

Fig. 4. Powder X-ray diffractometry (PXRD) patterns of TAM fumarate prepared with TAM and fumaric acid (1:1 and 2:1) on a large scale. Solid line (—), TAM fumarate form A; dotted line (---), TAM fumarate form B.

isopropyl alcohol, 2:1 (tamoxifen/L-tartaric acid) in isopropyl ether, 2:1 (tamoxifen/fumaric acid) in acetonitrile, 2:1 (tamoxifen/citric acid) in ethyl acetate, and 2:1 (tamoxifen/succinic acid) in acetone. Fumaric acid as a counter acid was detected in the well in a molar ratio of 1:1 (tamoxifen/fumaric acid) in toluene.

The Raman spectra of crystals in the wells with combinations of tamoxifen and fumaric acid are shown in Fig. 2. The Raman spectra of F1 in molar ratios of 1:1 and 2:1, as presented in Table I, showed the same patterns with distinct peaks at 1595 and 1638  $\text{cm}^{-1}$ . The Raman spectra of F2 in molar ratios of 1:1 and 2:1 showed the same patterns with distinct peaks at 1596, 1618, and 1637  $\text{cm}^{-1}$ . These results suggested that these crystals were identified as tamoxifen fumarate because their spectra were different from the spectra of either free base with a distinct peak at 1613  $\text{cm}^{-1}$  or fumaric acid with the distinct peak at 1686  $\text{cm}^{-1}$ .

The Raman spectra of the crystals in the wells with combinations of tamoxifen and citric acid are shown in Fig. 3. Raman spectra of C1 in molar ratios of 1:1 and 2:1, as

presented in Table I, showed the same patterns with distinct peaks at 1595 and 1635  $\text{cm}^{-1}$ . Raman spectra of C2 in molar ratios of 1:1 and 2:1 showed the same patterns with the distinct peaks at 1598 and 1608  $\text{cm}^{-1}$ . These results suggested that these crystals were identified as tamoxifen citrate because their spectra were different from the spectra of either free base with a distinct peak at 1613  $\text{cm}^{-1}$  or citric acid with distinct peaks at 1693 and 1735  $\text{cm}^{-1}$ .

These results indicated that tamoxifen would prefer to form salts in a 1:1 molar ratio (tamoxifen/polybasic acid), and the excess amount of nonsalt-forming tamoxifen free base tended to be detected in the rows of the plate displaying a binary mixture of tamoxifen and polybasic acid in a molar ratio of 2:1.

#### Characterization of Salts by Scaled-Up Preparation

Tamoxifen fumarate and citrate prepared on a 300-mg scale were characterized using PXRD and ion chromatogra-

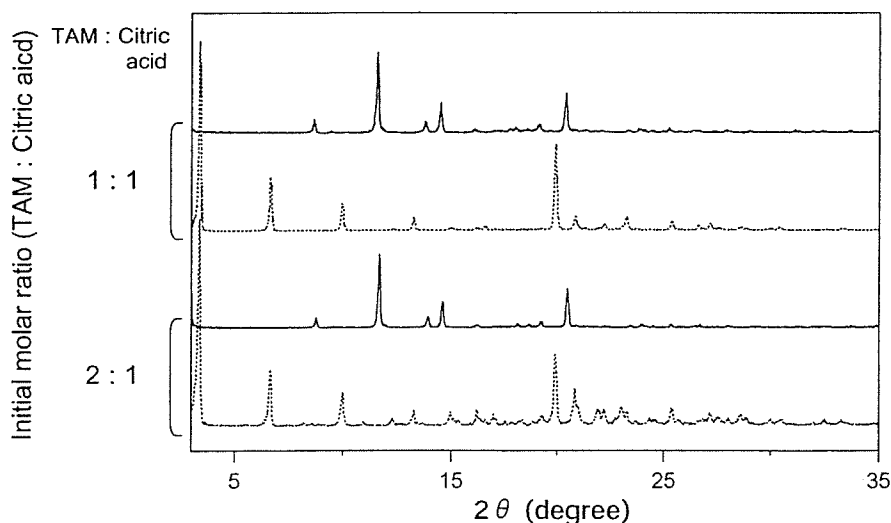


Fig. 5. PXRD patterns of TAM citrate prepared with TAM and citric acid (1:1 and 2:1) on a large scale. Solid line (—), TAM citrate form A; dotted line (---), TAM citrate form C.

phy. Tamoxifen fumarate prepared in molar ratios of 1:1 or 2:1 (tamoxifen/fumaric acid) was recrystallized in 12 solvents, and two crystalline forms were detected by PXRD in each preparation. PXRD patterns of these crystalline forms assigned as forms A and B, which were prepared in a 1:1 molar ratio, were confirmed to be the same as forms A and B prepared in a 2:1 molar ratio, respectively (Fig. 4). Ion chromatography indicated that the molar ratios of fumaric acid to tamoxifen free base were 1.02 and 1.03 for tamoxifen fumarate prepared in molar ratios of 1:1 and 2:1 (tamoxifen/fumaric acid), respectively. These results clearly suggested that crystals obtained were tamoxifen monofumarate.

Tamoxifen citrate was prepared in the same manner as tamoxifen fumarate, and at least two crystalline forms were detected by PXRD. Because forms A and B were the forms already reported (36), the new form was designated as form C. The PXRD patterns of the two crystalline forms assigned as forms B and C, which were prepared in a 1:1 molar ratio, were found to be the same as forms B and C prepared in a 2:1 molar ratio, respectively (Fig. 5). Ion chromatography indicated that the molar ratios of citric acid to tamoxifen were 1.01 and 0.99 for tamoxifen citrate prepared in molar ratios of 1:1 and 2:1 (tamoxifen/citric acid), respectively. These results suggested that the crystals obtained were tamoxifen monocitrate.

Characterization of the salts produced in the scaled-up preparation gave the same stoichiometrical information on tamoxifen fumarate and citrate salts as salt screening using the 96-well plates. These results suggested that salt screening with the 96-well plates would provide not only potential polymorph information but also prediction of stoichiometrical information on the salts.

## DISCUSSION

We have first demonstrated that salt screening using multiwell plates and a Raman microscope can suggest stoichiometrical information on polyprotic salts. Salt screening using multiwell plates could be satisfactorily performed with less than 100 mg of drug candidate, and stoichiometrical information was easily obtained by comparing the Raman spectra of a drug candidate in the free base and counter acid condition, the free acid and counter base condition, and the salts found on the multiwell plates.

In the process of drug development, Raman microscopes have been widely used as an analytical tool for the chemical and physical identifications of either or both drugs and contaminants within pharmaceutical systems, which is also referred to as mapping of the dosage form (37,38). Physical indication, focusing on polymorph detected by Raman microscopy in place of PXRD, has been increasingly reported over the last few years (39). Attention has been also drawn to polymorphic evaluation by Raman microscopy of salt and polymorph screening of pharmaceutical drug molecules (22,24). However, to the best of our knowledge, chemical information obtained by Raman microscopy was not discussed.

