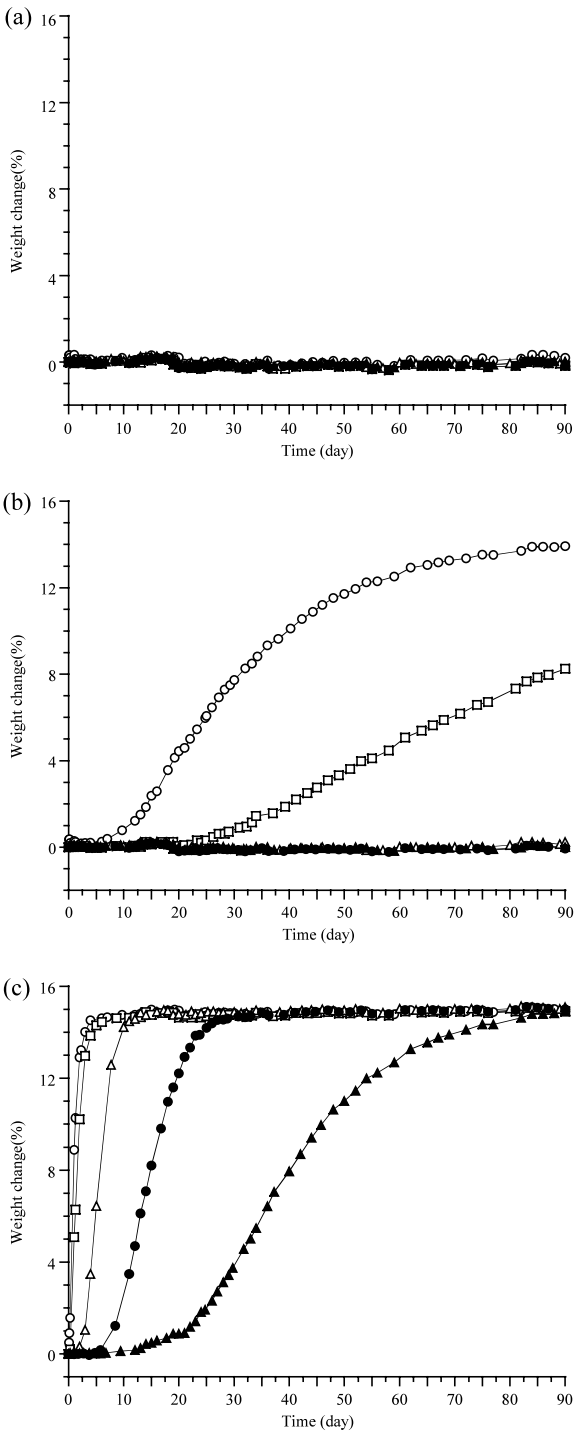

Fig. 1.

slit, 0.04 mm; second slit, 0.06 mm; and received slit, 0.1 mm.

3. Results and discussion

3.1. Water vapor adsorption behavior

The isothermal hydration profiles at 75, 83 and 95% RHs and 25 °C for anhydrous forms prepared by heating carbamazepine dihydrate at various temperatures are shown in Fig. 1. At 75% RH, no weight gain of the anhydrous forms was observed within the storage period of 3 months. At 83% RH, the weights of anhydrous forms prepared at 60 and 80 °C increased by about 13 and 7% due to water vapor adsorption after 3 months of storage, respectively. All the anhydrous forms stored at 93% RH exhibited weight gains of 15.0%, which corresponded to the stoichiometric value calculated for the dihydrate. The wide-angle powder X-ray diffraction patterns of high water content (15.0%) samples were identical to that of the dihydrate form. Even though, all the anhydrous forms transformed to dihydrate at 93% RH, the individual transformation rates from anhydrous state to hydrate state were significantly different. The anhydrous form prepared at 60 °C changed to dihydrate after 5 days in storage, while that prepared at 140 °C needed 3 months to be completely changed. That is, the period required for the transformation of the anhydrous form prepared at 140 °C to dihydrate was 18 times longer than that for the sample prepared at 60 °C. It is noteworthy that the water vapor adsorption rates of the prepared anhydrous forms were observed to decrease with the increasing heating temperature of the dihydrate.

