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# Determination of Heat of Hydration and Hydration Kinetics of Theophylline by Thermal Analysis[1]

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**Heat of hydration of theophylline anhydrate to the monohydrate at 298 K was evaluated by three different methods. The values determined by heat of solution with a microcalorimeter and heat of dehydration with a differential scanning calorimeter were $-9.34 \pm 0.65$ and $-9.82 \pm 0.48$ kJ/mol, respectively. The values obtained directly with a heat conduction microcalorimeter under 97.3, 95.4 and 93.7% relative humidities were $-9.48 \pm 0.49$, $-9.28 \pm 0.63$ and $-9.37 \pm 0.74$ kJ/mol, respectively. From thermograms obtained with a microcalorimeter at the isothermal transition of theophylline anhydrate to monohydrate, hydration rates were analyzed by a deconvolution method. Hydration rates were in good agreement with those obtained by the Karl Fischer method. Hydration mechanisms were also analyzed on the basis of solid-state kinetic models and the transition followed a mechanism of random nucleation and two-dimensional growth of nuclei.**

**Key words** theophylline; hydration kinetics; phase transition; microcalorimetry; differential scanning calorimetry

It is well known that many solid pharmaceuticals are capable of existing as polymorphs, solvates and amorphous forms. In the preparation of solid dosage forms, phase transitions of the active ingredient may influence drug dissolution and/or bioavailability.[2] In the case of anhydrates, transition to hydrates during manufacturing processes and storage may occur. Therefore, it is exceedingly important to evaluate stability, heat of hydration and hydration kinetics. Phase transitions are determined by various techniques, such as X-ray powder diffractometry, differential scanning calorimetry, isothermal thermogravimetry, infrared spectrophotometry and microcalorimetry.[3,4] However, few attempts have been made to analyze hydration rates with a microcalorimeter in detail. Furthermore, heat of hydration is almost always determined directly by calorimetry and is not often calculated by other methods.

The purpose of this paper is to calculate heat of hydration by three different methods and evaluate whether the values obtained are reasonable or not. Furthermore, it is to measure simply, continuously and quantitatively the isothermal hydration rates of anhydrate with a microcalorimeter and analyze hydration mechanisms on the basis of solid-state kinetic models. Theophylline was selected as a model compound since it is capable of existing in the solid state as anhydrate or monohydrate and has been previously used for hydration and dehydration experiments.[3]

## Experimental

**Materials** Theophylline anhydrate was of JP XII grade. The fraction that passed through a 100 mesh sieve was used. The sample was dried at 60 °C for 5 h under vacuum over $P_2O_5$ and then stored in a desiccator containing $P_2O_5$.

**Preparation of Saturated Salt Solution** Salts used were of analytical grade and distilled water was used as solvent. It has been reported that the relative humidities (RHs) of the saturated salt solutions ($K_2SO_4$, $Pb(NO_3)_2$, $KNO_3$, LiCl) were 97.3, 95.4, 93.7 and 11.3% at 25 °C, respectively.[5] A series of saturated salt solutions were prepared at 50 °C and equilibrated for one week at 25 °C prior to measurements.

**Microcalorimetry** Calorimetric measurements were carried out using a twin type heat conduction microcalorimeter described in the previous paper.[6] All measurements were carried out at 298 K in a room maintained at $298 \pm 1$ K.

**Determination of Hydration Rate with a Microcalorimeter** For determination of hydration rate, 20 ml of saturated salt solution, containing fine crystals was used as solvent. Sample powder was measured precisely (300 mg) and placed in an ampule. The tip of the ampule was sealed with a gas burner. The ampule, installed with an ampule-breaking attachment, was placed in a polyethylene bag and inserted into a reaction vessel coated with Teflon, containing the solvent. After a thermal stationary state had been attained, the ampule containing the sample powder was broken, and the heat of hydration was measured. For the purpose of obtaining a thermogram of the heat generated instantaneously in the reaction vessel, a Nichrome wire was used. The Nichrome wire in a polyethylene bag was inserted into the reaction vessel by a similar method to that described above. Heat was generated by passing an electric current for 0.1 second through the Nichrome wire, transforming the voltage from 130 to 80 V.