In salt screening with Raman microscopy, it is possible to detect drug molecules, counter acids/bases, and salts individually. In salt formation of ionic drug molecules with polyprotic counterions, it is possible to form salt in more than one

stoichiometric combination. Some ionic drug candidates form only one stoichiometric salt in combination with some polyprotic counterions, such as mono salt, and the other candidates form several combinations of salts, such as mono and hemi salts. In the crystalline form selection process, possible salts in various combinations should be prepared on a large scale and subsequently characterized because each combination of salt would show different physical properties (40). Therefore, it is important to obtain stoichiometrical information for efficient preparation of polyprotic salts.

The case that an ionic drug candidate formed only hemi salt with polyprotic counterion in salt screening has been previously reported (25). In the report, sertraline hemi-L-tartrate was obtained in 1:1 molar ratio (sertraline/L-tartaric acid); however, only polymorphism of salts was discussed, and stoichiometrical information of sertraline L-tartrate on multiwell plate was not fully elucidated (25). In this study, we performed tamoxifen salt screening on multiwell plate, and free base, counter acids, and salts could be identified by Raman microscope to obtain stoichiometrical information. Combining the information of Raman spectra of all crystals on multiwell plate, we could predict salt formation and stoichiometrical information of polybasic acid salts in addition to polymorph information. As the analytical tools for crystalline form selection, PXRD gives physical information and Raman microscopy provides both physical and chemical information. Physical information suggests the crystallinity and existence of polymorphism, whereas chemical information suggests salt formation and stoichiometrical combination of polyprotic salts. Therefore, Raman microscopy would be another useful analytical tool for salt screening, and further investigation for screening may be expected to expand.

In addition to salt screening for ionic drug candidates, cocrystals have been recently investigated as a pharmaceutical development option for neutral drug candidates (18,41). Cocrystals, categorized as multicomponent crystals such as solvate and salt, have the potential to improve drug candidate properties. Cocrystal preparations by melt crystallization, grinding, and recrystallization from solvents have been reported (11,41,42). Cocrystal screening could be performed with drug candidates and pharmaceutically acceptable excipients on multiwell plates. Cocrystal screening using Raman microscopes will also provide effective information for scaled-up preparation because there would be numerous stoichiometrical combinations with drug candidates and excipients.

In conclusion, our investigation enabled the successful development of salt screening methodology by using a Raman microscope, providing information on salt formation and stoichiometrical combinations of polyprotic salts, as well as polymorphism. Stoichiometrical information of polyprotic salts with small amount of drug candidate allows efficient crystalline form selection process by saving bulk.

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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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## 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.

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**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; Haleblan, 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 tableting (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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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  $-40^{\circ}\text{C}$ . The solution was maintained at this temperature until most of the mefenamic acid was crystallized and then the crystals were filtered and dried at  $70^{\circ}\text{C}$ . 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,  $10^{\circ}$ – $30^{\circ}$  ( $2\theta$ ); step size,  $0.02^{\circ}$ ; scanning speed,  $1^{\circ}/\text{min}$ . 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,  $10^{\circ}\text{C}/\text{min}$ ;  $\text{N}_2$  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  $37^{\circ}\text{C}$  in a constant temperature water bath (Incubator M-100, Taiyo Scientific Industrial Co., Japan) at a shaking speed of 60 rpm. 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  $70^{\circ}\text{C}$  at 97% RH controlled with aqueous saturated solution of  $\text{K}_2\text{SO}_4$ .

### 2.5. Solubility studies

The solubilities in water, 50% ethanol and ethanol were determined at  $40^{\circ}\text{C}$ . 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 rpm 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  $0.45\ \mu\text{m}$  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 (Polanyi-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 (Ginstling-Brounshtein equation)

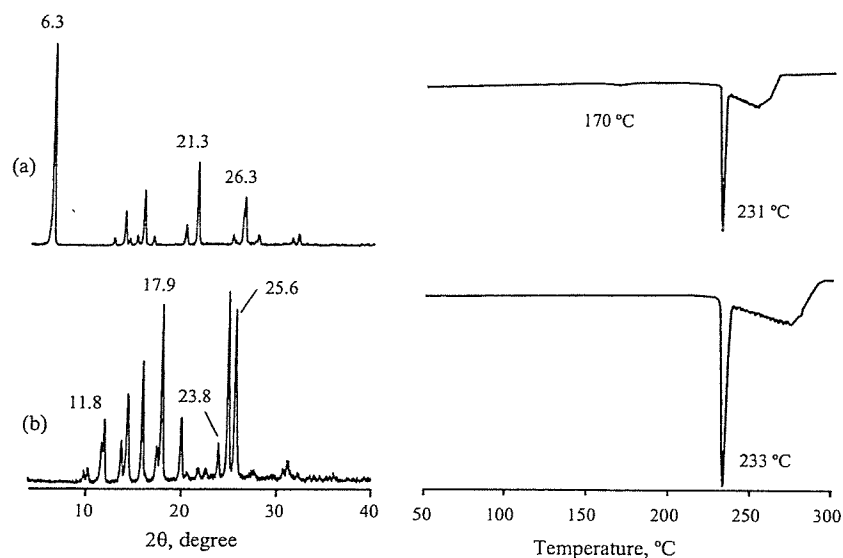


Fig. 1. Powder X-ray diffraction patterns and DSC profiles of forms I and II: (a) form I; (b) form II.

### 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  $6.3^\circ$ ,  $21.3^\circ$  and  $26.3^\circ$  ( $2\theta$ ), while those of form II were observed at  $11.8^\circ$ ,  $17.9^\circ$ ,  $23.8^\circ$  and  $25.6^\circ$  ( $2\theta$ ). 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. DSC profiles of form I showed two endothermic peaks at 170 and  $231^\circ\text{C}$  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  $233^\circ\text{C}$  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  $28^\circ\text{C}$ . 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 trans-

formation 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  $28^\circ\text{C}$ . Moreover, the results of SEM