3.2. Dissolution behavior by dispersed amount method

The dissolution behaviors of the dihydrate and

Fig. 1. Isothermal water vapor adsorption profiles at 75, 83, and 93% RH and 25 °C for anhydrous carbamazepine prepared by heating at various temperatures. (a) 75% RH, (b) 83% RH, (c) 93% RH. Key, heating temperature, ○, 60 °C; □, 80 °C; △, 100 °C; ●, 120 °C; ▲, 140 °C.

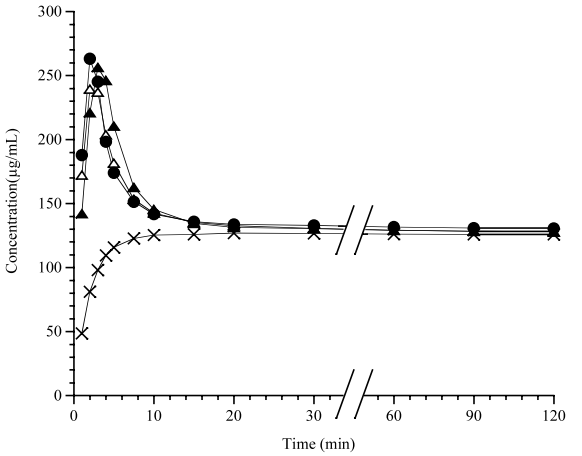

Fig. 2. Dissolution profiles at 25 °C in water for carbamazepine dihydrate and anhydrous forms prepared by heating at various temperatures. Key, ×, dihydrate form; △, anhydrous form prepared at 100 °C; ●, anhydrous form prepared at 120 °C; ▲, anhydrous form prepared at 140 °C.

the anhydrous forms prepared by heating at 100, 120, and 140 °C were investigated by the dispersed amount method in distilled water at 25 °C. The dissolution profiles are shown in Fig. 2. For the anhydrous forms, the maximum concentrations, about 250 μg/ml, were observed at the initial dissolution stage, and then the concentrations decreased gradually. After 30 min, the concentrations observed in the anhydrous forms reached the equilibrium concentration of about 130 μg/ml, which was the same level as the dihydrate. The anhydrous forms showed characteristic convex dissolution curves, suggesting that a phase transformation occurred during the dissolution process in water. Conversion of the anhydrous form to dihydrate was confirmed by powder X-ray diffraction of the solid phase collected after the dissolution test.

3.3. Intrinsic dissolution rate

The intrinsic dissolution rate was determined by the rotation disk method at 25 °C. The dissolution curves of the three anhydrous forms prepared by heating at 100, 120, and 140 °C and dihydrate are shown in Fig. 3. The slope of the dissolution curve of dihydrate was constant throughout the dissolution test, while those of the anhydrous forms varied gradually within 4 min and finally agreed with the slope of the dihydrate. The initial dissolution rates of the three anhydrous forms were identical but the times required for changing the slopes of three anhydrous forms differed from each other. According to the study by Nogami et al. (1969), the dissolution parameters could be calculated from the dissolution curves by using the following equations:

$$\frac{dC}{dt} = k_t C_{SH} \tag{1}$$

$$\left(\frac{dC}{dt}\right)_{t=0} = k_t C_{SA} \tag{2}$$

$$b = \frac{k_t(C_{SA} - C_{SH})}{k_r} \tag{3}$$

where C represents the concentration of carbamazepine in bulk solution, t is the time, and k_t and k_r represent the rate constants of the transport process and phase transformation process, respectively. C_{SH} and C_{SA} represent the saturated concentrations of dihydrate and anhydrous form, respectively. Then, b is the intercept obtained by extrapolation of the linear portion of the dissolution curve of the anhydrous form.

