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Effect of Surface Modification on Hydration Kinetics of Carbamazepine Anhydrate Using Isothermal Microcalorimetry

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ABSTRACT

The purpose of this research was to improve the stability of carbamazepine (CBZ) bulk powder under high humidity by surface modification. The surface-modified anhydrates of CBZ were obtained in a specially designed surface modification apparatus at 60°C via the adsorption of n-butanol, and powder x-ray diffraction, Fourier-Transformed Infrared spectra, and differential scanning calorimetry were used to determine the crystalline characteristics of the samples. The hydration process of intact and surface-modified CBZ anhydrate at 97% relative humidity (RH) and 40 ± 1°C was automatically monitored by using isothermal microcalorimetry (IMC). The dissolution test for surface-modified samples (20 mg) was performed in 900 mL of distilled water at 37 ± 0.5°C with stirring by a paddle at 100 rpm as in the Japanese Pharmacopoeia XIII. The heat flow profiles of hydration of intact and surface-modified CBZ anhydrates at 97% RH by using IMC profiles showed a maximum peak at around 10 hours and 45 hours after 0 and 10 hours of induction, respectively. The result indicated that hydration of CBZ anhydrate was completely inhibited at the initial stage by surface modification of n-butanol and thereafter transformed into dihydrate. The hydration of surface-modified samples followed a 2-dimensional phase boundary process with an induction period (*IP*). The IP of intact and surface-modified samples decreased with increase of the reaction temperature, and the hydration rate constant (*k*) increased with increase of the temperature. The crystal growth rate constants of nuclei of the intact sample were significantly larger than the surface-modified sample's at each temperature. The activation energy (*E*) of nuclei formation and crystal growth process for hydration of surface-modified CBZ anhydrate were evaluated to be 20.1 and 32.5 kJ/mol, respectively, from Arrhenius plots, but the *E*s of intact anhydrate were 56.3 and 26.8 kJ/mol, respectively. The dissolution profiles showed that the surface-modified sample dissolved faster than the intact sample at the initial stage. The dissolution kinetics were analyzed based on the Hixon-Crowell equation, and the dissolution rate constants for intact and surface-modified anhydrates were found to be 0.0102 ± 0.008 $mg^{1/3}$ min^{-1} and 0.1442 ± 0.0482 $mg^{1/3}\cdot min^{-1}$. The surface-modified anhydrate powders were more stable than the nonmodified samples under high humidity and showed resistance against moisture. However, surface modification induced rapid dissolution in water compared to the control.

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KEYWORDS: carbamazepine, anhydrate, surface modification, stability, hydration kinetic analysis, dissolution kinetics

INTRODUCTION

Using a metastable polymorphic form or amorphous form improves the dissolution behavior of pharmaceuticals, but it is chemically unstable and easily transformed into a stable form during storage.[1-3] The interaction of water with pharmaceuticals plays an especially important role in many aspects of drug development, from synthetic design and dosage form to effective product packaging and drug bioavailability. Therefore, many investigators[4-8] have reported the moisture sorption kinetics for pure crystalline forms and/or mixtures of unstable crystalline forms of pharmaceuticals under conditions of relatively high humidity. The US Food and Drug Administration (FDA) reported that the in vitro dissolution rate of a commercial carbamazepine (CBZ) preparation that had been exposed to 97% relative humidity (RH) for 2 weeks was up to one third

smaller than that of an unexposed preparation.[9] Findings of the potentially unfavorable hydration effects may help explain why the FDA occasionally receives reports of lack of efficacy for the commercial tablets.[9] Therefore, to obtain pharmaceutical preparations containing metastable solids, it is necessary to evaluate physicochemical stability and to choose an appropriate formulation, then validate production processes. Isothermal microcalorimetry (IMC) was developed for an automatic analytical method in the chemical and pharmaceutical fields.[10-23] Since the instrument has a high sensitivity (0.1 μW) and a smaller sample capacity (several grams) and almost all chemical, physical, and biology processes that occur with the instrument are accompanied by small heat exchanges, IMC is an effective method of investigating changes in the physicochemical properties of pharmaceutical preparations under ambient conditions.