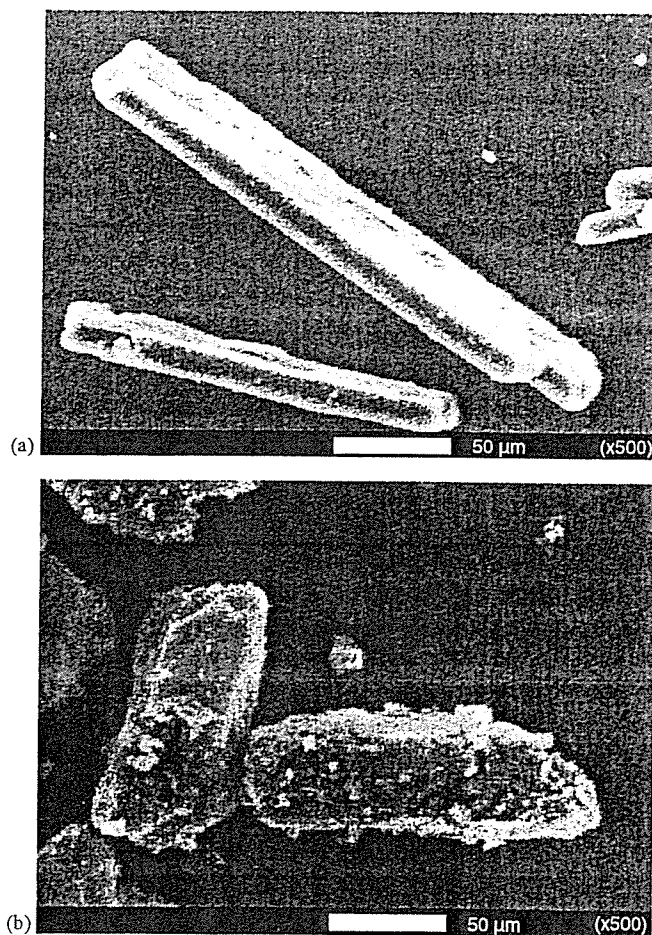


Fig. 2. SEM photographs of forms I and II: (a) form I; (b) form II.

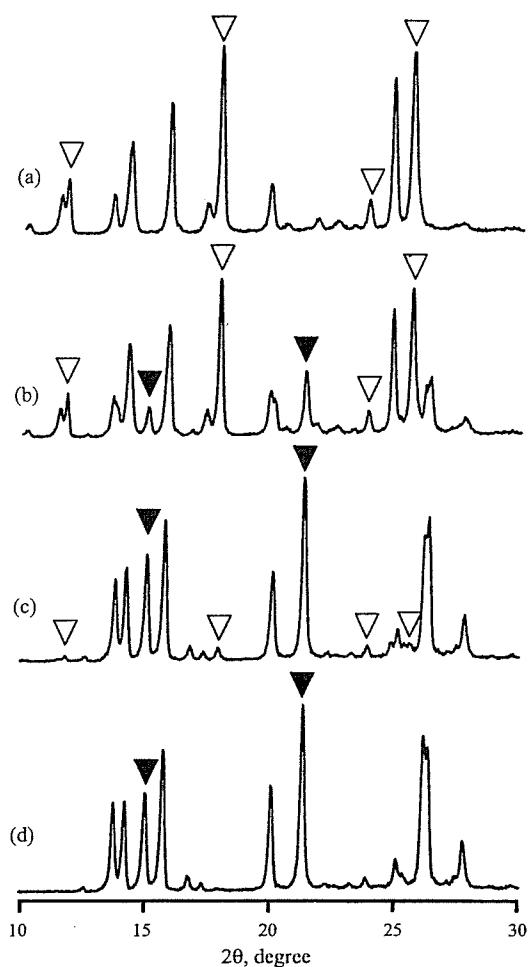


Fig. 3. Change of powder X-ray diffraction patterns of form II after being suspended in water at 28°C: (a) 120 h; (b) 192 h; (c) 312 h; (d) 456 h. Closed and open triangles represent the characteristic peaks attributable to forms I and II, respectively.

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.

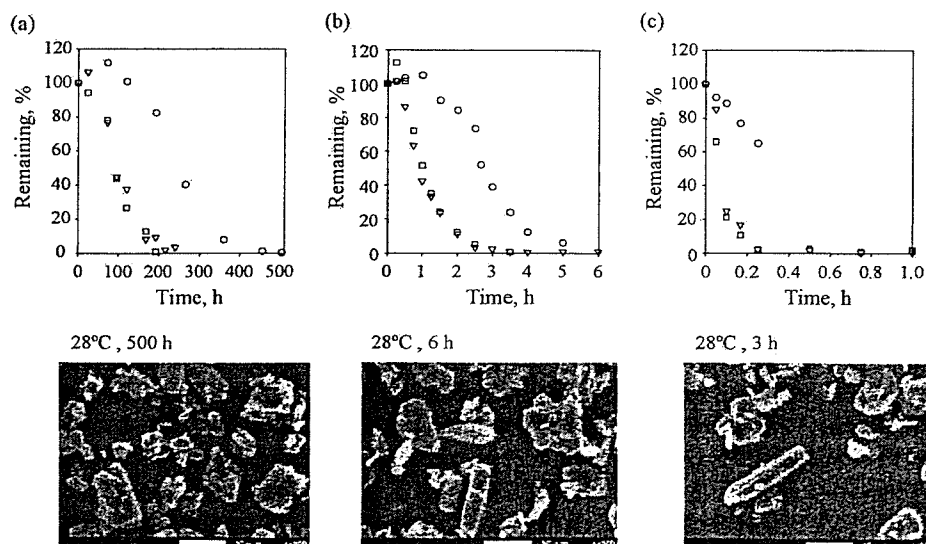


Fig. 4. Percent remaining and SEM photographs of form II after being suspended in water, 50% ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (○) 28°C; (▽) 33°C; (□) 37°C.

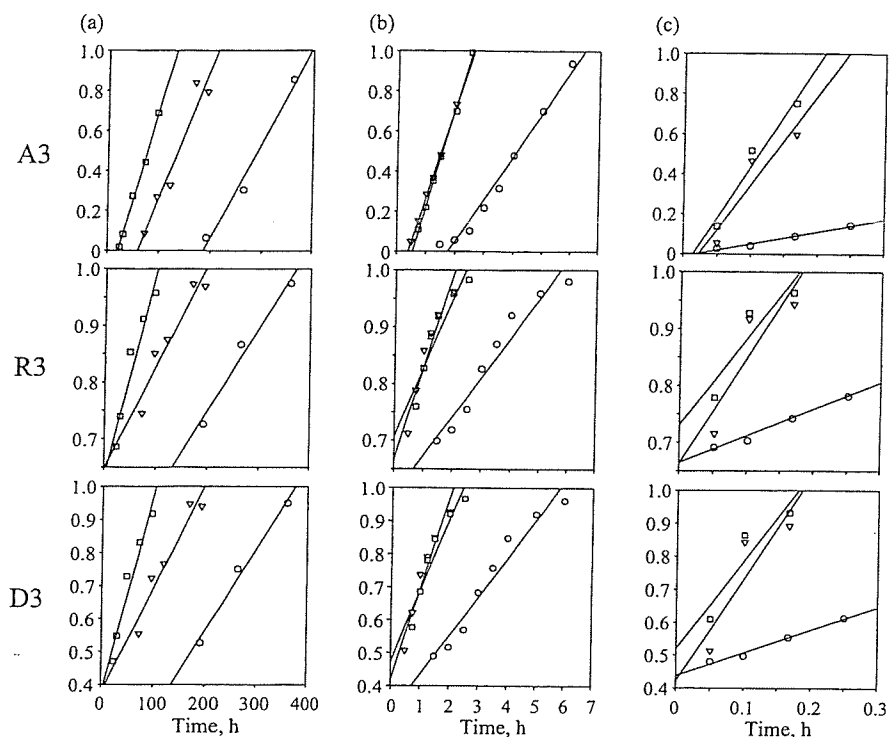


Fig. 5. Dependence of the function  $g(x)$  on time for the content of form II suspended in water, water-ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (○) 28 °C; (▽) 33 °C; (□) 37 °C.