Input rate can be calculated by deconvolution of the thermogram for the heat of hydration by using the thermogram for heat evolved by passage of an electric current through the Nichrome wire as a characteristic response in the convolution equation. It is assumed to correspond to the heat generation rate when isothermal hydration of anhydrate to monohydrate occurred. The input rate can then be converted into the hydration rate, Thus, hydration rates were determined by deconvolution of the thermograms. Deconvolution was carried out on the basis of a method described in the literature.[7] All measurements were carried out three times and the average was used for deconvolution analysis.

**Measurement of Heat of Solution** The measurement of the heat of solution was carried out according to the procedures previously described.[6] For measurement of the heat of solution for distilled water and theophylline, containing various amounts of moisture, 50 ml of *N*,*N*-dimethylformamide (DMF) was used as solvent.

**Measurement of Moisture Content** For determining hydration rate of theophylline anhydrate, samples were stored in desiccators kept at 97.3, 95.4 and 93.7% RHs and withdrawn at appropriate hourly intervals. Moisture contents of the samples were determined using a Karl Fisher titration instrument (AQV-6 AQUACOUNTER; Hiranuma Co., Ltd.).

**X-Ray Powder Diffraction** The X-ray diffraction profiles of samples were measured with a RAD type diffractometer (Rigaku Co., Ltd.) at room temperature. The X-ray source was Cu-$K_\alpha$, and the diffracted beam was monochromated by a bent graphite monochromator. Measurement conditions were as follows: filter, Ni; voltage, 35 kV; current, 10 mA; receiving slit, 0.3 mm. Sample powder was packed in a glass plate.

**Differential Scanning Calorimetry (DSC)** A DSC 8230 differential scanning calorimeter (Rigaku Co., Ltd.) was used. The DSC apparatus was calibrated with indium as the standard. Accurately weighed amounts (4—6 mg) of sample were transferred to aluminum sample

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pans and the sides of the cover were crimped. Samples were run at a scanning rate of 10 K/min.

## Results and Discussion

**Estimation of Heat of Hydration** Heat of hydration for theophylline anhydrate to monohydrate was determined by the following three methods.

1) Estimation by Heat of Solution: Heat of hydration was evaluated from the heat of solution of theophylline anhydrate ($\Delta H_{\text{anhydrate}}$), monohydrate ($\Delta H_{\text{monohydrate}}$) and distilled water ($\Delta H_{\text{water}}$) at infinite dilution in DMF at 298 K. Values for the heat of solution are summarized in Table 1.

The heat of hydration was calculated using the following equation:

$$\Delta H_{\text{h298}} = \Delta H_{\text{anhydrate}} + \Delta H_{\text{water}} - \Delta H_{\text{monohydrate}}$$

where $\Delta H_{\text{h298}}$ is the heat of hydration at 298 K. Consequently, the hydration enthalpy at 298 K was estimated to be $-9.34 \pm 0.65$ kJ/mol.

2) Estimation by Heat of Dehydration: The heat ($\Delta H_t$) and temperature ($T_t$) relating to transition from theophylline monohydrate to anhydrate were measured by DSC. The DSC curve is shown in Fig. 1.

A broad endothermic peak around about 338—368 K is due to the dehydration and the subsequent evaporation of water. $\Delta H_t$ and $T_t$ were estimated to be $53.36 \pm 0.55$ kJ/mol and $344.4 \pm 0.35$ K, respectively. $\Delta H_t$ contain heat of dehydration and evaporation of water. Since the heat of evaporation of water at $T_t$ is 42.01 kJ/mol,[7] heat of dehydration is calculated to be $11.35 \pm 0.55$ kJ/mol. Therefore, heat of hydration ($\Delta H_{\text{ht}}$) at $T_t$ is $-11.35 \pm 0.55$ kJ/mol since the signs of heat of dehydration and hydration are opposite. The change in free energy of hydration ($\Delta G_t$) at $T_t$ can be expressed by means of the following formula:

$$\Delta G_t = \Delta H_{\text{ht}} - T_t \Delta S_t$$

where $\Delta S_t$ is the change in entropy of hydration at $T_t$. $\Delta G_t$ equals zero, because theophylline monohydrate and anhydrate are in equilibrium at $T_t$. Since it is reasonable to consider $\Delta S_t$ as approximately constant between 298 K and $T_t$, the following equation is formed:

$$\Delta S_t = \Delta H_{\text{ht}}/T_t \approx \Delta H_{\text{h298}}/298$$

Consequently, $\Delta H_{\text{h298}}$ was estimated to be $-9.82 \pm 0.48$ kJ/mol.

3) Estimation by Heat of Hydration: The heat of hydration from theophylline anhydrate to monohydrate at 298 K was measured directly with a microcalorimeter under 97.3, 95.4 and 93.7% RHs. It is considered that the heat of adsorption of water vapor for theophylline anhydrate may be small compared to the heat of hydration. Briggner *et al.*[4b)] described that the heat of vaporization and sorption were almost equal and the signs were reversed, so heat evolution resulted in a small composite peak. In fact, little heat was generated in the course of water vapor adsorption to the powder sample under 97.3, 95.4 and 93.7% RHs. The values of heat of hydration obtained from the thermograms are summarized in Table 2. These results indicated that the heat of hydration was almost the same, regardless of RH.

The values derived by the three methods agreed very closely. Consequently, the values determined by these three methods were reasonable. From these results, the isothermal transitions of theophylline anhydrate to monohydrate at 298 K were almost complete when taking direct measurements with the microcalorimeter under 97.3, 95.4 and 93.7% RHs.

Table 1. Heat of Solution at Infinite Dilution in DMF at 298 K

| Sample | Heat of solution ±S.D. (kJ/mol) |
|---|---|
| Theophylline anhydrate | $14.53 \pm 0.51$ |
| Theophylline monohydrate | $20.45 \pm 0.40$ |
| Distilled water | $-3.42 \pm 0.05$ |

Each value represents the mean ± S.D. of 4 experiments.

Table 2. Heat of Hydration from Theophylline Anhydrate to Monohydrate at 298 K

| RH (%) | Heat of hydration ±S.D. (kJ/mol) |
|---|---|
| 97.3 | $-9.48 \pm 0.49$ |
| 95.4 | $-9.28 \pm 0.63$ |
| 93.7 | $-9.37 \pm 0.74$ |

Each value represents the mean ± S.D. of 3 experiments.

