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# The Dehydration Kinetics of Theophylline Monohydrate Powder and Tablet[1)]

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The dehydration of theophylline monohydrate in powder and tablet forms was studied by using an infrared water-content measuring instrument. Intact theophylline powder was recrystallized from distilled water, and ground powder was obtained by grinding in a ceramic mortar with a pestle. The samples were dehydrated as follows. The intact and ground powders were placed on a plate 8 cm in diameter. A powder bed was formed on a plate 3 cm in diameter as a model of a loosely packed tablet, and a tablet 2.0 cm in diameter was obtained by compression at 1.0 t/cm$^2$. Dehydration kinetic mechanisms of various dosage forms of theophylline monohydrate were clarified by using various kinds of solid-state kinetic models. The dehydrations of intact and ground powders followed two-dimensional growth of nuclei and three-dimensional growth of nuclei equations, and the activation energies ($E_a$) were 20.1 and 23.0 kcal/mol, respectively. The dehydrations of powder bed and tablet followed two-dimensional phase boundary and three-dimensional phase boundary equations, and the $E_a$ values were 15.4 and 11.5 kcal/mol, respectively. It seems that the dehydration of intact powder starts randomly at each particle and proceeds two-dimensionally, but that of ground crystals proceeds three-dimensionally from the cracks in particles. In the case of the powder bed the dehydration proceeds two-dimensionally from the surface particles of the powder bed into the inner particles. The dehydration of a tablet proceeds three-dimensionally from the outside of the tablet into its inside.

**Keywords**——theophylline; hydrate; thermal kinetics; dehydration; dosage form

## Introduction

The physico-chemical properties of the bulk powder of a pharmaceutical preparation affect the bioavailability through their effects on the disintegration time and the dissolution rate of tablets or granules. Shefter and Higuchi[2)] reported on the dissolution behavior of monohydrate and anhydride forms of theophylline. Shefter *et al.*[3)] reported on the dehydration kinetics of theophylline monohydrate by using the X-ray diffraction technique. In the present study we investigated the dehydration of theophylline monohydrate powder and tablet by using a kinetic method.

## Experimental

**Materials**——Theophylline (JP XI) was recrystallized from distilled water. Sample powder was passed through a No. 42 mesh screen (350 $\mu$m). The crystal shape of the intact sample was a long needle. The sample powder (30 g) was ground for 3 min in a ceramic mortar (inside diameter, 16 cm) with a pestle by hand. The tablet of theophylline monohydrate was compressed by using a punch and die of 2.0 cm diameter (for infrared (IR) spectra) at 1.0 t/cm$^2$.

**Measurement of Powder Characters**——The specific surface area ($S_w$) was measured by using the air permeability method (SS 100; Shimadzu Co., Ltd.), the particle was assumed to be a sphere, and $S_w$ and specific surface area diameter ($D$) were calculated. The porosity of powders was measured by using a type PT powder tester (Hosokawa Micro. Labo. Co., Ltd.). The tapped porosity was measured after tapping for 5 min.

**X-Ray Diffraction Analysis**——The X-ray diffraction profiles of samples were measured with a type JDX 7E X-ray diffractometer (Nihon Denshi Co., Ltd.) at room temperature. The measurement conditions were as follows:

target, Cu; filter, Ni; voltage, 30 kV; current, 6 mA; receiving slit, 0.2 mm; time constant, 2 s; counting range, $6 \times 10^3$ cpm; scanning speed, 1 °/min.

**Dehydration Apparatus**——The measuring system for dehydration rate is shown in Fig. 1. The infrared water-content measuring instrument (Kyoto-Denshi Kogyo Co., Ltd.) was placed in a drying box where the humidity was kept below 10% relative humidity with dry air. The samples were placed on a steel plate under conditions I, II and III as described in the next section. The sample weight was converted into a current by using a transducer and recorded on chart paper.

**Dehydration Conditions**——Condition I, 1 g of theophylline powder was scattered on a steel plate holder 8 cm in diameter (50.3 $cm^2$) by using a No. 12 mesh screen. Condition II, 1 g of the powder was formed into a powder bed about 3 cm in diameter (7.1 $cm^2$) and about 0.33 cm in thickness on a steel plate by using a glass container 3 cm in diameter. Condition III, a tablet (1 g) 2 cm in diameter was put on a holder made of steel wire and removed from the steel plate.