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	$5.37 \times 10^{-3}$	$5.66 \times 10^{-1}$	$5.66 \times 10$	$2.85 \times 10^{-2}$	1.68	$7.31 \times 10$
33	$1.71 \times 10^{-2}$	$2.48 \times 10^{-1}$	$4.35 \times 10$	$4.75 \times 10^{-2}$	3.99	$3.08 \times 10^2$
37	$4.76 \times 10^{-2}$	$2.71 \times 10^{-1}$	$6.87 \times 10$	$7.55 \times 10^{-2}$	4.10	$1.33 \times 10^2$

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	$4.76 \times 10^{-3}$	$2.13 \times 10^{-1}$	$6.03 \times 10^{-1}$	$5.76 \times 10^{-3}$	$4.58 \times 10^{-1}$	7.44
33	$6.51 \times 10^{-3}$	$4.52 \times 10^{-1}$	4.51	$8.84 \times 10^{-3}$	$6.69 \times 10^{-1}$	7.27
37	$9.10 \times 10^{-3}$	$4.99 \times 10^{-1}$	5.15	$1.58 \times 10^{-2}$	1.07	$1.40 \times 10$



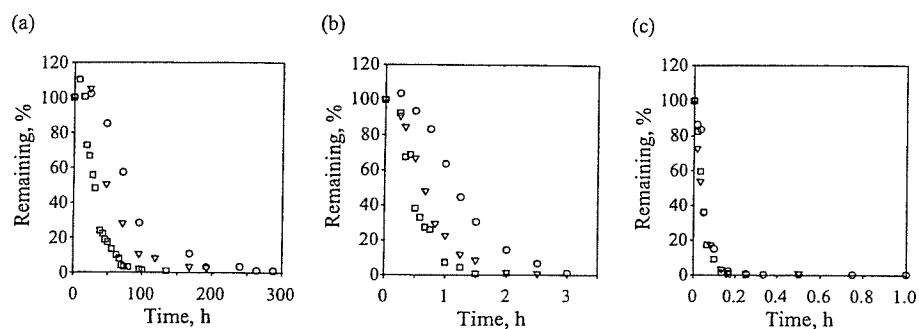


Fig. 6. Percent remaining of form II with the addition of 1% form I seed crystal after being suspended in water, 50% ethanol and ethanol: (a) water; (b) 50% ethanol; (c) ethanol. (○) 28 °C; (▽) 33 °C; (□) 37 °C.

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  $0.08 \pm 0.01$ ,  $23.04 \pm 1.22$  and  $1045.2 \pm 32.7$  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

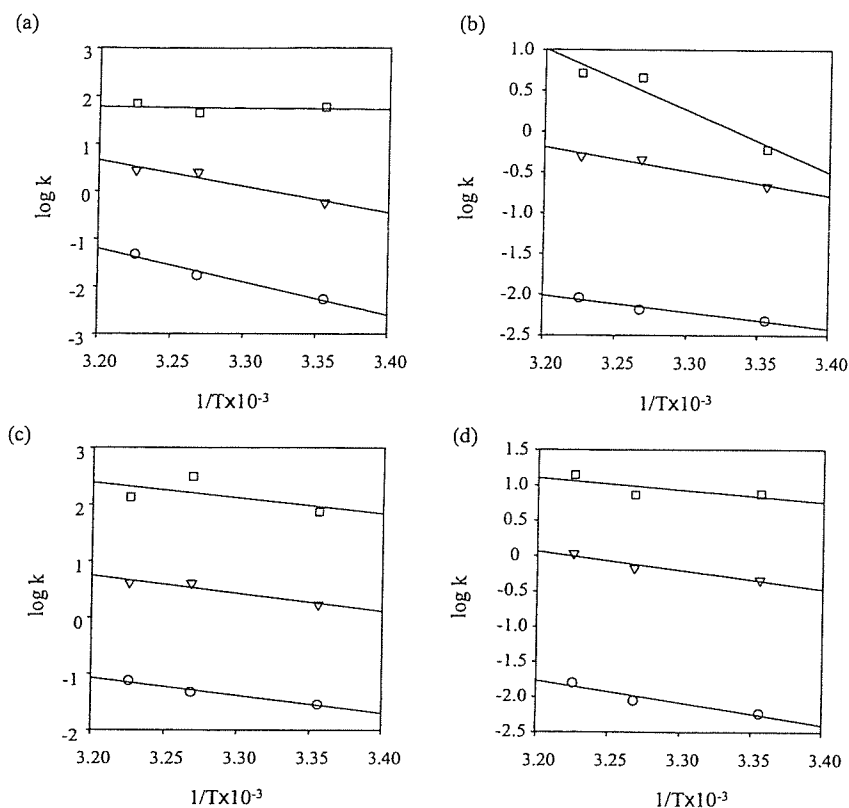


Fig. 7. Arrhenius plots for nuclei formation and growth processes of form II and those of form II + 1% form I seed crystals. Form II: (a) nuclei formation process; (b) nuclei growth process. Form II + 1% form I: (c) nuclei formation process; (d) nuclei growth process. (○) water; (▽) 50% ethanol; (□)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

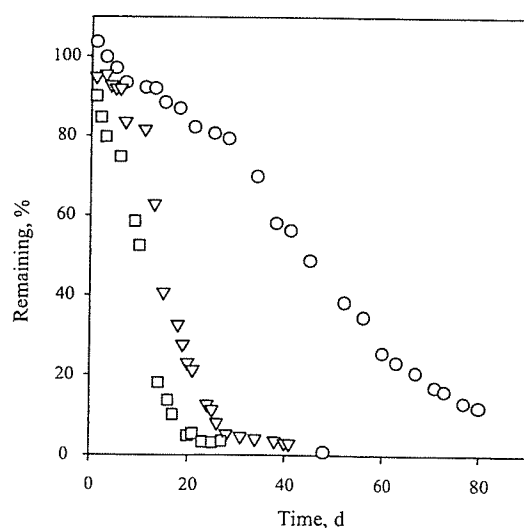


Fig. 8. Percent remaining of form II at 97% RH: (○) 50 °C; (▽) 60 °C; (□) 70 °C.