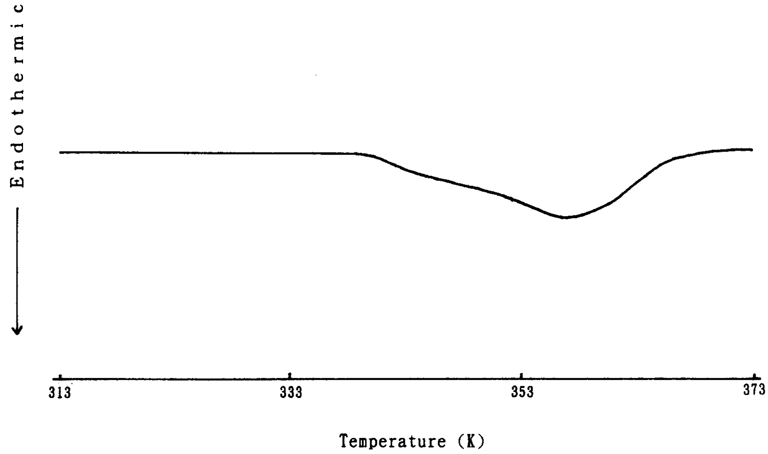

Fig. 1. DSC Curve of Theophylline Monohydrate

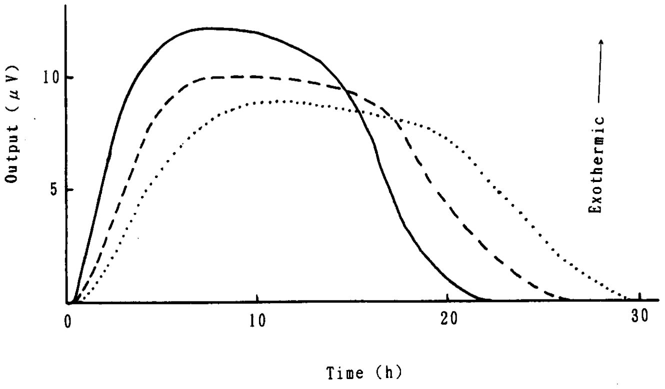

Fig. 2. Thermograms for Hydration of Theophylline Anhydrate Powder under 97.3, 95.4 and 93.7% RHs at 298 K

—, 97.3% RH ; ---, 95.4% RH; ···, 93.7% RH.

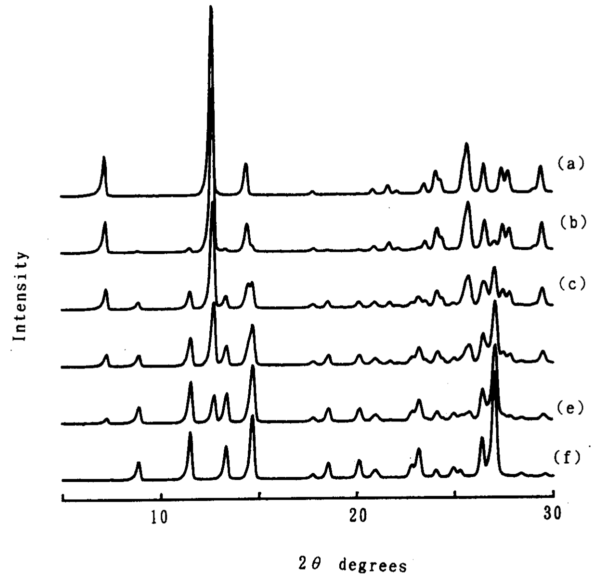

Fig. 3. Change of X-Ray Powder Diffraction Patterns of Theophylline Anhydrate Stored under 97.3% RH at 298 K

(a) stored for 0 h, (b) stored for 2 h, (c) stored for 5 h, (d) stored for 8 h, (e) stored for 12 h, (f) stored for 16 h.

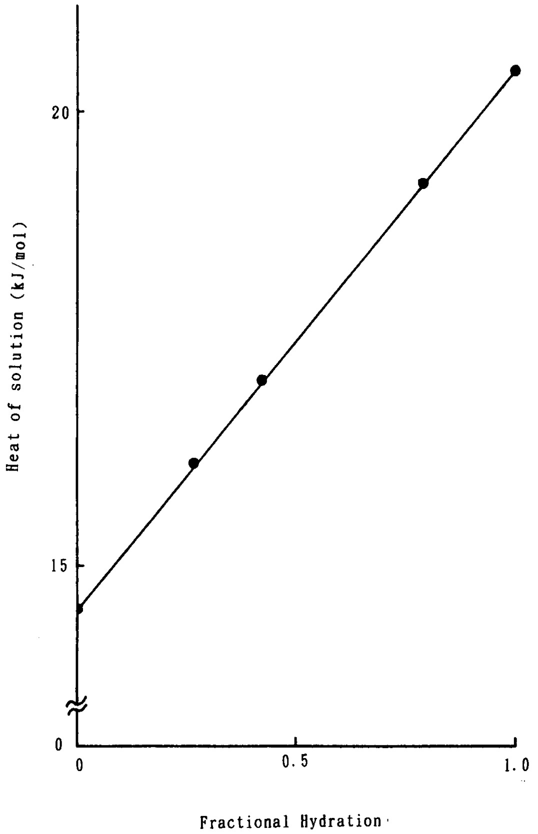

Fig. 4. Relationship between Fractional Hydration and Heat of Solution

**Thermograms for the Hydration of Theophylline** The thermograms measured directly by microcalorimeter under 97.3, 95.4 and 93.7% RHs were considered in some detail. To observe the heat evolved, except for the heat of hydration, measurement of the heat generated under 11.3% RH was carried out, because hydration does not take place under these conditions.[3c)] As a results, heat generated in the course of water vapor adsorption was scarcely observed. This result suggested that breaking energy and heat of water vaporization by breaking the ampules, heat of wetting of the powder by water vapor[4b)] and heat of solution of theophylline were small.

