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International Journal of Pharmaceutics 321 (2006) 18–26

INTERNATIONAL JOURNAL OF PHARMACEUTICS

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Kinetic study of the transformation of mefenamic acid polymorphs in various solvents and under high humidity conditions

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Received 10 January 2006; received in revised form 30 March 2006; accepted 11 April 2006
Available online 12 May 2006

Abstract

The transformation kinetics of mefenamic acid form II to form I in three kinds of solvents and under high humidity conditions were extensively investigated. Form II crystals were suspended in water, 50% ethanol and ethanol at 28, 33 and 37 °C, or stored at 50, 60 and 70 °C at 97% RH. Form II transformed to form I under all storage conditions and the rate of transformation depended on the kind of solvent. The transformation followed the three-dimensional nuclei growth mechanism, depending on temperature. The nuclei formation and growth processes were significantly accelerated in ethanol compared with water. The addition of seed crystals of the stable form I shortened the both nuclei formation and growth processes and therefore the transformation was accelerated.

Keywords: Mefenamic acid; Polymorphism; Solid-state transformation; Kinetic analysis

1. Introduction

Polymorphs are solid crystalline phases of a drug compound, resulting from at least two different molecular arrangements of the compound in the solid state. The various physical properties of drugs showing polymorphism, for example, crystal habit, intermolecular interaction, particle density, thermodynamic activity, solubility, dissolution rate and chemical and physical stability, have been reported (Matsuda and Tatsumi, 1990; Otsuka and Matsuda, 1995; Singh et al., 1998; Ashizawa, 2001; Kushida and Ahizawa, 2002). The differences of physical properties may affect the reproducibility of the manufacturing process of dosage forms and their performance. In addition, the solubility can affect the drug absorption and therefore its bioavailability (Aguiar and Zelmer, 1969; Kokubo et al., 1987). The pharmaceutical applications of polymorphs have also been reviewed (FDA guidelines; Haleblian, 1975; Byrn et al., 1995).

Since polymorphs have different lattice energies, the more energetic ones seek to revert to the most stable or the latest energetic form. Hence, polymorphs can transform to other crystal forms during manufacturing processes, including grinding, kneading and tabletting (Summer et al., 1976,1977; Otsuka et al., 1997, 1999a,b, 2000; Zhang et al., 2002; Airaksinen et al., 2003). It is also widely known that the storage conditions, such as temperature, humidity or pharmaceutical excipients, affect the stability of metastable crystal forms (Matsuda and Kawaguchi, 1986; Matsuda and Tatsumi, 1990; Otsuka et al., 1993; Zhang et al., 2002; Tang et al., 2002). It is therefore important to characterize the polymorph and clarify the physicochemical properties of bulk drugs during the manufacturing processes and storage period.

Mefenamic acid is a non-steroidal anti-inflammatory drug and widely used as an antipyretic analgesic and antirheumatic drug. It has been reported that mefenamic acid has two polymorphs, forms I and II, and that they showed different solubility and stability. Form II exhibited higher solubility than form I in several solvents (Aguiar and Zelmer, 1969; Romero et al., 1999). The dissolution profile of form II showed supersaturation accompanying the decrease down to the solubility of form I due to the transformation to form I. Conversely, form I transformed to form II at high temperature (142.5–150 °C) and this transformation followed the zero-order reaction mechanism (Polany-Winger equation) (Umeda et al., 1985).

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doi:10.1016/j.ijpharm.2006.04.020

The purpose of this study was to more precisely investigate the stability of forms I and II at high humidity and in water and ethanolic suspensions, assuming the effect of the addition of kneading solvents in the granulation process. The kinetic transformation of form II to form I using several solid-state reaction models was also discussed.

2. Materials and methods

A bulk powder of mefenamic acid of JP grade was obtained from Yamamoto Chemical Co., Japan. Form I crystals were prepared by saturating 50 mL of acetone with an excess amount of the drug. The undissolved drug was filtered off and the saturated acetone solution was cooled slowly in an ice bath. This solution was left overnight, and the recrystallized crystals were filtered, washed with water and dried at room temperature. Form II crystals were prepared from an *N*,*N*-dimethylformamide solution of the drug (0.6 g/mL). After the crystals were dissolved in this solvent, the hot solution was cooled to $-40\,^{\circ}\mathrm{C}$. The solution was maintained at this temperature until most of the mefenamic acid was crystallized and then the crystals were filtered and dried at 70 °C. All other chemicals used were of analytical grade.