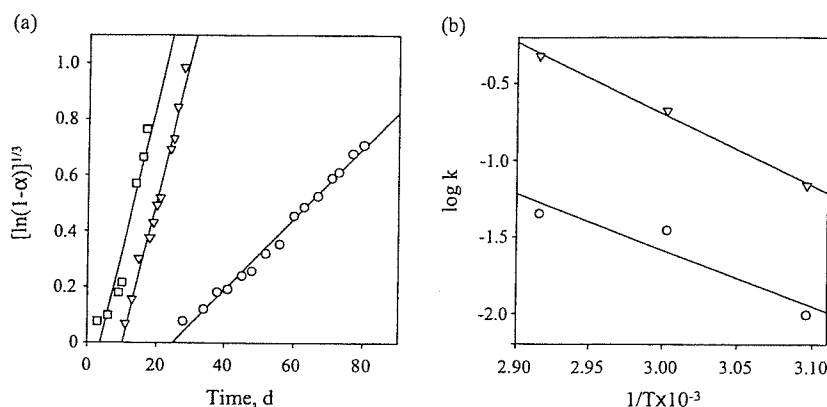


Fig. 9. A3 plots of form II (a) and the Arrhenius plots for nuclei formation and growth processes of form II (b) at 97% RH. (a): (○) 50 °C; (▽) 60 °C; (□) 70 °C; (b): (○) nuclei formation process; (▽) nuclei growth process.

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  $\text{h}^{-1}$ , and the rate constants of nuclei growth processes were 0.013, 0.051 and 0.053  $\text{h}^{-1}$ , 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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## ▶ 一般試験法の改正点

# 粉体物性に関連する試験法

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## はじめに

原薬や医薬品添加剤の大多数が結晶または固体状態で製造されているという現状に鑑みると、このようなバルク医薬品の粉体物性を規格化し適切な品質管理のもとに製剤化を行うことは、最終剤形のいかに関わらず、工程の円滑化や製品の品質確保・保証を的確に行ううえにおいて極めて重要である。このような観点から、日・米・EUのいずれの薬局方においても粉体物性の規格化の重要性に対する認識がますます深まっており、国際調和のもとに共通の測定・評価基準を設定し、これを各薬局方中に取り込む作業が順調に進行している。現在、3極で審議・検討(調和済のものを含む)されている、粉体物性に関連する一般試験法または参考情報は、粉体の粒子密度測定法、固体または粉体の密度、比表面積測定法、かさ密度およびタップ密度測定法、ふるい分け法、光学顕微鏡法、粉体の流動性、粉体の細かさ、レーザー回折法による粉体粒度測定、粉体の吸湿性測定法などである。

## 粒度測定法

粉体粒度測定法については、試料の物性・性状や目的に応じて種々の原理に基づく測定

法が利用されている。これらの測定法のうち、日本薬局方(以下、日局)ではふるい分け法が十三改正第一追補において初めて収載された。次いで、同第二追補で光学顕微鏡法が収載されたのに伴って両試験法は粉体粒度測定法として統合され、後者が第1法、前者が第2法として位置づけられた。その後、これらの試験法は3薬局方によって2004年6月に国際調和に達し、各薬局方は調和文書を取り込むことになった。十五改正における粒度測定法は、十四改正と基本点に関する変更はないものの、国際調和文書に基づいて制定されているため、文章および基本項目の構成については全面的に改められている。なお、測定法の名称は本文中の“粉末状等の…”の表現からも明らかのように、対象粒子は必ずしも固体粒子とは限らないとしたため、十四改正における名称中の「粉体」を削除し、「粒度測定法」に改められた。また、試験法中における◆・・・◆内の文章は、日本薬局方による独自記載部分(補足的な説明など)であり、十四改正の内容が踏襲されている。

主な変更点は、以下の通りである。

### ● 第1法 光学顕微鏡法

- ① 十四改正では0.5~100  $\mu\text{m}$ の範囲にある粒子に適用できるとされていたが、1  $\mu\text{m}$ 以下の微粒子を対象とする場合には、走査型電子顕微鏡による観察および測定による方

がはるかに優れているため、顕微鏡の分解能に基づいて測定下限が1  $\mu\text{m}$ に改められ、上限は設定されなくなった。

- ② 結晶性の要件が満たされているかを確認するために、「結晶性の評価」の項目で、より詳細な記述がなされている。
- ③ 「顕微鏡法による粒子径の限界試験」が新項目として設定されたが、十五改正において適用を受ける各条品目はない。
- ④ 「粒子径の評価」の項目が設定され、顕微鏡法で汎用されているフェレー径、マーチン径、ヘイウッド径などが定義されている。
- ⑤ 「粒子形状の評価」の項目が設定され、形状に関する用語とその定義が記述されている。
- ⑥ 「一般的観察」の項目が設定され、粒子の形態、凝集の程度、状態、表面特性などに関する用語とその定義が記述されている。

## 第2法 ふるい分け法

十五改正では国際調和文書が取り入れられたため、全体的により詳細でかつ解説的な記述が増している。

- ① 「ふるい分け法の原理」が新たに設定された。
- ② 「試験用ふるい」の項目が設定され、ISO公称ふるい番号、USP(米国薬局方)ふるい番号、EP(欧州薬局方)ふるい番号、日本薬局方ふるい番号の相互対応関係をまとめた表が提示されている。
- ③ 「終点の決定」の項目において、十四改正では“連続して5分間ずつふるい分け操作を繰り返し行ったとき、いずれのふるい上の試料の質量変化も5%又は0.1g以下となったときをふるい分けの終点とする。”とされていたが、これに“所定のふるい上の残留量が全試料質量の5%未満となった場合には、終点は、そのふるい上の質量変化を直前の質量に対して20%まで引き上げる。”な

どの記述が追加された。

- ④ 「ふるい分け法」の項目が設定され、この中で 1) 機械的振とう法 乾式ふるい分け法、2) 気流中飛散法 エアー・ジェット及びソニック・シフター法に関する解説と留意点が記述されている。
- ⑤ 「結果の解析」においては、結果は積算質量基準分布に変換すると便利であること及び、分布を積算ふるい下質量基準で表示するのが望ましい場合には、用いたふるい範囲に全試料が通過するふるいを含めておくことが記載されている。

## 比表面積測定法

本試験法は十三改正第二追補において初めて収載され、次いで、同第二追補において若干の追加・修正(本法の定義、アボガドロ数、窒素及びクリプトン分子1個の有効吸着断面積の数値)がなされた。その後、EPによって作成・提案された国際調和案が3薬局方で審議された結果、2003年11月に合意に達し、これら3者によって国際調和文書に調印された。これに基づいて、十五改正では本試験法は国際調和文書がそのまま収載されている。したがって、十四改正と基本点に関する変更はないものの、文章および基本項目の構成については全面的に改められている。なお、試験法中における◆・・・◆内の文章は、日本薬局方による独自記載部分(補足的な説明など)であり、十四改正の内容がそのまま踏襲されている。

主な変更点は、以下の通りである。

- ① BET吸着等温式中の吸着平衡圧及び測定温度における吸着気体の蒸気圧の単位が、国際調和により、いずれもkPaからPaに改められた。
- ② 十四改正における液体窒素の沸点(-196°C)

が国際調和により $-195.8^{\circ}\text{C}$ に改められた。

- ③ 十四改正ではBET多点法と一点法が簡単に述べられていたが、十五改正ではこれらについて詳細な記述がなされ、多点法では直線回帰における統計的厳密性が要求されている。
- ④ 十四改正では第2法：容量法については装置の概略図は示されていなかったが、十五改正では第2法も第1法：動的流動法と同様に概略図が示されている。