## Results and Discussion

Figure 2 shows the X-ray diffraction profiles of theophylline monohydrate and anhydride. The samples gave typical monohydrate and anhydride X-ray diffraction patterns,[3] respectively.

The fractional dehydration of theophylline powder was calculated from the theoretical water content value of theophylline monohydrate. Figure 3 shows the dehydration curves of theophylline monohydrate. Figure 3 shows the dehydration curves of theophylline monohydrate powders and tablet. The intact and ground powders were dehydrated under condition I, and the powder bed and the tablet were dehydrated under conditions II and III, respectively. The theoretical thicknesses of the ground and intact powders under condition I were calculated from the loose apparent volume of samples and the area of the scattered sample; the thicknesses of intact and ground powder layers were about 46 and 52 $\mu$m, respectively. Since the powders under condition I had over 70% porosity, a large area of scattered sample powder and a small powder thickness, there was no hindrance to the diffusion of water vapor during the dehydration. Therefore, the dehydrations of intact and ground powders under condition I were presumed to be truly dehydrations without a diffusion process in the interparticle void of the powder beds. However, the powder bed under condition II was about 0.33 cm in thickness and the diffusion process in the interparticle void of the powder bed

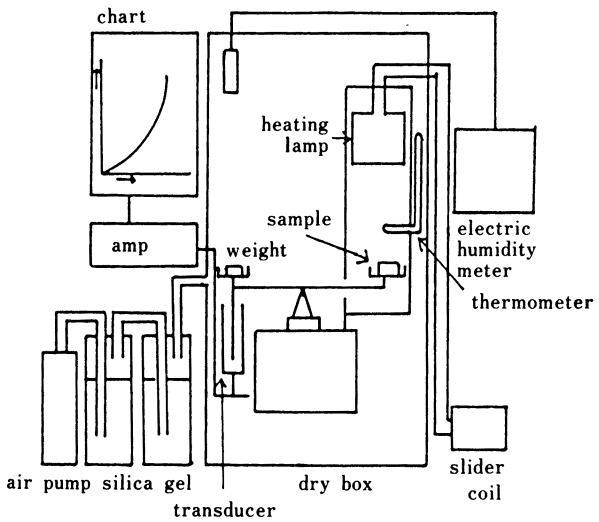


Fig. 1. Dehydration Apparatus

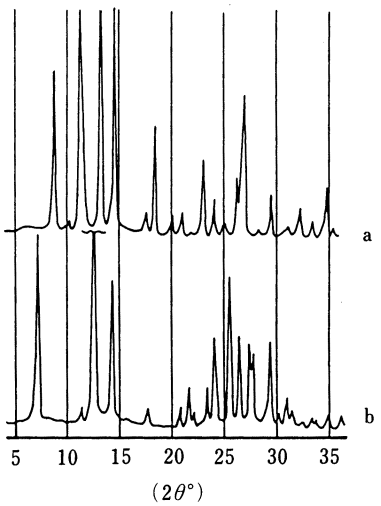


Fig. 2. X-Ray Diffraction Profiles of Theophylline Powders

a) monohydrate, b) anhydride.

might not be negligible. This powder bed under condition II was presumed to be a model of a loosely packed tablet. The time required for dehydration (T.D.), the porosities of packed and loose powders, the particle size ($D$) and $S_w$ of theophylline powders are summarized in Table I.

The T.D. of ground powder was slightly faster than that of intact powder because the $S_w$ of ground powder was about 45% larger than that of intact powder. The porosity of intact powder was almost the same as that of ground powder. The T.D. of the powder bed and tablet were about 2.5 and 4.5 times longer than that of intact powder. This result suggested that the dehydration of powder bed and tablet was affected by a diffusion of water vapor or thermal conductivity in the interparticle void.