2.1. Powder X-ray diffraction analysis

Powder X-ray diffraction (XRD) profiles were taken with an X-ray diffractometer (RINT 2100 Ultima, Rigaku Co., Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 20 kV; current, 20 mA; receiving slit, 0.3 mm; scan range, 10°–30° (2θ); step size, 0.02°; scanning speed, 1°/min. About 50 mg of the sample powder was carefully loaded into a glass holder, and the sample surface was flattened softly to avoid particle orientation using a spatula and glass plate and then the sample weight was accurately measured. The calibration curve for quantification of the content of form II was established based on the total intensity of the highest four independent diffraction peaks, which were normalized against the sample weight.

2.2. Thermal analysis

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

2.3. Scanning electron microscopy (SEM)

The samples were coated with gold in an ion sputter JFC-1100 (Jeol Datum Co., Japan), and photomicrographs of samples were taken with a scanning electron microscope (model JSM-5200LV, Jeol Datum Co., Japan).

2.4. Storage conditions

The stability under two storage conditions was evaluated as follows. The samples (each 2 g) were suspended in 20 mL of distilled water, 50% ethanol or pure ethanol. They were stored at 28, 33 and 37 °C in a constant temperature water bath (Incubator M-100, Taiyo Scientific Industrial Co., Japan) at a shaking speed of 60 spm. Small amount of samples of suspension were withdrawn at suitable time intervals and then immediately filtered and dried under vacuum at room temperature. Other 2 g samples were stored at 50, 60 and 70 °C at 97% RH controlled with aqueous saturated solution of K_2SO_4.

2.5. Solubility studies

The solubilities in water, 50% ethanol and ethanol were determined at 40 °C. An excess amount of solid sample was weighed and then placed in a 50 mL screw-capped vial. Afterwards, 50 mL of each solvent was added to vials and they were tightly capped. The vials were shaken at 75 spm in a water bath for 24 h. The concentration of mefenamic acid dissolved was measured at 347.0 nm with a UV spectrophotometer (UV-160A, Shimadzu Co., Japan) after filtering through a 0.45 μm membrane filter (DISMIC, PTFE, ADVANTEC, Japan).

2.6. Kinetic analysis of the transformation

The kinetic transformation was analyzed based on nine kinds of solid-state reaction models, as shown in Table 1 (Hancock and Sharp, 1972; Kaneniwa et al., 1985). The kinetic equation for form II remaining involves the function $f(x)$, and its integrated form is the function $g(x)$ ($x = 0.05$–0.95) where x is the fraction at time t. The model providing the best fit was selected based on the statistical parameter, the correlation coefficient r, to most closely represent the kinetics of the transformation process.

Table 1
Kinetic equations for the most common mechanism of solid-state reactions

Symbol	$g(x)$	Mechanism
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)

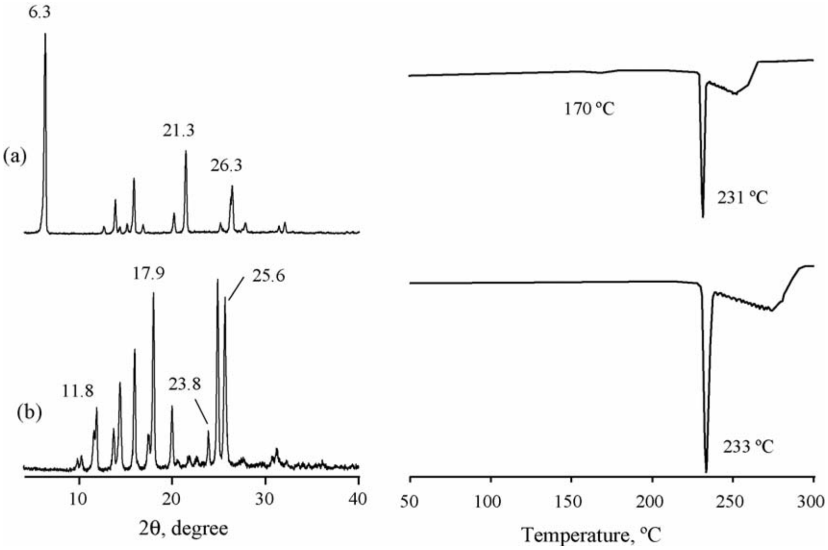

Fig. 1. Powder X-ray diffraction patterns and DSC profiles of forms I and II: (a) form I; (b) form II.