## 粉体の粒子密度測定法

本測定法は十四改正第二追補において新たに収載された試験法であり、国際調和過程では現在Stage 4段階にある。この調和原案に示された3種類の固体の密度(結晶密度、粒子密度、かさ密度及びタップ密度)のうち、日局では粒子密度を分離して「粉体の粒子密度測定法」として一般試験法に収載し、調和原案における前文に相当する部分は、後述の「固体又は粉体の密度」の名称で[参考情報]としての取り扱いをすることとされた。

本測定法で規定される粒子密度は気体置換型ピクノメータ法により測定するものであるが、この方法では気体が侵入し得るすべての空隙および細孔部分の体積を除いて粉体の体積と評価するため、結晶密度にほぼ等しい測定値が得られる。本測定法では、同一の試料について同一条件下での測定をくり返すとき、連続して測定した試料体積が0.5%以内で一致することを確認することとされている。なお、十五改正の段階で改正点はない。

## かさ密度及びタップ密度測定法

本測定法は十四改正第一追補において新たに収載された試験法であるが、国際調和過程においては現在EPによる原案がStage 4段階にあり、最終調和にはまだ至っていない。本測定法は、粉末状医薬品を容器に圧密せずゆるやかに充てんすることにより得られるみかけの密度(かさ密度)と、この粉体を入れた測定用容器を機械的にタップすることにより得られるみかけの密度(タップ密度)を測定する方法である。一般に充てん性と流動性の間には密接な関係が成立し、これらは製剤工程におけるカプセルや錠剤機の臼中への粉体の高速充てんに伴う製剤の質量偏差に直接に影響するので、かさ密度及びタップ密度は粉体の充てん性を評価するための重要なパラメータである。十四改正においてはかさ密度及びタップ密度のいずれについても、測定法として第1法(定質量法)と第2法(定容量法)が示されているが、十五改正における改正点はない。

## 固体又は粉体の密度[参考情報]

十四改正第二追補において新たに収載された項目であるが、前述のように、本項のような国際調和原案(EP作成)中の前文に相当する部分は日局の一般試験法として馴染まないとの判断に基づいて、これを分離し[参考情報]として取り扱うこととされた。

固体の密度を(1)結晶密度、(2)粒子密度、(3)かさ密度及びタップ密度に分類し、これらについて定義がなされている。なお、(2)粒子密度については、前述のピクノメータ法による測定のほか、水銀圧入法による測定についても記述されている。また(3)かさ密度及び

タップ密度については国際調和原案では定質量法についてのみ述べられているが、別に日局では定容量法による測定も規定していることが明記されている。十五改正における改正点はない。

## 粉体の流動性[参考情報]

本測定法は2004年6月における国際調和文書に基づいて十五改正薬局方において新たに取り入れられたものであるが、内容的に日局の一般試験法には馴染まないとの判断から、十五改正では[参考情報]として取扱うこととされた。

冒頭でも述べたように、固形製剤の製造工程の円滑化を図り適切な製品特性を維持するためには、粉末状医薬品の流動性及び充てん性を的確に評価し、これらの物性を所定の管理範囲内に収めておくことが極めて重要である。しかし、前項のかさ密度及びタップ密度は測定条件を比較的規格化しやすいのに対して、流動性については関係する因子が多岐に及ぶため、規格の設定は極めて困難であり、得られた測定値の評価についても信頼性・有用性や再現性の点においてかなりの問題点が残る。したがって、JISにおいても流動性測定法の規格化は、一部の工業用粉体に限られている。

本測定法では、異なった原理または粉体現

象に関係する、1)安息角測定法、2)圧縮度及びHausner比測定法、3)オリフィスからの流出速度測定法、4)せん断セル法が流動性の評価パラメータとしてあげられている。これら4種類の測定法について、基本的測定法、推奨される測定手順、測定に関して留意すべき点などが述べられているが、いずれもガイドライン的な内容に止まっており、当然、判定基準などは明示されていない。

## レーザー回折法による粉体粒度測定[参考情報]

最近、粉体を扱うあらゆる工業分野で汎用されているレーザー回折法による粒子径測定法を医薬品粉体にも適用する目的で、EPによって国際調和原案が作成されており、現在、Stage 4段階にある。この調和作業の進行を睨みながら日局でも審議・検討した結果、十五改正では新たに[参考情報]として収載されることとなった。標題中では粉体粒度測定とされているが、粉体粒度測定用標準粒子を用いて装置の校正が適切に行われていれば、エマルションの粒子径測定も可能である、とされている。構成は、1.レーザー回折法の原理、2.装置、3.測定、4.データ解析、5.測定に際しての留意点から成り、ガイドライン的な内容としてまとめられている。なお、標準粒子はいまだ公的には規定されていないが、参考例があげられている。

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# 原薬の光安定性の評価 — 製剤の開発過程における プレフォーミュレーション研究 —

Evaluation of photostability of active ingredients  
— Preformulation studies during the pharmaceutical development process —

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The photodegradation of solid pharmaceutical drugs and preparations is one of typical topochemical reactions. In review this article, based on the results of several research works performed by the authors, some essential and important problems and factors concerning the evaluation of photostability of photo-labile drugs are presented and extensively discussed from the view points of both appearance change (discoloration) and photodegradation.

## はじめに

医薬品の開発過程は、しばしば長大な河の流れに例えられるが、その源流領域をカバーするプレフォーミュレーション過程では、原薬について分子レベルから結晶、さらには粉体レベルに至るあらゆる品質パラメータを定性的かつ定量的に解明しておくことが要求される。したがって、ここでの大きな課題は、化学構造や各種の物性をいかにして工業化や臨床の場で活かすか、ということであろう。医療現場で使用されている医薬品原体の95%以上は晶析工程を経て製造されているが、このような状況を鑑みると、原薬の固体状態における物性を的確に把握し、これらの情報を集積しておくことは、その後の開発計画を円滑に進めるうえで極めて重要である。

ところで、近年、ジヒドロピリジン骨格を持つカルシウム拮抗薬などを中心として、光に対して不安定な医薬品が増加している。このような医薬品の固形製剤については、これまで、その安定化と品質保証は主として包装設計によってなされてきたといえる。しかし、最近の医療機関における調剤システムにおいては、元封が開封された後、一包化システムによって処方成分が再構成されるケースが多いにもかかわらず、このようなシステムに

おける包装素材では満足すべき光遮蔽効果は期待できない状況にある。したがって、薬剤が患者に交付された後の保管状況によって、安定性の確保に少なからぬ影響を及ぼすことが予想される。

そこで、本稿では、著者らの研究成果を中心に、光に対する固体医薬品の挙動と安定性の評価に関する問題点について概説する。なお、著者は本誌において、すでに光安定性に関する解説<sup>1)</sup>を著しており、内容が一部重複していることをあらかじめご容赦いただきたい。