Figure 4 shows microphotographs of theophylline crystals during dehydration. The

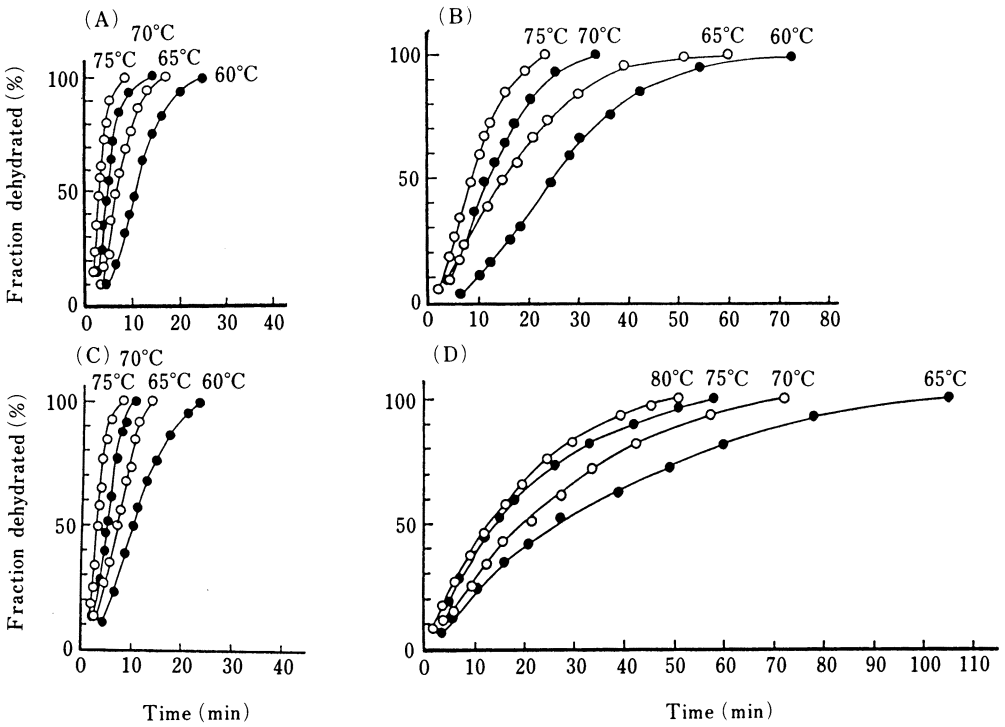


Fig. 3. Isothermal Dehydration Curves of Various Theophylline Powders
(A) intact powder, (B) ground powder, (C) powder bed, (D) tablet.

TABLE I. Time Required for 50% Dehydration (T.D.), Porosity, Specific Surface Area Diameter ($D$) and Specific Surface Area ($S_w$) of Powders and Tablets of Theophylline Monohydrate

| Sample | T.D. (min) | | | | | Porosity (%) | $D^{a)}$ | $S_w^{a)}$ |
|---|---|---|---|---|---|---|---|---|
| | 60 °C | 65 °C | 70 °C | 75 °C | 80 °C | loose tapped | ($\mu$m) | ($cm^2/g$) |
| Intact crystals | 10.2 | 6.9 | 5.1 | 3.0 | — | 71.5 60.7 | 18.6 | 2160 |
| Ground crystals | 9.8 | 6.5 | 4.8 | 2.7 | — | 74.5 48.9 | 12.7 | 3160 |
| Powder bed | 24.6 | 16.0 | 12.0 | 8.5 | — | 71.5 60.7 | 18.6 | 2160 |
| Tablet | — | 26.1 | 19.1 | 13.9 | 12.8 | 10.7 | | |

*a*) $D$ and $S_w$ were measured by using the air permeability method (Shimadzu Co., Ltd., SS 100).