In a previous study,[24] to improve the stability of nitrofurantoin bulk powder under high humidity, a surface of nitrofurantoin anhydrate crystal was modified by hydrophobic treatment by alcohol vapors, and their transformation kinetics under high humidity were investigated by using differential scanning calorimetry (DSC) and x-ray powder diffractometry. The hydration kinetics results indicated that the surface-modified anhydrates were more stable under high humidity than intact samples. In this study, to improve stability of CBZ bulk powder under high humidity, a surface of CBZ anhydrate crystal was modified by hydrophobic treatment and the kinetic transformation at various temperatures under high humidity leading to solid-state crystallization using IMC. The effect of humidity on thermodynamic parameters of surface-modified CBZ was investigated.

MATERIALS AND METHODS

Materials

CBZ bulk powder of Japanese Pharmacopoeia XIII grade (lot CEE-9-5) was obtained from Katsura Chemical Co (Tokyo, Japan). All other chemicals were of analytical grade.

Preparation of Polymorphs

The CBZ bulk powder was identified as being of form II (anhydrate, CBZ).[25] The dihydrate form (form IV)[25] was obtained by recrystallization as follows: the CBZ bulk powder was dissolved in 50% ethanol solution in a water bath at 70°C and filtered. After the saturated CBZ solution samples were cooled to room temperature, the crystalline samples were filtered and dried in a desiccator containing silica gel at room temperature in vacuo for 3 hours. All the CBZ samples were passed through a No. 200 mesh (75-μm) screen.

Preparation of Surface-Modified Sample Powder

The surface modification apparatus[24] was placed in a thermobath at 60°C. After anhydrate sample powder (5 g) was dried in the sample test tube for 2 hours in vacuo, n-butanol vapor was introduced in the sample tube and held for 15 hours at 60°C.

X-ray Powder Diffraction Analysis

X-ray powder diffraction profiles were recorded on an x-ray diffractometer (XD-3A, Shimadzu Co, Kyoto, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 20 kV; current, 20 mA; receiving slit, 0.1 mm; time constant, 1 second; scanning speed 4° 2θ/ min.

Thermal Analysis

DSC was performed with a type 3100 instrument (Mac Science Co, Tokyo, Japan). The operating conditions in an open-pan system were as follows: sample weight, 5 mg; heating rate, 10°C/min; N_2 gas flow rate, 30 mL/min.

Fourier Transformed Infrared (FT-IR) Spectroscopy

The sample powder was dispersed in micronized KBr powder (sample concentration, 0.625w/w%) by pestle and mortar without destruction of the sample particles and analyzed. FT-IR spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer (type FT-IR Spectrum One, Perkin Elmer Co., Yokahama, Japan) and modified using the Kubelka-Munk equation.

IMC Analysis

Isothermal behavior was measured using an isothermal microcalorimeter (Model 4400, Calorimetry Science Corp, Salt Lake Ctiy, UT), which consisted of a reference and 3 sample cells. One 2-mL glass tube contained 50 mg of the sample powder and the other contained saturated aqueous salt solutions (K_2SO_4

saturated solutions were for 97% RH at 30, 40, and 50°C) to control the RH. After the 2 glass sample tubes were sealed with a rubber cap, they were placed into a 40-mL glass vial. The glass vial was placed into a preheating box for around 30 minutes. After prestorage, the rubber seal of the sample tube was pierced with a needle and the measurement started.

Isothermal Kinetic Analysis of the Crystallization

The polymorphic transformation kinetics of surface-modified CBZ were analyzed based on 10 kinds of solid-state reaction models, as shown in **Table 1**.[20,21] The fraction of hydrate (α) was evaluated based on the area under the heat flow curve (AUC) at time *t*, assuming that 100% of fraction hydrate was the total AUC. The kinetic equation of crystallinity involves a function $f(\alpha)$, and its integrated form is the function $g(\alpha)$ ($\alpha = 0.05$-0.95), where α is the function of crystallinity at time *t*.