## 1. 光安定性の評価における問題点

光に対して不安定な医薬品製剤のインタビューフォームを通観すると、光安定性情報の取り扱いについては、最近まで各社まちまちであり、長らく統一的な評価基準が望まれていた。すなわち、ICH(日米EU三極医薬品承認審査ハーモナイゼーション国際会議)において光安定性試験法のガイドライン策定に向けた最終合意がなされるまでは、製薬企業で用いられてきた光安定性評価のための実験条件は、企業間で十分な整合性が確認されてきたとはいえないのが実情であろう。

一方、学界においても光安定性に関する報告例は、他の研究テーマに比較して極端に少ないが、これらの状況

\*本稿は、「第22回製剤と粒子設計シンポジウム」(2005年10月、浜松)での特別講演の内容を加筆してまとめたものである。

は原薬の固体状態における光安定性を評価する際に、常に以下の難点が付きまとうことに起因している<sup>1)</sup>。すなわち、①光による医薬品の物性変化は、粒子表面またはその近傍に極限されたトポケミカルな不均一系反応である。したがって、固体光化学反応においてはscale effectが関係し、必然的に溶液系におけるように普遍的な分解率を定義することができない、②用いる光源によって照射強度や分光放射エネルギー分布が異なる、③医薬品側においても、光感受性において波長依存性を示す、などである。特に③については、後述するように、分解に関係する波長は医薬品分子中の官能基の光吸収特性と密接な関係を持つので、光源の種類によって光安定性に関する挙動が当然異なることを示唆している。

これらの問題点を考慮して、光安定性を評価する際に留意すべき実験条件をあげると、①光源の種類、②光源の強度および分光エネルギー分布、③照射波長、④積算照射量、⑤試料の形状、大きさ(粒子径)、充填密度、表面状態など、⑥容器の素材および色などとなり、安定性に及ぼす実験条件は極めて多岐にわたり、かつ複雑である。なお、①の光源において、強度を任意に設定でき、かつ単一波長光線を波長ごとに照射できる回折格子型照射分光器は、波長依存性を精査するためには不可欠であり、光安定性研究においては決定的な武器となる。

## 2. 光安定性試験のためのガイドライン

前述したように種々の複雑な因子が関係するために、これまで光安定性試験においては温度や湿度のように統一的な試験条件の設定が困難であったが、ICHにおいて、最近ようやく、新原薬および新製剤を承認申請する際に必要とされる光安定性に関する情報を得ることを目的として、「新原薬及び新製剤の光安定性試験ガイドライン」<sup>2)</sup>が合意された。なお、これによって医療用の新有効成分含有医薬品の光安定性試験で、平成10年4月1日以降に開始する試験は、本ガイドラインに従って行われることが推奨されている。また、本ガイドラインは投与後(使用時)の光安定性については適用されない。本ガイドラインによれば、試験条件の概要は以下のとおりである。

### ・光源

次に示す2つのオプションの光源のいずれかを用いる。

#### A: オプション1

D65またはID65の放射基準に類似の出力を示すように設計された光源

(例)可視光と紫外放射の両方の出力を示す昼光色蛍光ランプ、キセノンランプ、ハロゲンランプなど

ここで、D65は、ISO10977(1993)に規定されている屋外の昼光の標準として国際的に認められたもの。また、ID65は、それと同等の室内の間接的な昼光の標準。

#### イ: オプション2

白色蛍光ランプと近紫外蛍光ランプによる照射を同一の試料を用いて行う。ここで、白色蛍光ランプは、ISO10977(1993)に類似の出力を示すもの。また近紫外蛍光ランプは320~400nmにスペクトル分布を持ち、350~370nmに放射エネルギーの極大を示すもの。

### ・試験の実施方法

光安定性を確認するための試験(確認試験)では、試料は総照度として120万lx・h以上および総近紫外放射エネルギーとして200W・h/m<sup>2</sup>以上の光に曝す。

### ・試料の配置

固体原薬の場合には、適切な量の試料を採り、適切なガラスまたはプラスチック製の皿状容器に入れる。一般的には3mm以下の厚さになるように容器中に広げる。

### ・試料の分析

曝光終了時に、試料の物理的性質(外観など)の変化を検討するとともに、光分解過程で生じ得る分解物について適切にバリデートされた方法を用いて、含量および分解物の量を測定する。なお、著者らの長年にわたる経験に基づいて上記の試験条件を検討した場合、まだかなり曖昧な部分が残されており、光源の種類を除いては必ずしも厳密な条件設定がなされているとは言い難い。

## 3. 光安定性の評価

### (1) 物理的安定性

#### (a) 局方における医薬品の光に対する性状表示

前述のガイドラインでも触れているように、固体医薬品の光に対する挙動として外観変化(着色、変色など)と内部変化(化学的変化)があるが、両者の間には何らかの関係を有する場合が少なくない。したがって、外観変化は第1選択の簡易的な評価項目として有用であるが、評価基準や表示法については、いまだ公的に統一見解が見出されるまでには至っていない。そこで、局方中で“本品は、光によって徐々に着色する”と表示されている5種類のスルホンアミド錠について蛍光灯下で総照度50万lx・hで照射した錠剤の着色度(色差)の変化を経時的に追跡したところ、表示通り著しい着色が認められたものもあるが、逆に過酷な照射条件下でも肉眼的にまったく

着色せず、光に対して安定な試料もあった<sup>3)</sup>。このことは、同じ基本骨格を持つ化合物であっても官能基の違いによって安定性が著しく異なることを示している。同時に、これらの結果から判断すると、局方における原薬性状の表示は妥当性を欠いていることになる。

### (b) 光安定性における作用スペクトル

局方収載の医薬品の中から光に対して敏感であるという表示のある8種類の試料を選び、回折格子型照射分光器によって300~475nmの波長範囲内(ガイドライン中、オプション2に該当する波長領域)で一定強度の光を単一波長ごとに照射した際の錠剤表面の着色度の波長依存性を検討したところ、着色の程度や安定性に及ぼす照射波長の影響は試料によって著しく異なることが判明した<sup>4)</sup>。したがって、分光放射エネルギーの異なる光源を用いた場合には、これらの医薬品の着色度の順位は光源によって異なるはずである。事実、4種類の光源のもとで曝光させた着色度の経時変化は、これらの光源間で必ずしも一致しなかった。これらの結果から、光安定性は、今後、前述の「ガイドライン」に基づいた光源を用いて合理的に評価する必要がある。