3. Results and discussion

3.1. Physicochemical characterization of forms I and II

Fig. 1 shows the XRD patterns and DSC profiles of forms I and II. The characteristic XRD peaks of form I were observed at 6.3°, 21.3° and 26.3° (2θ), while those of form II were observed at 11.8°, 17.9°, 23.8° and 25.6° (2θ). These results coincided with those reported previously (Aguiar and Zelmer, 1969). Therefore, the quantitative analysis was performed by using these peak intensities of form II. DCS profiles of form I showed two endothermic peaks at 170 and 231 °C due to the transformation to form II and the melting of form II, respectively (Umeda et al., 1985). Form II exhibited only an endothermic peak at 233 °C due to the melting of form II. Fig. 2 shows SEM photographs of forms I and II crystals. Forms I and II crystals were stick- and cube-shaped particles, respectively, indicating that they were quite different in their particle morphology.

3.2. The effect of the kind of suspension medium on the transformation of forms I and II

Form I did not show any morphological change during suspension under any storage conditions. It is therefore indicative that form I was stable in this study. Fig. 3 shows powder XRD patterns of form II after being suspended in water at 28 °C. The main diffraction peaks attributable to form II (as indicated with open triangles) decreased and those of form I (shown with closed triangles) increased with the elapse of suspension time. The percent remaining calculated from the diffraction intensity of form II after each suspension time were (a) 101%, (b) 82%, (c) 40% and (d) 0.1%, suggesting that form II crystals gradually transformed to form I. Fig. 4 shows the percent remaining and SEM photomicrographs of form II after being suspended in various suspension media. There were significant differences in the transformation rate among these media. The results of transformation of form II in various media at different temperatures suggested that the transformation rate of form II increased with the rise of temperature and concentration of ethanol; it took about 0.5 h to transform to form I in ethanol, whereas it took more than 400 h in water at 28 °C. Moreover, the results of SEM

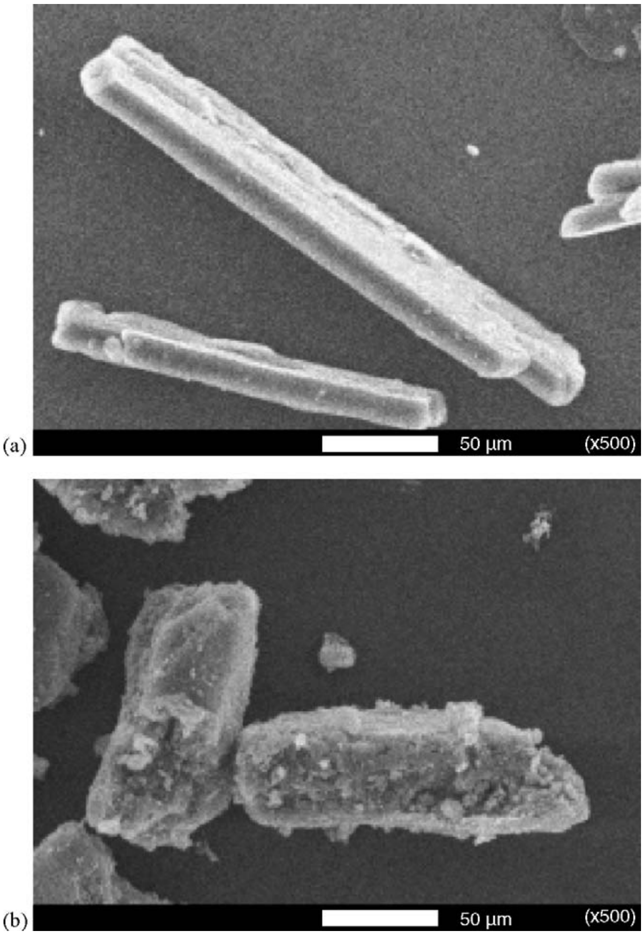

Fig. 2. SEM photographs of forms I and II: (a) form I; (b) form II.

photomicrographs revealed that the transformation of form II progressed in a three-dimensional direction.