Dissolution Test

CBZ sample powder (20 mg) was introduced into 900 mL of distilled water in a covered 1000-mL round-bottomed flask. The flask was fixed on the sample holder in a thermostatically regulated water bath maintained at 37 ± 0.5°C and stirred by a paddle at 100 rpm. Aliquots (5 mL) of the sample were withdrawn at appropriate time intervals with a syringe. The sample was filtered through an 0.8-μm membrane filter and diluted with the dissolution medium for spectrophotometric analysis (UV 160A, Shimadzu Co) at 285 nm. The loss in volume was compensated by the addition of dissolution medium maintained at the same temperature.

RESULTS AND DISCUSSION

Physiochemical Properties of Surface-Modified CBZ Anhydrate by n-Butanol

X-ray diffractograms, DSC curves, and FT-IR spectra of intact anhydrate and surface-modified CBZ anhydrate were measured for change of physicochemical properties by surface modification. The x-ray diffraction result suggested that the crystalline characteristics of anhydrate were identified to form II CBZ[25] and not affected by surface modification using the adsorption of n-butanol. The DSC curve of the intact sample showed a small exothermic peak at 142ºC due to transformation to form I and an endothermic peak at 195ºC due to melting, as reported previously.[25] The DSC curve of CBZ anhydrate was not affected by

Table 1. Kinetic Equations for the Most Common Mechanism of Solid-State Reactions

	Equation	Solid-State Mechanism[24]
R1	x	Zero-order mechanism (Polany-Winger equation)
R2	$2[1-(1-x)]^{1/2}$	Two-dimensional phase-boundary mechanism
R3	$3[1-(1-x)]^{1/3}$	Three-dimensional phase-boundary mechanism
F1	$-\ln(1-x)$	First-order mechanism
A2	$[-\ln(1-x)]^{1/2}$	Two-dimensional growth of nuclei mechanism (Avrami equation)
A3	$[-\ln(1-x)]^{1/3}$	Three-dimensional growth of nuclei mechanism (Avrami equation)
D1	x^2	One-dimensional diffusion mechanism
D2	$(1-x)\ln(1-x)+x$	Two-dimensional diffusion mechanism
D3	$[1-(1-x)^{1/3}]^2$	Three-dimensional diffusion mechanism (Jander equation)
D4	$(1-2x/3)-(1-x)^{2/3}$	Three-dimensional diffusion mechanism (Ginstiling-Brounshtein equation)

surface modification. The surface-modified anhydrate exhibited an almost identical FT-IP spectrum as the intact sample powder. After heating at 150ºC in vacuo for 10 hours, the weight of surface-modified anhydrate was unchanged. The FT-IR and DSC results indicated that the adsorbed amount of alcohol was insignificant. If n-butanol adsorbed and forming a monolayer membrane on the surface of CBZ anhydrate, the adsorbed amount of n-butanol is possible to estimated from the adsorbed n-butanol amount per unit weight of CBZ powder, the molecular volume of adsorbed n-butanol, the specific surface area and powder density of CBZ anhydrate powder. The amount of adsorbed n-butanol on surface was estimated to be 0.95 ng/g CBZ. Therefore, it seemed that the weight and infrared spectral intensity changes by surface modification could not detected. The crystalline structure of anhydrate did not change by surface modification treatment, and it appeared that a very small amount of alcohol formed an alcoholic monolayer on the surface of the anhydrate crystals.

Stability of Surface-Modified CBZ Anhydrate Under High Humidity by Using IMC

Figure 1 shows the heat flow profiles of hydration of intact and surface-modified CBZ anhydrates at 97% RH and 40ºC by using IMC. The heat flow profiles of intact anhydrate peaked at around 10 hours. In contrast, the profile of surface-modified anhydrate peaked at around 45 hours after 10 hours of induction. This suggested that hydration of CBZ anhydrate was completely inhibited at the initial stage by surface modification of n-butanol and thereafter transformed into dihydrate.