### (c) 加速試験による光安定性の予測

前項の結果から明らかなように、照射強度の大きい光源を用いた加速試験の結果から、蛍光灯などによる通常の照射条件下での安定性を薬品間で比較・評価することは、一般には困難であるといえる。しかし、同一の医薬品(ニフェジピン)については、たとえ光源が異なってもその医薬品の着色または分解に参与する波長範囲内での総照射エネルギー量が同じであれば、ほぼ同一水準まで着色する<sup>5)</sup>。このような関係が成立する場合には、加速照射実験によって、通常の光源下における長時間照射後の着色状態を概略的に推測することが可能である。なお、著者らは曝光前後の色差( $\Delta E$ )の経時変化については、照射時間( $t$ )との間に反応速度式に類似した、式(1)の関係(ただし、 $k$ および $n$ は定数)が広範囲に成立することを確認している<sup>4)</sup>。

$$d(\Delta E)/dt = k(\Delta E)^n \quad \dots(1)$$

上式を積分すると、式(2)のように $\Delta E$ と $t$ の間には、両対数紙上で直線関係が成立することになるので、この関係を利用すれば比較的短時間の照射によって得られた数点のデータから、直線部の外挿によって規定の総照度



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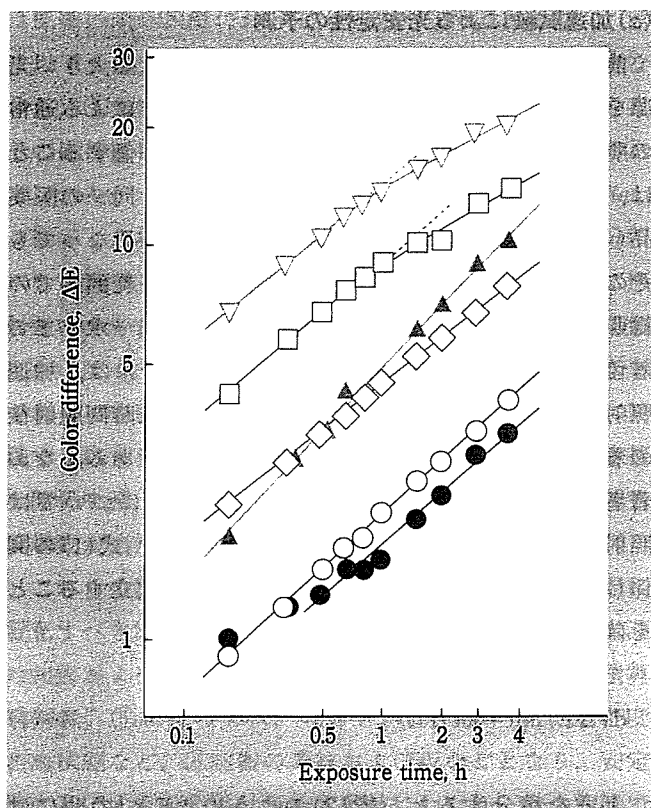


Fig. 1 Double-logarithmic plots for coloration process of furosemide modifications under irradiation by mercury vapor lamp.

Tablet : (○) form I, (□) form III, (▽) DMF solvate, (◇) dioxane solvate. Powder : (●) form I, (▲) form II

(例えば, 120万lx・h)における色差値を推測することも可能である。

$$\log \Delta E = [1/(1-n)] \log t + [1/(1-n)] \log [(1-n)k] \quad (n \neq 1) \quad \dots (2)$$

#### (d) 多形現象を示す医薬品の光安定性

光に対して不安定な医薬品で, かつこれが多形現象を示す場合には, 結晶間で結晶格子に関するパラメータが異なるので, 光に対する挙動に相違が生じることが予想される。“光によって徐々に着色する”と表示されているフロセミドは4種類の多形のほかに, 無晶形および2種類の溶媒和物が存在する<sup>6)</sup>が, 安定形(I形)は過酷照射条件下でもほとんど着色せず, 外観的には安定であったのに対して, 他の結晶形や溶媒和物は著しく着色し, かつ結晶間でも有意な相違が認められた(Fig. 1)。著者らのこのような結晶間での光安定性の相違に着目して, Villiersら<sup>7)</sup>は, フロセミドの光分解に核形成および核成長過程からなる固体反応モデルを適用した結果, I形と

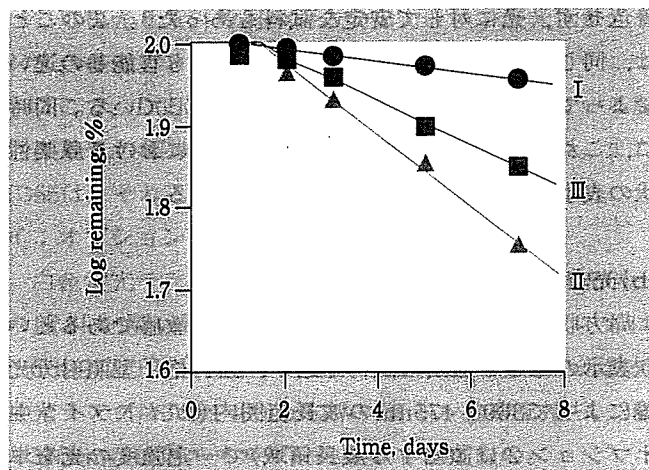


Fig. 2 The apparent first-order plots for solid-state photodegradation of carbamazepine polymorphs at the irradiation intensity of  $3.0 \text{ J cm}^{-2} \cdot \text{s}^{-1}$  under near-UV fluorescent light

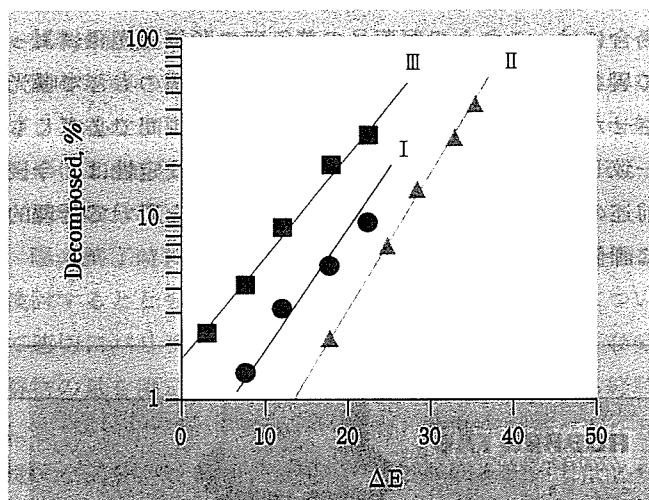


Fig. 3 Relationship between color difference ( $\Delta E$ ) and percent decomposition of carbamazepine polymorphs

II形の間で速度論的パラメータにおいて明確な差異が認められたことを報告している。

一方, カルバマゼピンには3種類の結晶形が確認されている<sup>8)</sup>が, これらは光照射によっていずれも少なくとも2種類の分解物を生成することが判明した<sup>9)</sup>。そこでこれらの結晶をペレットに成形した試料について, FT-IR正反射スペクトルを測定し, 光分解に関係した特定波数におけるピーク強度の変化に着目し, 検量線を利用して得られた2次元残存率は, Fig. 2のように, 見掛け上, 1次反応式に従って減少し, かつ結晶形間で顕著な相違を示した。また, これらの直線部から求めた残存率( $C_t$ )と着色に伴う色差( $\Delta E$ )の間にはFig. 3に示すように式(3)で表される良好な相関関係が得られた(ただし, KおよびBは定数)。