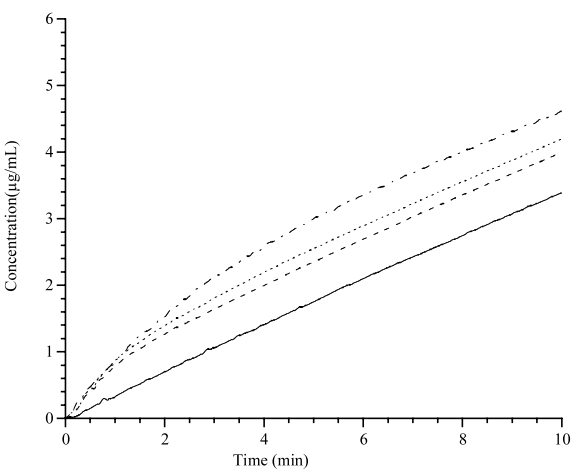

Fig. 3. Initial dissolution curves at 25 °C in water for carbamazepine dihydrate and anhydrous forms prepared by heating at various temperatures, (—) dihydrate form; (– – –) anhydrous form prepared at 100 °C, (· · · ·) anhydrous form prepared at 120 °C; (– · – · –) anhydrous form prepared at 140 °C.

Table 1
Dissolution parameters obtained from the rotating disk experiments of anhydrous forms and dihydrate of carbamazepine in water at 25 °C

Sample	Initial slope (μg/ml min)	Final slope (μg/ml min)	Intercept (μg/ml)	k_t (per min)	k_r (per min)	Solubility (μg/ml)
Anhydrous form prepared at 100 °C	0.74	0.30	0.75	–	0.60	321
Anhydrous form prepared at 120 °C	0.74	0.30	1.0	–	0.45	319
Anhydrous form prepared at 140 °C	0.72	0.30	1.6	–	0.27	309
Dihydrate	–	0.29	–	0.0022		126

k_t, Dissolution rate constant; k_r, rate constant of phase transformation process.

The C_{SH} value was obtained from the dispersed amount method described above. The parameters, k_t, k_r, and C_{SA}, were calculated from the above equations and the results are shown in Table 1. The saturated concentrations of the anhydrous forms prepared by heating at different temperatures were estimated to be about 315 μg/ml. This value was greater than the maximum concentration of the anhydrous forms observed in the dispersed amount method, which was 250 μg/ml. The reason for having obtained different solubilities by the dispersed method and rotating disk method was speculated as being, because, the phase transformation from the anhydrous form to dihydrate was completed before the solubility of anhydrous form could reach its equilibrium value in the dispersed method. Therefore, the apparent solubility of the anhydrous forms by the dispersed amount method should be lower than that obtained by the rotating disk method. In the previous study (Ono et al., 2001), the apparent solubility of the anhydrous theophylline prepared at 60 °C could not be measured exactly by the dispersed amount method as the transformation from anhydrous theophylline to monohydrate was so fast.

On the other hand, the rate constants of the phase transformation process from the anhydrous form to the dihydrate decreased with the increase of heating temperature. The rate of phase transformation of the anhydrous form prepared at 100 °C was about 2.2 times faster than that of the anhydrous form prepared at 140 °C. The phase transformation process from the anhydrous form to the dihydrate during the dissolution process in water was found to be closely correlated to the water vapor adsorption behavior of the anhydrous form.

3.4. Wide-angle powder diffraction

Wide-angle powder X-ray diffraction patterns of the dihydrate and the anhydrous forms prepared at various heating temperatures are shown in Fig. 4. The patterns of the anhydrous forms were quite different from that of the dihydrate. From the precise comparison of the patterns of all anhydrous forms, slight differences were observed among them at the diffraction angles of $2\theta = 13$, 17, 18, and 21°. Krahn and Mielck (1987) prepared a different crystal form of anhydrous carbamazepine by heating carbamazepine dihydrate at low temperature in a vacuum desiccator over P_2O_5. Rustichelli et al. (2000) obtained the same anhydrous form, which they designated as form II, from an ethanolic solution and reported that form II transformed to form I at 140 °C. The diffraction patterns of anhydrous forms prepared at 60, 80, and 100 °C were observed as being the diffraction peaks due to form II in comparison with the reported diffraction pattern of form II. Consequently, differences observed among the X-ray diffraction patterns of anhydrous carbamazepine samples could be due to the co-existence of anhydrous carbamazepine form II combined with anhydrous carbamazepine form I in the samples prepared at low temperatures.