Figure 2 shows the hydration process of intact and surface-modified CBZ anhydrates at 97% RH and 40ºC by using IMC. The intact and surface-modified anhydrate transformed into 100% dihydrate form at around 45 and 120 hours, respectively. This indicated that surface modification by n-butanol significantly inhibited the hydration process of CBZ.

To clarify the mechanism of phase transformation under high humidity, the hydration process was evaluated based on 10 kinds of kinetic equations (**Table 1**) with an induction period (IP) as shown in Equation 1:

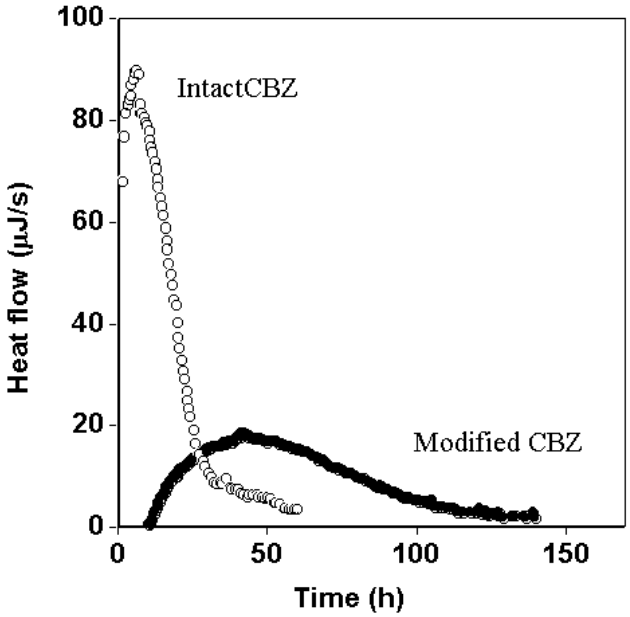

Figure 1. Effect of humidity on heat flow profiles of surface-modified anhydrate of CBZ at 97% RH and 40ºC. ○, Intact CBZ; ●, surface-modified CBZ.

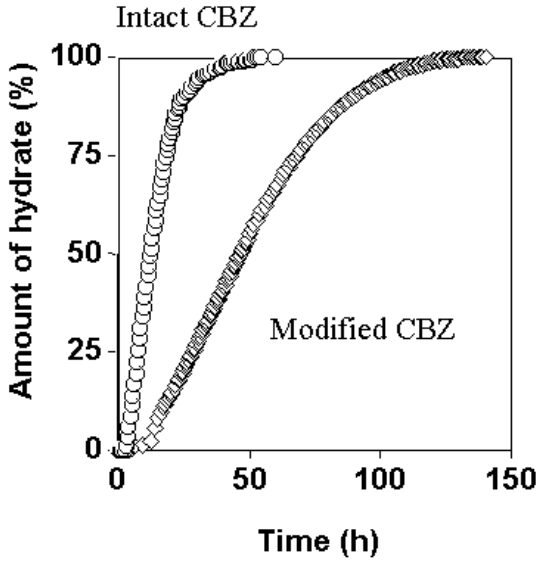

Figure 2. Effect of humidity on hydration process of surface-modified anhydrate of CBZ at 97% RH and 40ºC. ○, Intact CBZ; ◇, surface-modified CBZ.

$$g(\alpha) = k(t - IP) \quad (1)$$

where $g(\alpha)$ refers to various kinds of solid-state reaction model equations, α is the weight fraction of

Table 2. Correlation Coefficients of Plots of g(x) Against Time of Hydration of Surface-Modified CBZ*

	Kinetic Models								
Samples	**R2**	**R3**	**F1**	**A2**	**A3**	**D1**	**D2**	**D3**	**D4**
Intact	0.9978†	0.9955	0.9968‡	0.9966	0.9789	0.9798	0.9942	0.9864	0.9960
n-Butanol	0.9979†	0.9950	0.9778	0.9978‡	0.9972	0.9892	0.9785	0.9454	0.9698

*See Table 1 for kinetic model equations. CBZ indicates carbamazepine.
†Most linear plot.
‡Second most linear plot.

monohydrate at time *t*, and *k* is the hydration rate constant.