3.3. Kinetic interpretation of form II to form I

Kinetic analysis was carried out using nine solid-state reaction models, shown in Table 1. Fig. 5 shows the plots of $g(x)$ applied to the A3, R3 and D3 models against time for the content of form II suspended in suspension media. The results of the fitting of transformation kinetic models evaluated by the least-squares method (Table 2) suggested that the A3 model exhibits the best correlation (0.990, 0.969 and 0.998 at 28, 33 and 37 °C, respectively). These results also suggested that form II transformed to form I following the three-dimensional growth of nuclei mechanism. The fact that the x-axis intercepts were observed under any storage conditions also strongly suggested that the transformation consisted both of nuclei formation process during the induction period (initial stage) and nuclei growth process at later stage. Thus, the induction period and rate constant of the nuclei growth process were calculated from the intercept and slope of the line, respectively. The rate constant in the nuclei formation process was calculated as the reciprocal of the induction period (Otsuka et al., 2002). Tables 3 and 4 show the kinetic parameters for nuclei formation and nuclei growth processes thus obtained. In ethanol, the nuclei formation rate constant was almost the same regardless of the temperature, while the nuclei growth rate constant was accelerated with the rise of temperature. The transformation rate constant in ethanol depended on the nuclei growth process and temperature. On the other hand, both the nuclei formation and the nuclei growth rate constant were accelerated with the rise of temperature in water and 50% ethanol. The nuclei formation and nuclei growth rate constants in ethanol were about 1430 and 570 times greater than those in water and 50% ethanol at 37 °C, respectively. These results suggested that the transformation of form II was by far faster in ethanol than in water.

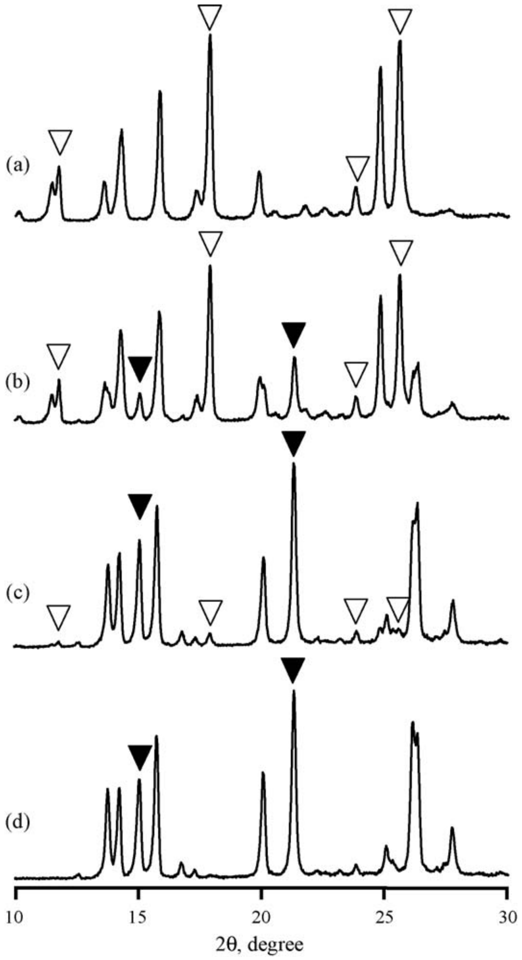

Fig. 3. Change of powder X-ray diffraction patterns of form II after being suspended in water at 28 °C: (a) 120 h; (b) 192 h; (c) 312 h; (d) 456 h. Closed and open triangles represent the characteristic peaks attributable to forms I and II, respectively.