Figure 2 shows the thermograms for theophylline anhydrate powder exposed to water vapor under 97.3, 95.4 and 93.7% RHs.

Only a little initial evolved heat was observed under these RHs, and the time lag of the thermograms increased as RH decreased. These results indicated that the heat described above was scarcely generated, and initial nucleation decreased with decrease in RH, since heat evolved with nucleation. The thermograms rose rapidly after the time lag and soon tended to decrease slowly, regardless of the RH. When it seemed that the transition was completed, the curves decrease rapidly. With decreasing RH, the rapidly rising part of the curves after the time lag decreased and the gradually declining part increased. From these results, the rate of transition appears to decrease with decrease in RH. The thermograms were similar, independent of RH. This result suggests that the transition reaction followed a similar mechanism.

**Analysis of Hydration Rates by the Deconvolution Method** Determination of hydration rate by the deconvolution method was investigated. It was assumed that the heat obtained by passing an electric current through the Nichrome wire was generated instantaneously.

Figure 3 shows the change of X-ray powder diffraction patterns of theophylline anhydrate stored under 97.3% RH at 298 K.

From the X-ray powder diffraction profiles, it was found that theophylline anhydrate stored for 16 h was transformed completely into monohydrate, since the X-ray powder diffraction pattern was identical to that of theophylline monohydrate reported in the literature.[3b)] The transition proceeds through mixture states of anhydrate and monohydrate, and does not involve the formation of hemihydrate *etc.*, because the X-ray powder diffraction peaks showed only those derived by combination of theophylline anhydrate and monohydrate.

Samples stored under 97.3% RH at 298 K were taken out of the desiccator at appropriate time intervals during the 16 h period. The monohydrate fraction was de-

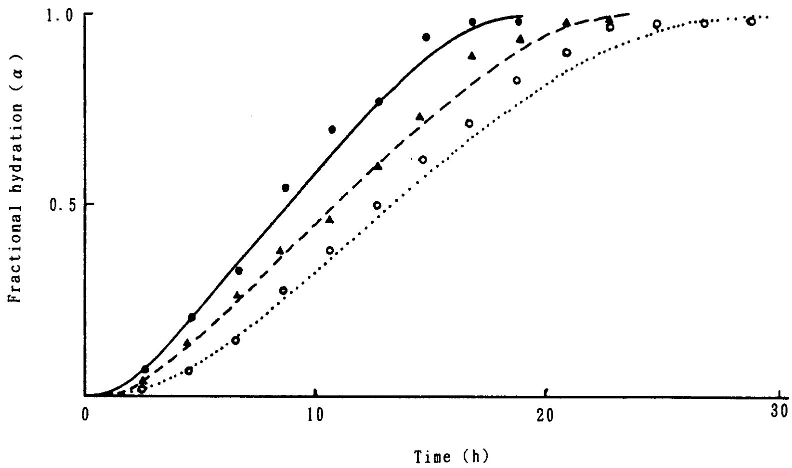

Fig. 5. Hydration Profiles of Theophylline Anhydrate Powder under 97.3, 95.4 and 93.7% RHs at 298 K

Deconvolution method: —, 97.3% RH; ----, 95.4% RH; ···, 93.7% RH. Karl Fischer method: ●, 97.3% RH; ▲, 95.4% RH; ○, 93.7% RH.