The linearity of the plots of *g* applied to all models against hydration time was evaluated by the least squares method, as shown in **Table 2**. The best plot for the hydration of CBZ anhydrate was the 2-dimensional phase boundary equation (R2) based on the average of correlation coefficient constants at all temperatures, as shown in **Figure 3**. IP and *k* were evaluated from the x-intercept and slope of the plots by the least squares method and are summarized in **Figures 4** and **5**, respectively. The IPs of intact and surface-modified samples both decreased with increase of the reaction temperature, and the *k*'s increased with increase of the temperature. The *k* of the intact samples was significantly larger than that of the surface-modified samples at each temperature, while the IP for intact samples was shorter than that of surface-modified samples. This result indicated that the hydration of CBZ anhydrate consisted of a nuclei where *J* is the nuclei formation rate, $[N]_c$ is the critical nuclei concentration required to initiate crystal growth, and *B* is a constant.

Figure 6 shows the Arrhenius plot for the nucleation process for hydration of CBZ anhydrate. The nuclei formation rate constants of the intact sample were significantly larger than those of the surface-modified samples at each temperature. The E and the frequency coefficient constant (A) were calculated from the slope and y-intercept of the Arrhenius plot by least squares method; they are summarized in **Table 3**. The E of the nuclei formation process for the intact sample was about 2.8 times larger than that of the surface-modified samples, but the A was $10^{6.8}$ times larger. This result suggests that surface modification by n-butanol decreased both the A and the E of nuclei formation, with the effect on A much larger than the effect on E.

formation process as an induction period (initial stage) and a growth process of nuclei (later stage) and that the surface-modified treatment affected both of the processes and inhibited the hydration of CBZ.

Effect of Surface Modification on E for Nucleation and Crystal Growth Processes for Hydration of CBZ

When the nuclei formation process follows first-order kinetics, the nuclei formation rate takes the form of the following equations. Therefore, the nuclei formation rate constant is proportional to the inverse of IP.

$$[N]_c = const. \tag{2}$$

$$J = \frac{ln[N]_c}{IP} = \frac{B}{IP} \tag{3}$$

Figure 7 shows the Arrhenius plot for crystal growth of nuclei for hydration of CBZ anhydrate. The crystal growth rate constants of the intact sample were significantly larger than for surface-modified samples at each temperature. The E and A are summarized in **Table 3**. The E of crystal growth process for the intact sample was about 82% of that of the surface-modified sample, but the A was 3.6 times larger. This result suggested that the surface modification by n-butanol decreased the A of crystal growth but increased the E. These kinetic parameters indicated that the hydration mechanism of CBZ was not significantly changed by surface modification but the frequency of the reaction was significantly decreased. Water vapor was not able to adsorb on the surface, since the adsorbed alcohol on the surface-modified CBZ anhydrate formed a monolayer on the surface by n-butanol, via the hydroxyl group. Therefore, this adsorbed alcoholic layer

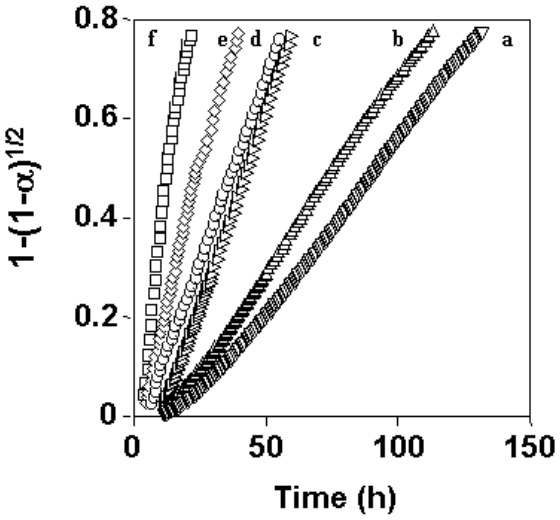

Figure 3. Effect of humidity and temperature on hydration kinetics of surface-modified anhydrate of CBZ at 97% RH. ○, ◇, □ intact CBZ; ▽, △, ▷ surface-modified CBZ; ○, ▽ at 30ºC; △, ◇ at 40ºC; □, ▽ at 50ºC.