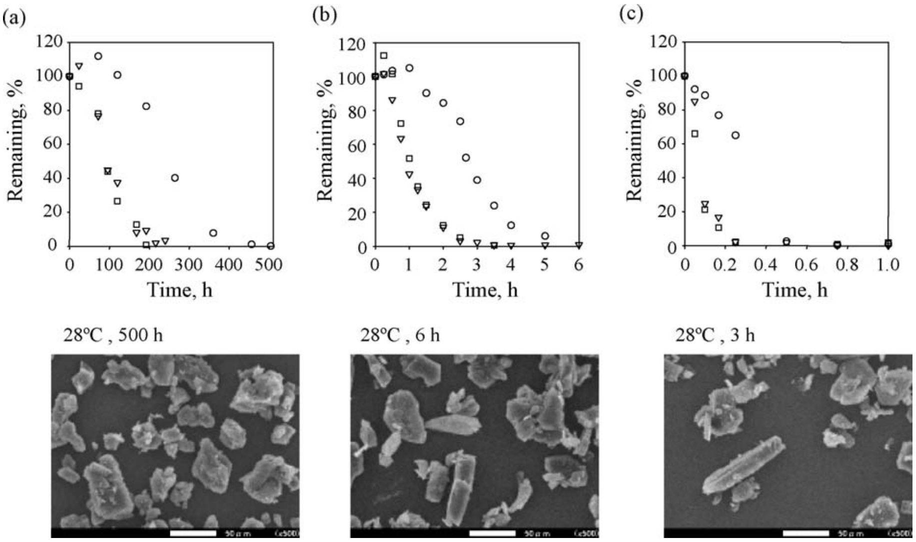

Fig. 4. Percent remaining and SEM photographs of form II after being suspended in water, 50% ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (◯) 28 °C; (▽) 33 °C; (□) 37 °C.

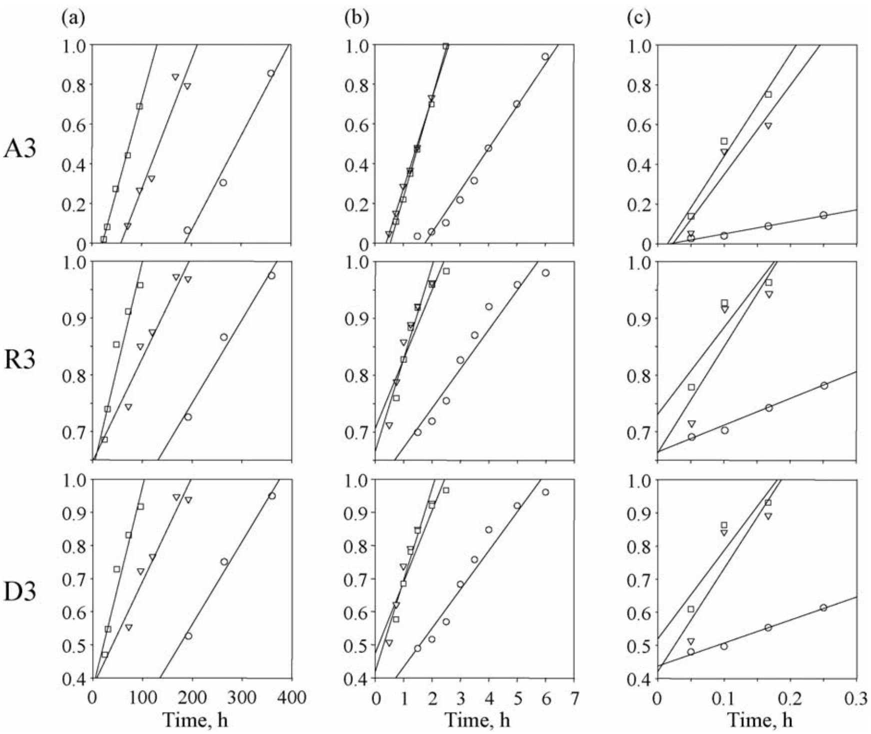

Fig. 5. Dependence of the function $g(x)$ on time for the content of form II suspended in water, water–ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (○) 28 °C; (▽) 33 °C; (□) 37 °C.

Table 2
Correlation coefficients of plots of $g(x)$ against the transformation time of form II

Function, $g(x)$	Temperature (°C)								
	Water			50% Ethanol			Ethanol		
	28	33	37	28	33	37	28	33	37
A3	0.990	0.969	0.998	0.990	0.932	0.977	0.988	0.999	0.999
R3	0.988	0.954	0.960	0.993	0.879	0.912	0.969	0.958	0.944
D3	0.993	0.993	0.970	0.992	0.885	0.919	0.975	0.969	0.955

Table 3
Rate constants for the nuclei formation process of form II and that of form II + 1% form I seed crystals

Temperature (°C)	Nuclei formation process					
	Form II			Form II + form I		
	Water	50% Ethanol	Ethanol	Water	50% Ethanol	Ethanol
28	5.37×10^{-3}	5.66×10^{-1}	5.66×10	2.85×10^{-2}	1.68	7.31×10
33	1.71×10^{-2}	2.48×10^{-1}	4.35×10	4.75×10^{-2}	3.99	3.08×10^{2}
37	4.76×10^{-2}	2.71×10^{-1}	6.87×10	7.55×10^{-2}	4.10	1.33×10^{2}