Table 3. Solid-State Reaction Rate Equations, *m* Values and Mechanisms[8)]

| Equation | *m* | Mechanism |
|---|---|---|
| $\alpha=kt$ | 1.24 | Zero-order mechanism (Polany–Wigner equation) |
| $1-(1-\alpha)^{1/2}=kt$ | 1.11 | Phase boundary reaction, cylindrical symmetry |
| $1-(1-\alpha)^{1/3}=kt$ | 1.07 | Phase boundary reaction, spherical symmetry |
| $-\ln(1-\alpha)=kt$ | 1.00 | Random nucleation, one nucleus on each particle |
| $(-\ln(1-\alpha))^{1/2}=kt$ | 2.00 | Random nucleation, two-dimensional growth of nuclei (Avrami–Erofe'ev equation) |
| $(-\ln(1-\alpha))^{1/3}=kt$ | 3.00 | Random nucleation, three-dimensional growth of nuclei (Avrami–Erofe'ev equation) |
| $\alpha^2=kt$ | 0.62 | One-dimensional diffusion |
| $(1-\alpha)\ln(1-\alpha)+\alpha=kt$ | 0.57 | Two-dimensional diffusion |
| $(1-(1-\alpha)^{1/3})^2=kt$ | 0.54 | Three-dimensional diffusion (Jander equation) |
| $(1-2\alpha/3)-(1-\alpha)^{2/3}=kt$ | 0.57 | Three-dimensional diffusion (Ginstling–Brounshtein equation) |

termined by the Karl Fisher method. The heat of solution of their samples was determined by microcalorimetry, and results are shown in Fig. 4.

A linear relationship between fractional hydration and heat of solution was observed. This result indicates that the heat of hydration is proportional to the fraction of theophylline anhydrate.

From these results, it was shown that the heat generated upon hydration was directly proportional to the hydrated sample weight. Therefore, the thermograms obtained upon passing an electric current through the Nichrome wire correspond to an impulse response and thermograms for hydration of the samples were considered as a response for an arbitrary input. From these thermograms, the hydration rates of theophylline anhydrate could be obtained by the deconvolution method.

**Measurement of Hydration Rates** The hydration rates obtained by the deconvolution method under 97.3, 95.4 and 93.7% RHs were compared with those obtained by the Karl Fisher method. The relationship between fractional hydration ($\alpha$) and time ($t$) obtained by both methods is shown in Fig. 5.

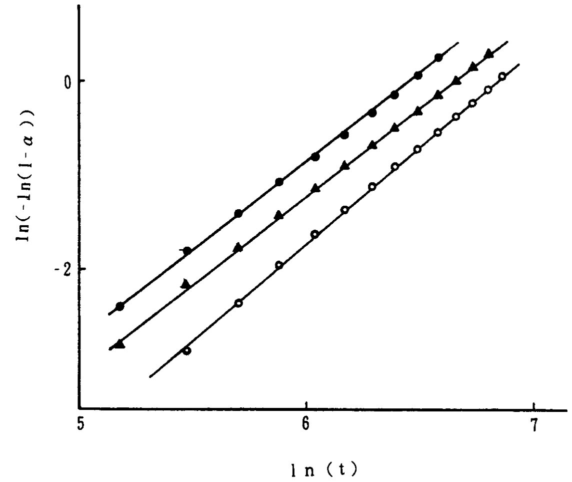

Fig. 6. Plots of $\ln(-\ln(1-\alpha))$ *versus* $\ln t$ for the Isothermal Transition of Anhydrate to Monohydrate under 97.3, 95.4 and 93.7% RHs at 298 K

●,97.3% RH; ▲, 95.4% RH; ○, 93.7% RH.

As expected from the thermograms, the results clearly demonstrate that hydration rates decrease with a decrease in RH. These results indicate that values obtained by the deconvolution method are in fair agreement with the values obtained by the Karl Fisher method. The deconvolution method is superior to the Karl Fisher method in terms of continuous determination and being a convenient technique. From these results, the importance of microcalorimetry for the determination of hydration rates continuously and quantitatively is demonstrated.