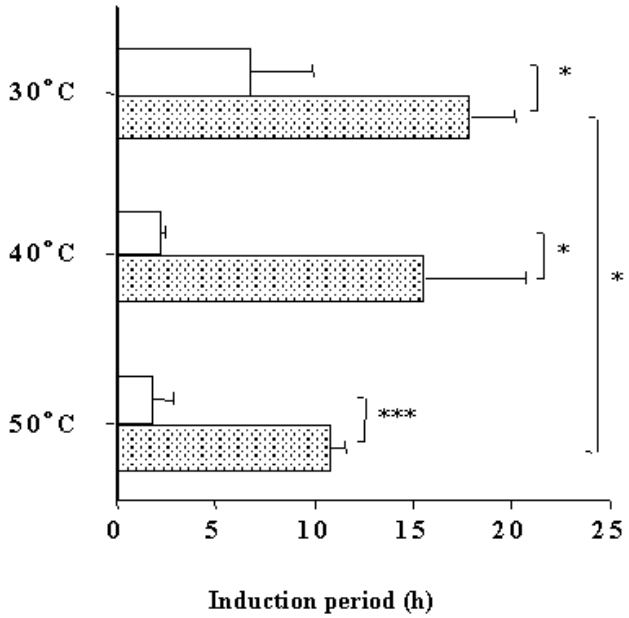

Figure 4. Effect of surface modification on IP of surface-modified anhydrate of CBZ at 97% RH. The open and closed bar represent intact and surface-modified CBZ. Line after each bar represents the SD (n = 3). Statistical analysis was performed by analysis of variance (*** $P < .005$; * $P < .05$).

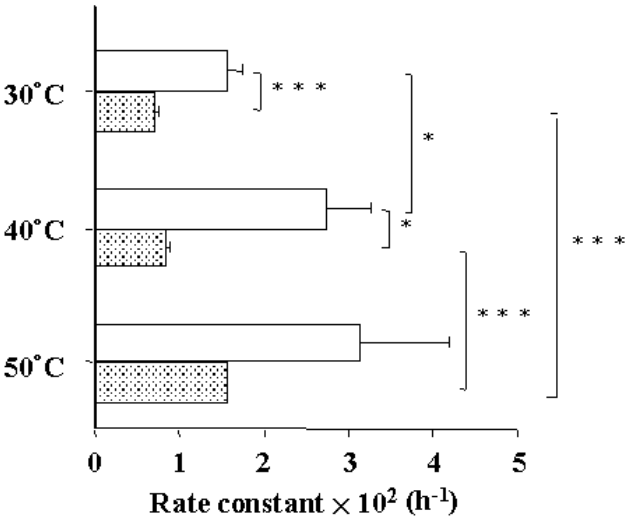

Figure 5. Effect of surface modification on the crystal growth rate constant of surface-modified anhydrate of CBZ at 97% RH. The open and closed bar represent intact and surface-modified CBZ. Line after each bar represents the SD (n = 3). Statistical analysis was performed by analysis of variance (*** $P < .005$; * $P < .05$).

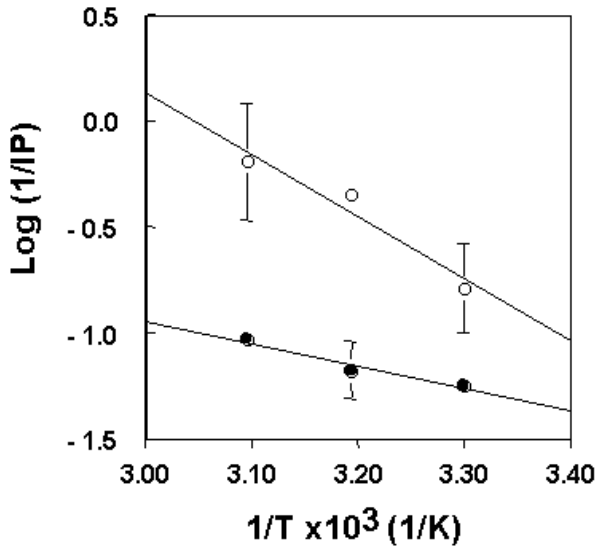

Figure 6. Effect of humidity on Arrhenius plot for nuclei formation process of surface-modified anhydrate of CBZ. ○, Intact CBZ; ●, surface-modified CBZ. Each bar represents the SD (n = 3).