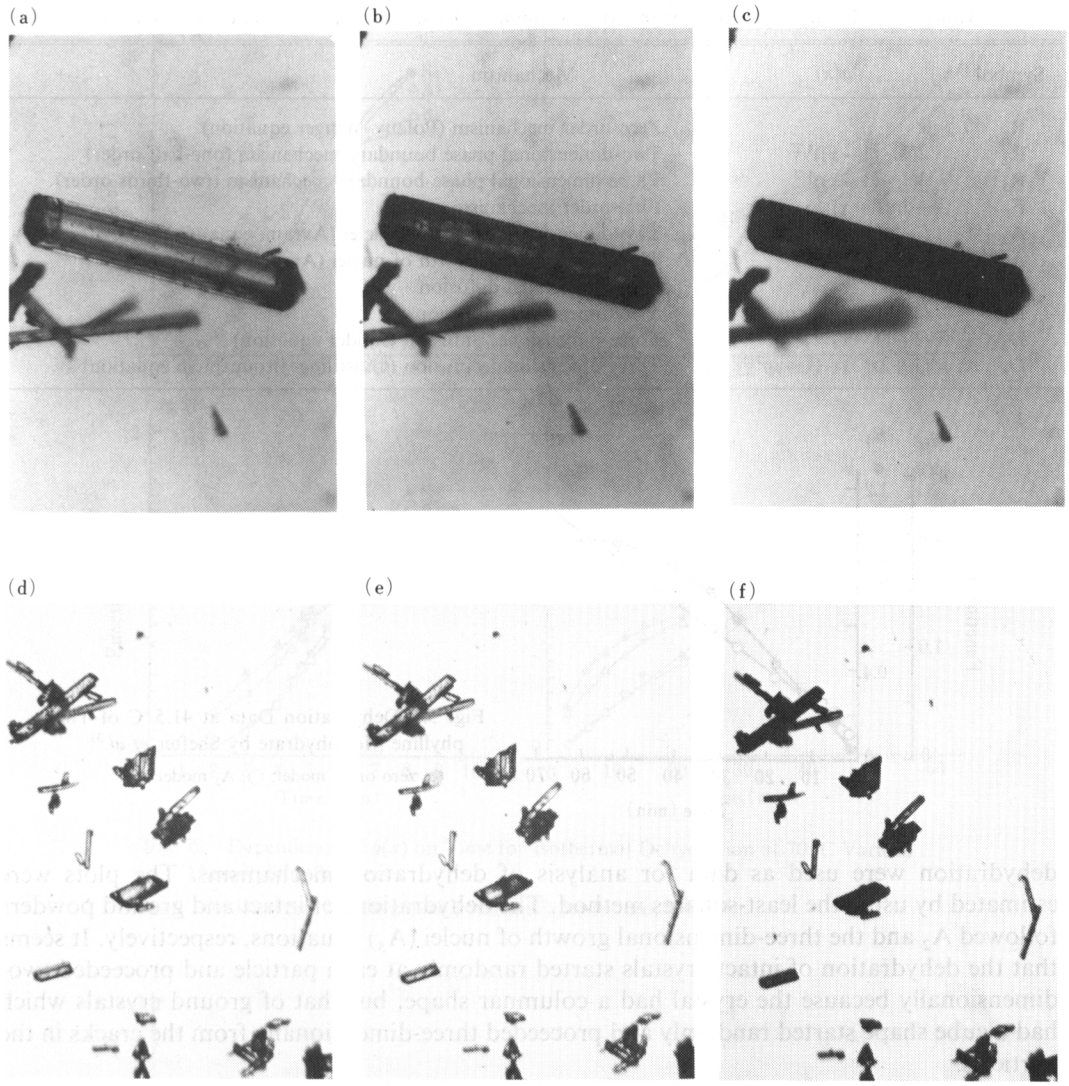


Fig. 4. Dehydration Process of Theophylline Monohydrate at 82 °C

a) intact crystal, b) after heating for 4 min, c) for 6 min, d) ground crystal, e) after heating for 2 min, f) for 4 min.

intact crystal was dehydrated from the side wall of the columnar crystal, but the shape of the ground crystal was similar to a cube, and the dehydration started randomly from cracks in the particle.

Figure 5 shows the data for the dehydration process presented by Shefter *et al.*,[3] who concluded that the dehydration of theophylline monohydrate followed a zero-order mechanism because the dehydration process at less than 50% fractional dehydration was linear. However, we recalculated their data by using various kinds of solid-state kinetic model equations (Table II) and this result suggested that the dehydration data was best fitted to the two-dimensional growth of nuclei equation ($A_2$) as shown in Fig. 5.