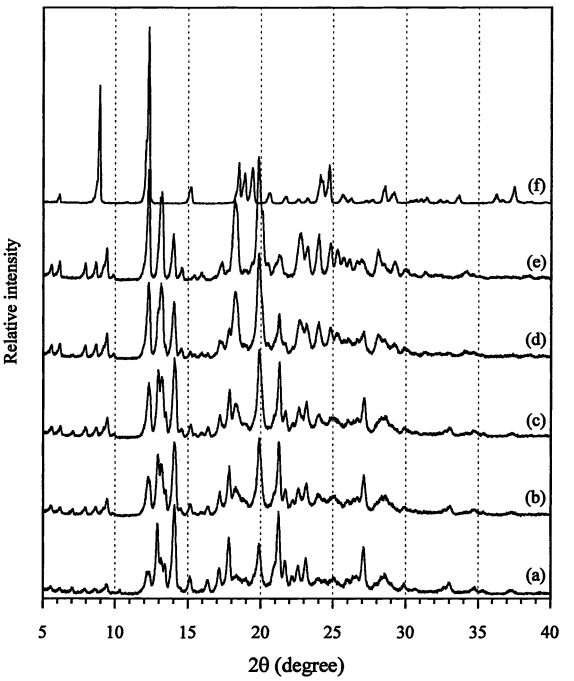

Fig. 4. Powder X-ray diffraction patterns of carbamazepine dihydrate and anhydrous carbamazepine prepared by heating at various temperatures. (a) Anhydrous form prepared at 60 °C, (b) anhydrous form prepared at 80 °C, (c) anhydrous form prepared at 100 °C, (d) anhydrous form prepared at 120 °C, (e) anhydrous form prepared at 140 °C, (f) dihydrate form.

3.5. Thermal analysis

DSC and thermogravimetry (TG) curves for anhydrous carbamazepine forms prepared at 60 and 140 °C and dihydrate are shown in Fig. 5. The dihydrate showed a broad endothermic peak around 70 °C and a sharp endothermic peak at 191 °C in the DSC curve. The first endothermic peak was due to the dehydration and weight loss of 13.1% from approximately 40 to 90 °C was shown on the TG curve. The stoichiometric value calculated for the dihydrate dehydration was 13.2%, and this value was almost identical to the value obtained from the TG analysis. The second endothermic peak was due to the fusion of anhydrous forms.

In contrast, the anhydrous forms prepared by heating at 60 and 140 °C showed only one endothermic peak at 191 °C due to the melting of the anhydrous carbamazepine and no weight loss was shown on the TG analysis. The DSC curve measured at a faster heating rate, 40 °C/min, showed a small endothermic peak at 185 °C due to form

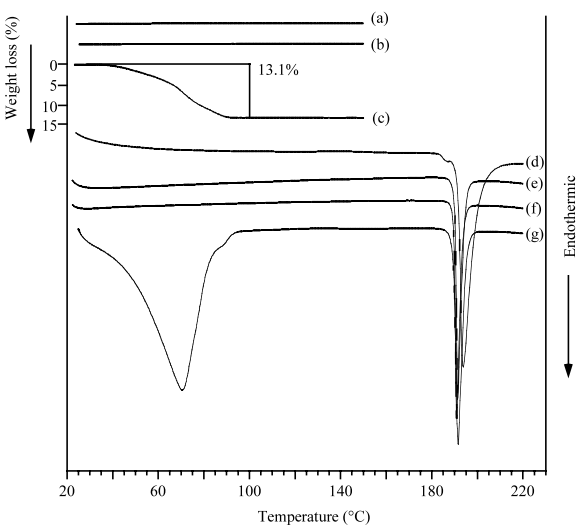

Fig. 5. TG and DSC curves of carbamazepine dihydrate and anhydrous forms. (a) TG curve of anhydrous form prepared at 60 °C, (b) TG curve of anhydrous form prepared at 140 °C, (c) TG curve of dihydrate form, (d) DSC curve of anhydrous form prepared at 60 °C (heating rate, 40 °C/min), (e) DSC curve of anhydrous form prepared at 60 °C, (f) DSC curve of anhydrous form prepared at 140 °C, (g) DSC curve of dihydrate form.