Table 3. Kinetic Parameters for the Hydration of Surface-Modified CBZ Anhydrate Under High Humidity*

Sample	Process	E, kJ/mol	A, h^{-1}	*r*
Intact	Nuclei formation	56.3	$10^{8.96}$	0.804
Intact	Crystal growth	26.8	$10^{2.84}$	0.769
Modified	Nuclei formation	20.1	$10^{2.21}$	0.774
Modified	Crystal growth	32.5	$10^{3.40}$	0.937

*CBZ indicates carbamazepine; E, activation energy; A, frequency constant coefficient.

might inhibit the hydration process on the surface of anhydrate powder.

Dissolution Behavior of Surface-Modified CBZ Anhydrate Powders

Problems of side effects and bioavailability of CBZ preparations with respect to their dissolution rate have been reported.[9] Therefore, the dissolution test is an important factor for the evaluation of surface characteristics of nitrofurantoin bulk powder. **Figure 8** shows the effect of surface modification on dissolution of CBZ anhydrate. The dissolution profiles of

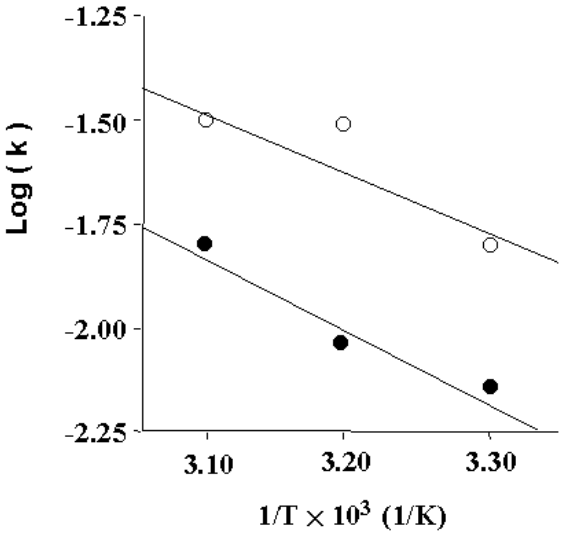

Figure 7. Effect of humidity on Arrhenius plot for crystal growth process of surface-modified anhydrate of CBZ. ○, Intact CBZ; ●, surface-modified CBZ. Each bar represents the SD (n = 3).

intact and surface-modified samples showed that the surface-modified sample dissolved faster than the intact sample at the initial stage. The surface-modified sample powder immediately sank in water. The intact powder floated on the liquid surface temporarily. In the previous study,[24] dissolution of surface-modified nitrofurantoin was slower than that of intact. The dissolution behavior of CBZ conflicted with that of nitrofurantoin. Form I CBZ powder immediately sank in water but the intact CBZ (Form II) did not, because Form II rapidly transformed into dihydrate on the water surface and formed a fine fiber crystal layer on the particle surface, but Form I transformed after it sank, since the transformation rate of Form II was much larger than that of Form I, as reported.[26] Since the surface-modified CBZ was stabilized in water by surface modification, it seemed that the transformation in water had started after the particles sank, as had happened with Form I CBZ. Therefore, the observation of flotation suggested that wettability of the surface-modified sample was different from that of the intact sample, since CBZ anhydrate had a hydrophobic surface due to phase transformation.

To quantitatively evaluate the dissolution process of the surface-modified sample, we assumed that the dissolution profiles followed the Hixon-Crowell equation (4).[27] The dissolution kinetics are based on the dissolution of monodispersed particle size powder under sink conditions.

$$W_0^{\frac{1}{3}} - W^{\frac{1}{3}} = R \bullet t \qquad (4)$$

where W_0 is the initial mass, W is the undissolved amount of drug at time t, and R is the dissolution rate constant.