Table 4
Rate constants for the nuclei growth process of form II and that of form II + 1% form I seed crystals

Temperature (°C)	Nuclei growth process					
	Form II			Form II + form I		
	Water	50% Ethanol	Ethanol	Water	50% Ethanol	Ethanol
28	4.76×10^{-3}	2.13×10^{-1}	6.03×10^{-1}	5.76×10^{-3}	4.58×10^{-1}	7.44
33	6.51×10^{-3}	4.52×10^{-1}	4.51	8.84×10^{-3}	6.69×10^{-1}	7.27
37	9.10×10^{-3}	4.99×10^{-1}	5.15	1.58×10^{-2}	1.07	1.40×10

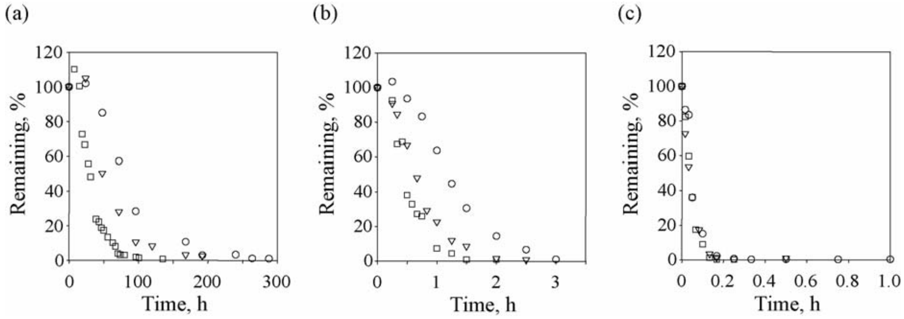

Fig. 6. Percent remaining of form II with the addition of 1% form I seed crystal after being suspended in water, 50% ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (○) 28 °C; (▽) 33 °C; (□) 37 °C.

Table 5
Correlation coefficients of plots of $g(x)$ against the transformation time of form II + 1% form I seed crystals

Function, $g(x)$	Temperature (°C)								
	Water			50% Ethanol			Ethanol		
	28	33	37	28	33	37	28	33	37
A3	0.988	0.979	0.991	0.994	0.995	0.979	0.971	0.999	0.991
R3	0.921	0.953	0.944	0.968	0.962	0.938	0.921	0.995	0.949
D3	0.934	0.956	0.951	0.977	0.969	0.951	0.930	0.997	0.957

3.4. Relationship between solubility and transformation rate of form II

The growth of crystal is a phase transformation from liquid to solid state. The solubilities of mefenamic acid in suspension media used in this study were investigated. The solubility of the drug in water, 50% ethanol and ethanol at 40 °C were 0.08 ± 0.01, 23.04 ± 1.22 and 1045.2 ± 32.7 mg/100 mL, respectively. These results supported that the transformation rate depended on the solubility of mefenamic acid in the suspending medium. Therefore, the transformation of form II to form I can be explained as the process where form II crystals partially dissolved in the medium and were subsequently crystallized as the stable form I.

3.5. Effect of the addition of seed crystals on the transformation of form II to form I in various suspension media

In order to clarify the behavior of nuclei for the transformation of form II to form I, the effect of the addition of 1% (w/w) form I seed crystals was examined.

Fig. 6 shows the percent remaining of form II in the presence of 1% form I crystals after being suspended in water, 50% ethanol and pure ethanol. The transformation was accelerated by adding seed crystals under all suspended conditions. The results of fitting transformation models of form II are summarized in Table 5. In this table, the best correlation was obtained for the three-dimensional nuclei growth equation. The kinetic parameters for nuclei formation and growth processes of form II with the seed crystals are shown in Tables 3 and 4. The rate constants of both nuclei formation and growth processes in the presence of 1% form I seed crystals were larger than those without seed crystals. The rate constants in the nuclei formation and growth processes in ethanol were about 10^4 and 10^3 times larger than those in water, respectively. The addition of form I crystals contributed not only to the rate constant of nuclei formation, but also that of nuclei growth process, indicating the increase of both parameters under all conditions. In particular, the rate constants of both nuclei formation and growth processes at 37 °C were significantly larger than those at lower temperatures and the transformation was much accelerated at high temperatures. Since the transformation mechanism followed the A3 model, these results suggested that the