Table 2
Specific surface area and density of anhydrous carbamazepine prepared by heating at various temperatures

Preparation temperature (°C)	Specific surface area (m^2/g)	Density (mg/m^3)
60	1.07	1.15
80	1.06	1.16
100	0.706	1.18
120	0.614	1.21
140	0.662	1.21

II (curve d). The co-existence of form II combined with form I was confirmed by DSC measurement. Consequently, it was found that the anhydrous form prepared at 60 °C was obtained as a mixture of form I and II, while the anhydrous form prepared at 140 °C was highly pure form I.

3.6. Measurement of specific surface area and density

It is well known that the water vapor adsorption and dissolution rate of a powder are influenced by the specific surface area. The specific surface areas of anhydrous forms prepared by heating at various temperatures are shown in Table 2. The specific surface areas of the anhydrous forms prepared at 60 and 80 °C were greater than those of the samples prepared above 100 °C.

Table 2 also shows the density of anhydrous forms prepared by heating at various temperatures. As the preparation temperature for the anhydrous form was raised, the density measured by helium gas increased. The true density of carbamazepine anhydrous form I (triclinic) was 1.31 mg/m^3, which was calculated from the X-ray data of a single crystal (Ceolin et al., 1997). These results suggested that the number of closed pores in the anhydrous forms prepared at 60 °C was greater than that of the anhydrous form prepared at 140 °C.

3.7. Small-angle X-ray scattering

A small-angle X-ray scattering method was useful for the investigation of small pore structure. This method was used to analyze the pore structure of a porous material (Ruike et al., 1999). The

pore structure of microcrystalline cellulose (MCC) was also investigated by a small-angle X-ray scattering method (Suzuki et al., 2001).

Scattering intensities of anhydrous forms prepared by heating at various temperatures were measured in the range of $2\theta = 0.01–0.3°$, and the scattering patterns are shown in Fig. 6. The pore parameters were calculated from the obtained scattering patterns by the method of Debye plots. The equations for pore parameter calculation were reported by Debye et al. (1957) and are shown as follows:

$$I(s) = I_e(\Delta\rho)^2\Phi_p(1-\Phi_p)V\int_0^\infty \gamma(r)\left(\frac{\sin sr}{sr}\right)4\pi r^2 dr \quad (4)$$

$$s = \frac{4\pi \sin\theta}{\lambda} \quad (5)$$

$$\Phi_p = 1 - \left(\frac{d_{ap}}{d_t}\right) \quad (6)$$

$I(s)$ is scattering intensity, I_e is a constant, $\Delta\rho$ is the difference in electron density between a particle and the external media, and Φ_p is the void fraction of samples. Assuming a random distribution of pores, the integration of Eq. (4) yields Eq. (7).

$$I(s) = \frac{I_e 8\pi a^3(\Delta\rho)^2\Phi_p(1-\Phi_p)V}{(1+a^2s^2)^2} \quad (7)$$

where a is the correlation distance. This parameter, a, represents the characteristic dimension of a sample. When a plot of $I(s)^{-1/2}$ against s^2 was obtained as a straight line, the parameter, a, can be calculated from the value of the slope and intercept of regression lines by Eq. (8).

$$a = \sqrt{\frac{\text{slope}}{\text{intercept}}} \quad (8)$$

The correlation distance, a, can be converted into the average size of the solid part, a_{solid}, average size of the pore, a_{pore}. The specific surface area of a sample, S_x, can be calculated from the parameter, a, by the following equations.