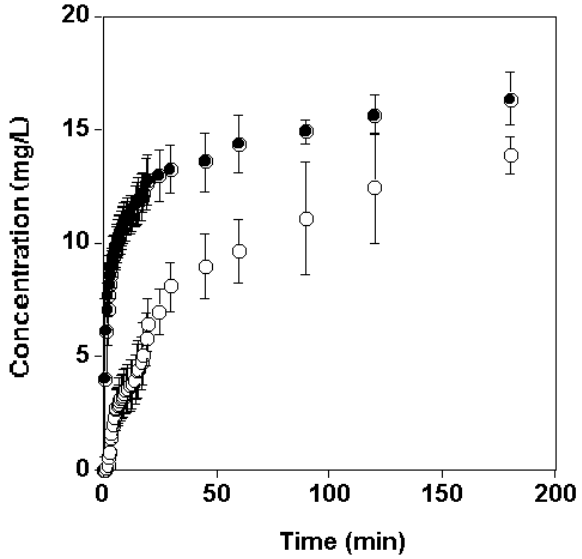

Figure 8. Dissolution profiles for surface-modified anhydrate of CBZ. ○ Intact CBZ; ●, surface-modified CBZ. Each bar represents the SD (n = 3).

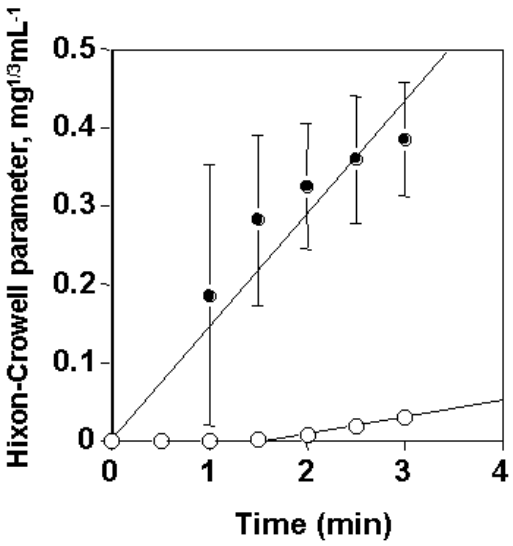

Figure 9. Hixon-Crowell plots for surface-modified anhydrate of CBZ under dynamic and static conditions. ○, Intact CBZ; ●, surface-modified CBZ. Each bar represents the SD (n = 3).

Figure 9 shows Hixon-Crowell plots for dissolution profiles of the intact and surface-modified samples. The plots of surface-modified anhydrate samples were linear. The dissolution rate constants for the intact and surface-modified samples were calculated to be 0.0102 ± 0.008 $mg^{1/3}\cdot min^{-1}$ and 0.1442 ± 0.0482 $mg^{1/3}\cdot min^{-1}$ by using the least squares method. The dissolution rate constant of the surface-modified sample was much larger than that of the intact sample. The profile of the intact sample had an induction period, but that of the surface-modified sample did not. The result indicated that wettability of the sample decreased because of surface modification of n-butanol. The absorbed n-butanol might form a monolayer on the surface of CBZ, but the surface became hydrophilic since n-butanol is water-soluble. Therefore, the surface-modified sample might have been easier to wet in water than the intact sample because CBZ anhydrate had a hydrophobic surface due to phase transformation, as explained above.

CONCLUSION

The surface-modified CBZ anhydrate was obtained by adsorption of alcohols. The crystallinity of the drug did not change after surface modification. The surface-modified anhydrate powders were more stable than the nonmodified samples under high humidity and showed resistance against moisture. However, surface modification induced rapid dissolution in water compared to the control. Since commercial drug preparations have fluctuations in the dissolution rate during the storage period at high humidity, the stability of surface-modified powders in high humidity may be an important factor in controlling the pharmaceutical properties of a preparation.

ACKNOWLEDGEMENTS

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