Figure 6 shows the predictions of model equations for the isothermal dehydration of various dosage forms of theophylline powders. Values in the range of 5—95% fractional

TABLE II. Kinetic Equations for the Most Common Mechanisms of Solid-State Decomposition

| Symbol | $g(x)$ | Mechanism |
|---|---|---|
| $R_1$ | $x$ | Zero-order mechanism (Polany–Winger equation) |
| $R_2$ | $2(1-(1-x))^{1/2}$ | Two-dimensional phase boundary mechanism (one-half order) |
| $R_3$ | $3(1-(1-x))^{1/3}$ | Three-dimensional phase boundary mechanism (two-thirds order) |
| $F_1$ | $-\ln(1-x)$ | First-order mechanism |
| $A_2$ | $(-\ln(1-x))^{1/2}$ | Two-dimensional growth of nuclei (Avrami equation) |
| $A_3$ | $(-\ln(1-x))^{1/3}$ | Three-dimensional growth of nuclei (Avrami equation) |
| $D_1$ | $x^2$ | One-dimensional diffusion |
| $D_2$ | $(1-x)\ln(1-x)+x$ | Two-dimensional diffusion |
| $D_3$ | $(1-(1-x)^{1/3})^2$ | Three-dimensional diffusion (Jander equation) |
| $D_4$ | $(1-2x/3)-(1-x)^{2/3}$ | Three-dimensional diffusion (Ginstiling–Brounshtein equation) |

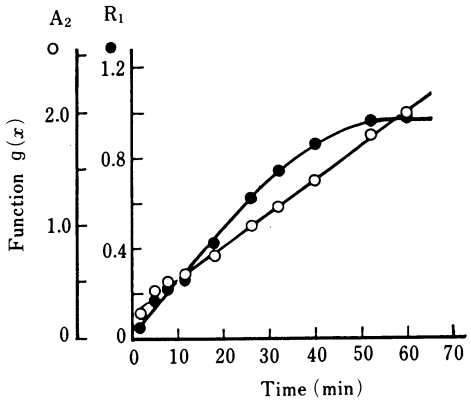


Fig. 5. Dehydration Data at 41.5 C of Theophylline Monohydrate by Shefter *et al.*[3]
●, zero order model; ○, $A_2$ model.

dehydration were used as data for analysis of dehydration mechanisms. The plots were estimated by using the least-squares method. The dehydrations of intact and ground powders followed $A_2$ and the three-dimensional growth of nuclei ($A_3$) equations, respectively. It seems that the dehydration of intact crystals started randomly at each particle and proceeded two-dimensionally because the crystal had a columnar shape, but that of ground crystals which had a cube shape started randomly and proceeded three-dimensionally from the cracks in the particles.

In the case of the powder bed, the dehydration followed the two-dimensional phase boundary ($R_2$) equation. The powder bed under condition II had a large interparticle void and was heated from a surface of the powder bed, so the dehydration proceeded two-dimensionally from the particles on the surface of the powder bed into the inside. There was a gradient of temperature between the surface of the powder bed and the inside, since the powder bed had a large interparticle void with poor thermal conductivity.

The dehydration of a tablet followed the three-dimensional phase boundary ($R_3$) equation. The tablet under condition III had smaller surface area and interparticle void than the powder bed under condition II. But the tablet was detached from the sample plate by using a holder, so the dehydration proceeded from both sides of the tablet. Therefore it seemed that the dehydration of a tablet proceeded three-dimensionally from the outside of the tablet. However, the dehydration of a tablet would involve a diffusion process of water vapor and thermal conductivity in the interparticle void, and would be very complex. Therefore the dehydration was delayed more than that of the intact powder under condition I or the powder bed under condition II.

Figure 7 shows the Arrhenius plots for dehydration of theophylline powders and the