Table 6
Activation energies for nuclei formation and growth processes for form II and those of form II + 1% form I seed crystals

	Nuclei formation process (kJ/mol)		Nuclei growth process (kJ/mol)	
	Form II	Form II + form I	Form II	Form II + form I
Water	135.2	60.4	37.7	61.0
50% Ethanol	106.4	60.7	57.3	51.6
Ethanol	6.7	53.3	145.5	34.0

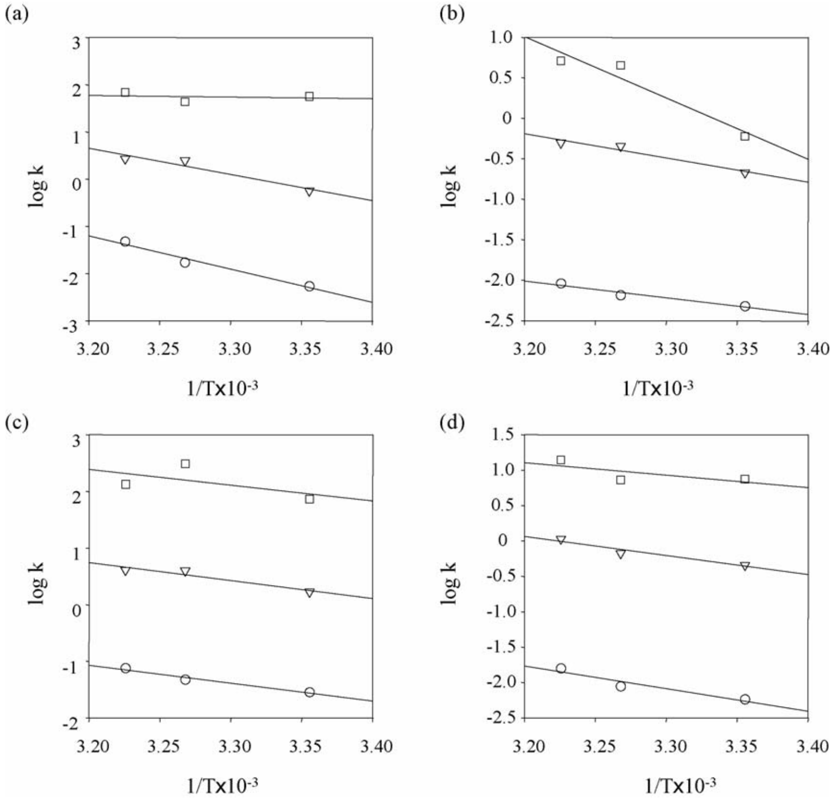

Fig. 7. Arrhenius plots for nuclei formation and growth processes of form II and those of form II + 1% form I seed crystals. Form II: (a) nuclei formation process; (b) nuclei growth process. Form II + 1% form I: (c) nuclei formation process; (d) nuclei growth process. (○) water; (▽) 50% ethanol; (□) ethanol.

addition of seed crystals mainly affected the nuclei formation process.

3.6. Arrhenius plots for nuclei formation and nuclei growth processes

Fig. 7 shows the Arrhenius plots for nuclei formation and nuclei growth processes of form II and form II containing 1% form I seed crystals. The transformations of both form II and form II containing form I exhibited a good correlation on the plots. These transformation rate constants clearly depended on the temperature during suspending period. Thus, the activation energies for transformation of form II to form I were calculated and listed in Table 6. The addition of form I seed crystals significantly decreased the activation energy of the nuclei formation process and thus the transformation was accelerated by the adding of seed crystals in water and 50% ethanol system. Conversely, the transformation accelerated due to great reduction of the activation energy of nuclei growth process in the ethanol system.