**Hydration Mechanism of Theophylline Anhydrate** Kinetic analysis of the isothermal hydration of anhydrate to monohydrate was carried out using the method of Hancock and Sharp.[9)] In this method, the slope ($m$) expressed by the following equation is used to distinguish reaction mechanism:

$$\ln(-\ln(1-\alpha))=m\cdot\ln t+\ln B$$

where B is a constant and $m$ is a constant related to an intrinsic value determined from various theoretical equa-

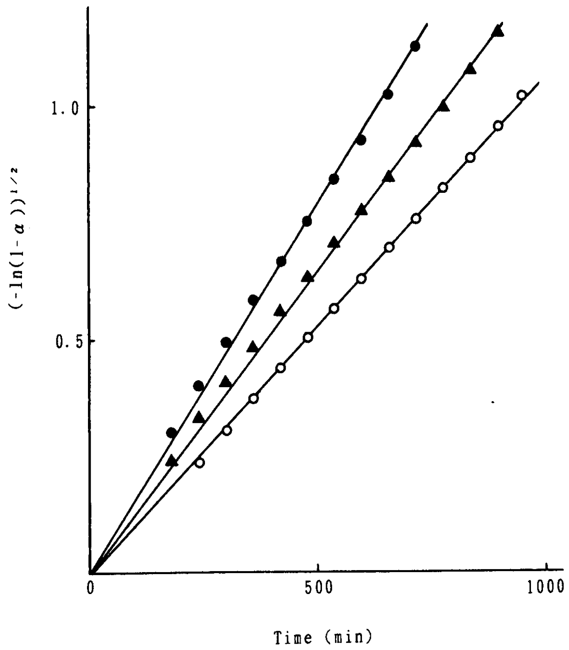

Fig. 7. Plots of $(-\ln(1-\alpha))^{1/2}$ *versus* Time for the Isothermal Transition of Anhydrate to Monohydrate under 97.3, 95.4 and 93.7% RHs at 298 K

●, 97.3% RH; ▲, 95.4% RH; ○, 93.7% RH.

tions for solid-state decomposition. Values in the range of 0.05—0.7 fractional transition were used as data for analysis of the hydration mechanism. Table 3 summarizes the relationship between the theoretical equation and the *m* value reported by Hancock and Sharp.[9]

Figure 6 shows a plot of $\ln(-\ln(1-\alpha))$ *versus* $\ln t$ for the isothermal transition of anhydrate to monohydrate under 97.3, 95.4 and 93.7% RHs at 298 K.

This plot gave a straight line, regardless of RH, from which the value of m for isothermal hydration of theophylline anhydrate to monohydrate was calculated to be $1.93 \pm 0.12$. This result suggests that this hydration reaction follows a mechanism of random nucleation and two-dimensional growth of nuclei, regardless of RH.

As the value of *m* was close to 2.00, it was found that the hydration rates could be applied to the Avrami-Erofe'ev equation,[10] shown in Table 3. Figure 7 shows plots of $(-\ln(1-\alpha))^{1/2}$ against *t* under 97.3, 95.4 and 93.7% RHs. The plots afforded straight lines, regardless of RH.

## Conclusion

The heat of hydration of theophylline anhydrate at 298 K was evaluated by three different methods. The first method involved measurement of heat of solution of theophylline anhydrate, monohydrate and distilled water at infinite dilution in DMF at 298 K with a microcalorimeter. The second involved calculation of heat of transition from monohydrate to anhydrate, measured by DSC. The third result was evaluated from the heat generated by isothermal transition from anhydrate to monohydrate, measured directly with a heat conduction microcalorimeter under various relative humidities at 298 K. Values estimated by these methods agreed approximately with one another.

Furthermore, application of the deconvolution method to determining rates of phase transition was performed. The hydration profiles obtained by the deconvolution method were compared with those obtained by the Karl Fisher method and it was shown that the values obtained by the calorimetric method was shown that the values obtained were in fair agreement. Consequently, the hydration rates of theophylline anhydrate under 97.3, 95.4 and 93.7% RHs could be determined simply, continuously and quantitatively using a microcalorimeter and the deconvolution method. According to analysis of the hydration rates using solid-state kinetic models, it was concluded that isothermal transitions of theophylline anhydrate to monohydrate followed a mechanism of random nucleation and two-dimensional growth of nuclei, regardless of RH.

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