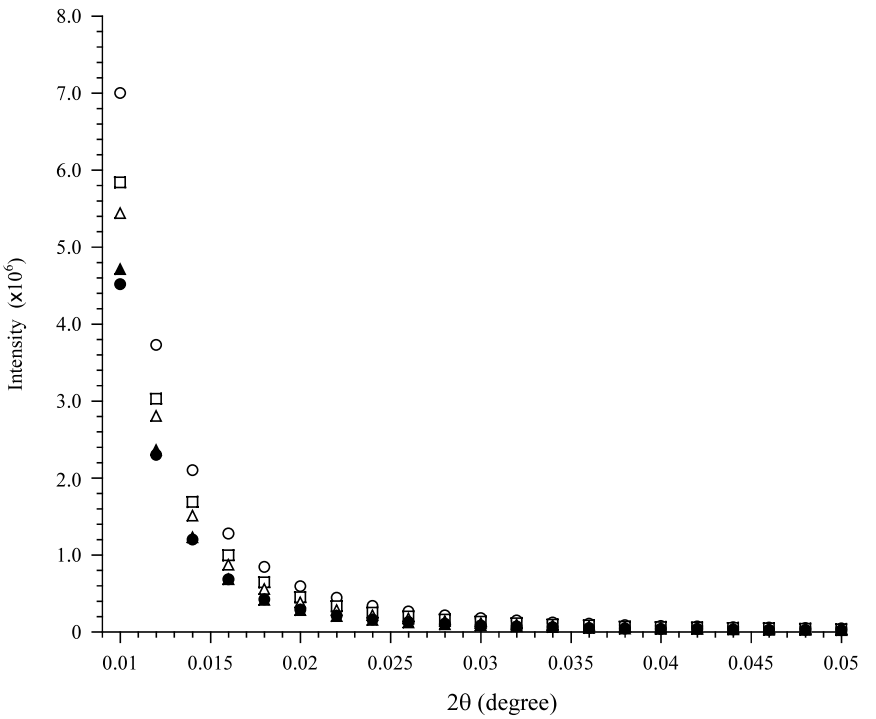

Fig. 6. Small-angle X-ray scattering patterns of anhydrous carbamazepine prepared by heating at various temperatures. Key, heating temperature, ○, 60 °C; □, 80 °C; △, 100 °C; ●, 120 °C; ▲, 140 °C.

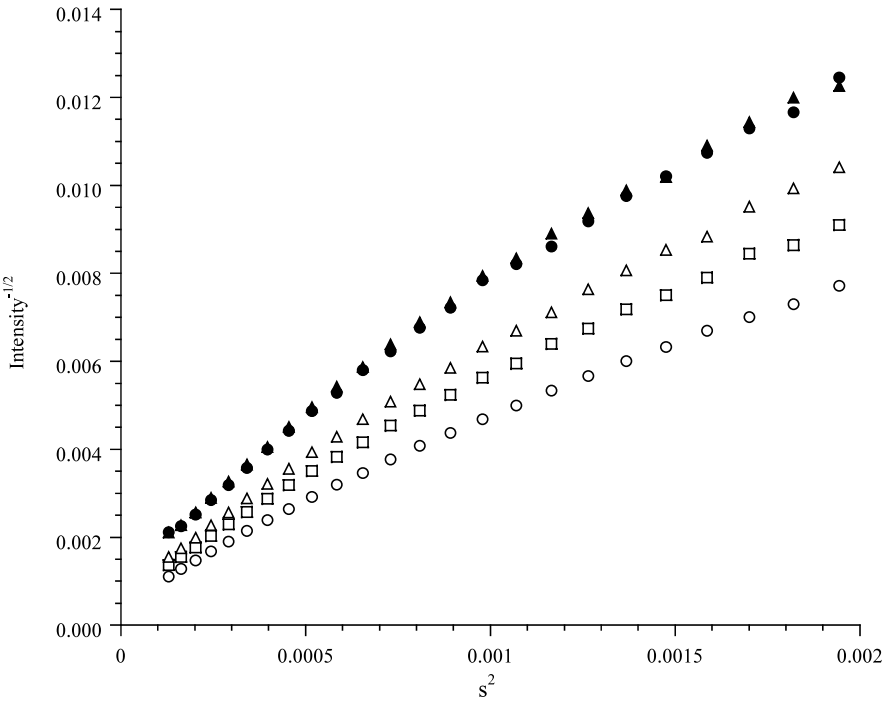

Fig. 7. Debye plots for small-angle X-ray scattering patterns of anhydrous carbamazepine prepared by heating at various temperatures. Key, heating temperature, ○, 60 °C; □, 80 °C; △, 100 °C; ●, 120 °C; ▲, 140 °C.