3.7. Effect of humidity on the transformation of form II to form I

From the results described above, it is easily estimated that form II may be possibly be transformed to form I under ambient humidity conditions. Fig. 8 shows the percent remaining of form II stored at 97% RH. It took more than 30 and 20 days to transform to form I at 60 and 70 °C, respectively. Fig. 9(a) shows the plots of $g(x)$ described by the A3 model (Avrami equation) against time during the storage of form II. The linearity of plots of the equation calculated by the least-squares method showed good correlation. On the other hand, for the other models (R3 and D3) the intercepts of the y-axis were positive, suggesting that the values of the induction period would be negative. Therefore the R3 and D3 models were not applicable

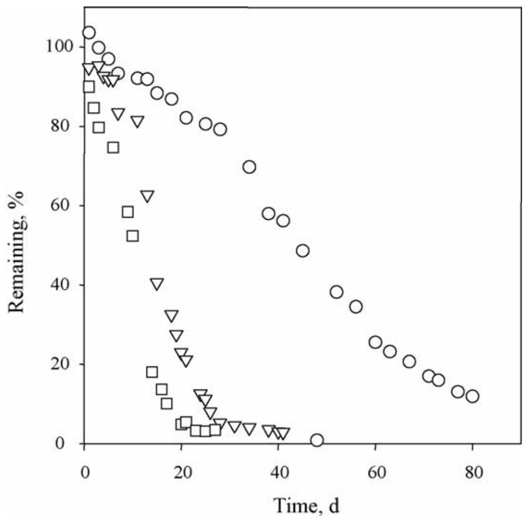

Fig. 8. Percent remaining of form II at 97% RH: (○) 50 °C; (▽) 60 °C; (□) 70 °C.

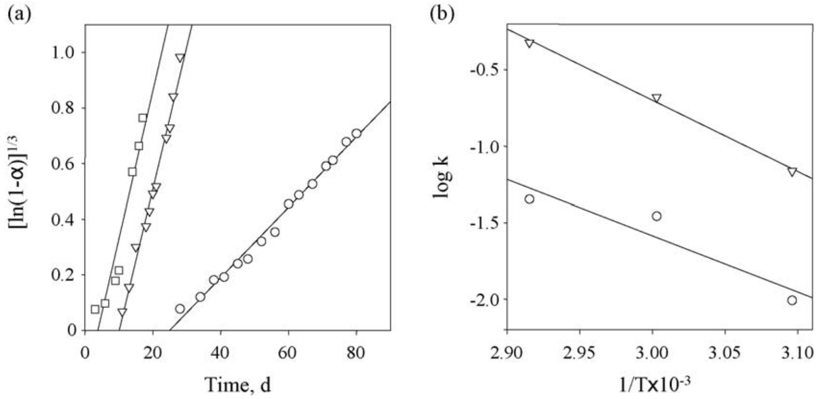

Fig. 9. A3 plots of form II (a) and the Arrhenius plots for nuclei formation and growth processes of form II (b) at 97% RH. (a): (○) 50 °C; (▽) 60 °C; (□) 70 °C; (b): (○) nuclei formation process; (▽) nuclei growth process.

to this system. The rate constants of the nuclei formation process at 50, 60 and 70 °C were 0.040, 0.099 and 0.262 h^{-1}, and the rate constants of nuclei growth processes were 0.013, 0.051 and 0.053 h^{-1}, respectively. The Arrhenius plots of the rate constants for the nuclei formation and nuclei growth processes at various temperatures are summarized in Fig. 9(b). It also showed good correlation on the plots, suggesting the temperature dependency for the transformation of form II. The activation energies for the nuclei formation and nuclei growth processes calculated were 86.6 and 66.7 kJ/mol, respectively. From the results of the suspension system, the transformation of form II at high humidity would also be accelerated by adding seed crystals.

4. Conclusions

When incorporating metastable polymorph crystals in the dosage forms, it is essential to investigate the stability of this crystalline form to ensure pharmaceutical quality and bioavailability. Form II crystals have higher solubility than that of form I and it is therefore preferable to use form II for pharmaceutical preparations. However, from the results of the present study, form II transformed to the stable form I, following the three-dimensional nuclei reaction mechanism under all storage conditions. Furthermore, the transformation was accelerated with the elevation of temperature, by adding seed crystals of form I (1%). The transformation rate depended on the solubility in the suspending media used.

Since the temperature of these samples is elevated to some extent under mechanical conditions during the grinding, kneading and drying processes, the transformation may be accelerated. Also, the transformation would surely be accelerated if a small amount of form I crystals are intermixed in the bulk samples. It is therefore concluded that attention is necessary during the wet granulation process of metastable crystalline drug.

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