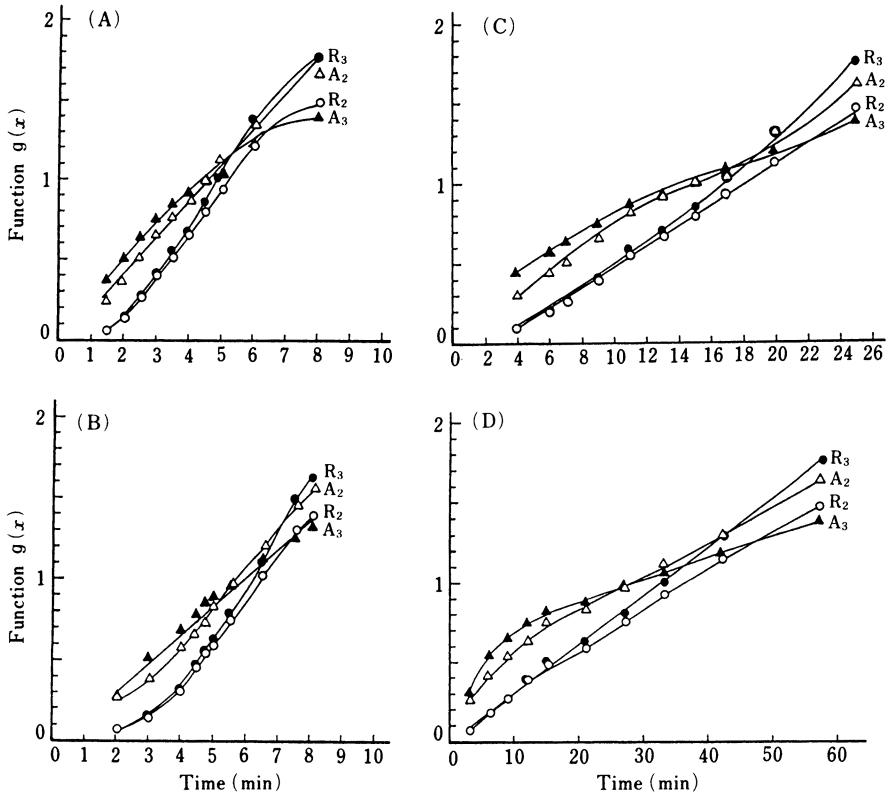


Fig. 6. Dependence of $g(x)$ on Time for Isothermal Dehydration at 70 °C Various Theophylline Powders

(A) intact powder, (B) ground powder, (C) powder bed, (D) tablet.

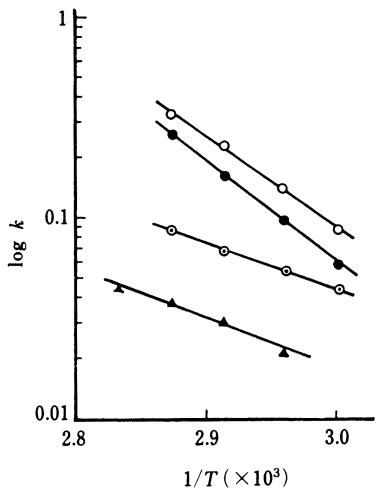


Fig. 7. Plot of $\log k$ against $1/T$ for the Dehydration of Various Theophylline Powders

○, intact powder; ●, ground powder; ⊙, powder bed; ▲, tablet.

TABLE III. The Activation Energy ($E_a$), Frequency Factor ($A$) and the Mechanism of Dehydration of Powders and Tablets of Theophylline Monohydrate

| Sample | $E_a$ (kcal/mol) | $A$ (min) | Mechanism |
|---|---|---|---|
| Intact powder | 20.1 | 1.47[12] | $A_2$ |
| Ground powder | 23.0 | 7.66[13] | $A_3$ |
| Powder bed | 15.4 | 4.19[8] | $R_2$ |
| Tablet | 11.7 | 1.06[5] | $R_3$ |

activation energies ($E_a$) and frequency factors ($A$) are summarized in Table III. The dehydration of intact powder followed the $A_2$ equation and the $E_a$ was 20.1 kcal/mol. On the other hand, the ground powder followed the $A_3$ equation and the $E_a$ was slightly larger than that of intact powder. The ground powder had a larger specific surface area than the intact powder, and the particles has a cubic shape with many cracks, so the dehydration mechanism of ground powder was different from that of the intact powder.

The dehydration of a powder bed and a tablet followed $R_2$ and $R_3$ equations and the $E_a$ values were 15.4 and 11.7 kcal/mol, respectively. The dehydrations of the powder bed and the tablet were not homogeneous reactions, because the dehydrations included the diffusion process of water vapor and the thermal conduction process in the interparticle void. Therefore the calculated values of $E_a$ are apparent parameters, but from the pharmaceutical viewpoint we can understand the dehydration mechanisms of powder bed and tablet from the plots, and estimate the half lives of dehydration of these dosage forms.

## Conclusion

The dehydrations of intact and ground crystals followed the $A_2$ and $A_3$ equations, but the dehydrations of the powder bed and the tablet followed the $R_2$ and $R_3$ equations, respectively. We conclude that the dehydration rate and mechanism of pharmaceutical preparations depends on the structure of the dosage form.

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### References and Notes

1) Presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 1985.
2) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).
3) E. Shefter, H. Fung and O. Mok, *J. Pharm. Sci.*, **62**, 791 (1973).