$$a_{\text{solid}} = \frac{a}{\Phi_{\text{p}}} \tag{9}$$

$$a_{\text{pore}} = \frac{a}{(1-\Phi_{\text{p}})} \tag{10}$$

$$S_{\text{x}} = \left[4 \times 10^3 \frac{\text{Fp}(1-\Phi_{\text{p}})}{d_{\text{ap}}}\right]\left(\frac{1}{a}\right) \tag{11}$$

The Debye plots of anhydrous forms prepared by heating at various temperatures are shown in Fig. 7, and these plots showed good linearity (correlation coefficients > 0.99). The parameters calculated from the Debye plots are summarized in Table 3. The average pore sizes, a_{pore}, of the anhydrous forms prepared at 60, 80, and 100 °C were almost the same, but those at 120 and 140 °C were small. In contrast, the order of the average size of the solid area and the specific surface area as calculated by the small-angle X-ray scattering of anhydrous forms was $60 > 80 > 100 > 120 \cong 140$ °C. From these results, it was suggested that the solid part of the anhydrous forms grew toward the outside with increasing heating temperature up to 100 °C. Then, as the growth of the solid part toward the outside reached the maximum at 120 °C, the growth of the solid was directed toward the inside and the pore became narrower over 120 °C. Since, increasing the heating temperature caused a decrease in surface area that was dependent on pore structure, the water vapor adsorption and phase transformation rates of the anhydrous form prepared at 140 °C were lower than those of the sample prepared at 60 °C. The ordering of the specific surface area of the anhydrous forms prepared at various heating temperatures obtained by the small-angle X-ray scattering measurement was similar to that obtained by the gas adsorption method; however, the values disagreed. The value calculated from the small-angle X-ray scattering measurement was derived from the difference in electron density between the solid region and the pores. In contrast, the specific surface area calculated by the gas adsorption method could be obtained by the access to and adsorption of gas

Table 3
Parameters obtained from Debye plots for X-ray small-angle scattering patterns of anhydrous forms of carbamazepine prepared by heating at various temperatures

Preparation temperature (°C)	a (nm)	a_{solid} (nm)	a_{pore} (nm)	S_x (m^2/g)
60	61.0	484	69.7	6.31
80	59.5	530	67.0	5.76
100	60.5	614	67.1	4.97
120	55.6	758	60.0	4.03
140	54.7	695	59.3	4.39

onto the surface. Therefore, the disagreement derived from the different measurement principle.

It was considered that the different hydration behavior took place for two reasons. One was the presence of the polymorphic anhydrous form II. From results of powder X-ray diffraction and DSC measurements, the anhydrous form prepared at 60 °C included form II combined with anhydrous form I. Since, the amorphous phase was also involved in the anhydrous form II (Rustichelli et al., 2000), it appeared that anhydrous form II was more hydrophilic than form I. It was thought that increasing the co-existence of form II accelerated the hydration reaction of the anhydrous form to dihydrate. Therefore, as the heating temperature was raised, the hydration rate decreased. The other reason for the decrease was variation in pore structure. It was found from small-angle X-ray scattering that the pore structure formed during the dehydration treatment varied with change in the heating temperature.

4. Conclusions

The water vapor adsorption and the dissolution behavior of anhydrous carbamazepine prepared by the dehydration of the dihydrate through heating at between 60 and 140 °C were investigated. The water vapor adsorption rate at 93% RH and 25 °C as well as the phase transformation rate in water decreased with the increase of the heating temperature. In order to clarify these differences, wide-angle powder X-ray diffraction, thermal analysis, and small-angle X-ray scattering experiments were conducted. There were two reasons for the differences in hydration behavior of anhydrous carbamazepine: the co-existence of a more hydrophilic polymorphic form II and the variation in pore structure that took place during the dehydration process. It was clarified that the hydration behavior of the anhydrous carbamazepine prepared by heating the dihydrate was significantly affected by heating temperature.

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