[Chem. Pharm. Bull. 32(1) 244—250 (1984)]

Dissolution Behavior of Chlorpropamide Polymorphs[1,2]

HARUHISA UEDA,* NAOKI NAMBU and TSUNEJI NAGAI

Faculty of Pharmaceutical Sciences, Hoshi University,[3]
Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received April 28, 1983)

The dissolution profiles of chlorpropamide (CPM) polymorphs, especially the metastable form II reported by Al-Saieq *et al.*, were investigated kinetically in detail by a dispersed amount method and a stationary disk method in comparison with those of the stable form. Form II showed a dissolution phenomenon involving simultaneous phase change from metastable form to stable form during dissolution. The saturated concentrations of metastable form II and stable form A, C_{sm} and C_{so}, the rate constant of the crystallization process K_r and the dissolution rate constant, K_t, were calculated by the stationary disk method.

By analyzing the values of C_{sm} and C_{so} obtained at various temperatures, the transition temperature and heat of transition were determined. Further, the activation energies of crystallization and the dissolution process were also determined by Arrhenius plots of K_r and K_t obtained at various temperatures.

Keywords——chlorpropamide; polymorphism; dispersed amount method; stationary disk method; dissolution rate; thermodynamic parameter; phase change

In a previous study,[4] two polymorphic forms of tolbutamide were characterized, and their dissolution rates were investigated in detail. The present work extends the investigation to chlorpropamide (CPM), another member of the sulfonylureas. Simmons *et al.*[5] reported that chlorpropamide had three polymorphic forms, which showed slight differences of dissolution rate but the same bioavailability in beagle dogs. On the other hand, Burger[6] suggested the existence of five polymorphic forms and one crystalline benzene solvate by thermomicroscopy, infrared (IR) spectroscopy and differential scanning calorimetry (DSC). Al-Saieq *et al.*[7] independently reported the preparation of five polymorphic forms of chlorpropamide. Two of these forms had not been previously reported. Four metastable forms have faster dissolution rates than the stable form as determined by the rotating basket method of U.S.P. XIX.

However, little work has been done on the dissolution behavior of these polymorphs. This paper deals with the dissolution behavior of these polymorphs as determined by the dispersed amount method and the stationary disk method.

Experimental

Materials——Chlorpropamide extracted from Diabinese® tablets was used after recrystallization from 80% aqueous ethanol solution. The solvents used for crystallization were all of reagent grade.

Preparation of the Polymorphs——Chlorpropamide polymorphs A, B and C were obtained by the method described by Simmons *et al.*[5] Chlorpropamide polymorphs I, II, III, IV, and V were also obtained by the method described by Al-Saieq *et al.*[7] The particles of chlorpropamide used for the dissolution study were those passing through a 100 mesh sieve (less than 149 μm).

Identification of Polymorphs——Powder X-ray diffractometry and IR spectroscopy were employed in the manner described in the previous paper.[8]

Solubility Measurement by the Dispersed Amount Method——Using a dissolution cell similar to that described by Sekiguchi *et al.*,[9] an excess of chlorpropamide was placed in 50 ml of HCl–KCl buffer solution (pH 2.0, $\mu=0.1$), which was maintained at 10, 20, 30 or 40 °C by circulating constant temperature water in the outer vessel.

Immediately after the addition, 800 rpm agitation was applied by means of a magnetic stirrer. Aliquots of the solution were taken at appropriate times, filtered through a membrane filter (pore size, 0.2 μm), and diluted, then the concentration of chlorpropamide was determined by the ultraviolet (UV) absorption method (233 nm).

Procedure for Determination of the Dissolution Rate——The dissolution rate was determined by a stationary disk method, using the apparatus described in a previous paper.[10] A 250 mg sample was compressed in a cylindrical die with a Shimadzu hydraulic press for KBr tablets for IR spectroscopy. It was confirmed by X-ray diffractometry that no phase transition took place during the compression. The compressed disk was not ejected from the die, and the die cavity was stoppered. The die carrying the compressed disk was set on the dissolution apparatus so as to make the disk face the stirrer. Every experiment was done under the following conditions: deionized water as the dissolution medium; at 10, 20, 30 or 40 °C; 50, 100 or 300 rpm stirrer velocity; 1.3 cm diameter disk of sample compressed under 200 kg/cm^2. Two ml of the solution was taken at appropriate time intervals and diluted, then the concentration was determined from the UV absorption at 231 nm.

Results and Discussion

Dissolution Behavior Observed by the Dispersed Amount Method

Eight polymorphs could be prepared as described in the literature.[5,7] However, as reported by Al-Saieq *et al.*,[7] form I of Al-Saieq corresponds to form C of Simmons, and form IV of Al-Saieq corresponds to form A of Simmons. Therefore, dissolution rate studies of the six distinct polymorphs were carried out.

When the six polymorphs was dispersed, the concentrations of form II and form C rose very quickly and then decreased gradually as shown in Fig. 1. In particular, form II showed a characteristic convex dissolution curve. In the case of other polymorphs, normal dissolution curves were observed. The dissolution curves of form II and form C in water obtained by the dispersed amount method were similar to that of *p*-hydroxybenzoic acid (involving a crystallization process together with a phase change from anhydrate to hydrate).[11]

As shown in Fig. 2, it was determined by X-ray diffractometry that the transformation of the dispersed form II and form C to form A was almost completed after a 6 h dissolution. These results indicated that the dissolution rates of form II and form C are extremely large compared with those of other polymorphs, and also that these two metastable forms changed rapidly to stable form A in water. Thus, it should be possible to determine the dissolution parameters of these two polymorphs quantitatively by the stationary disk method.

Dissolution Behavior Observed by the Stationary Disk Method

As shown in Fig. 3, the dissolution rate of form II in water did not follow the Noyes–Nernst equation. The slope of the dissolution curve of form II after transformation

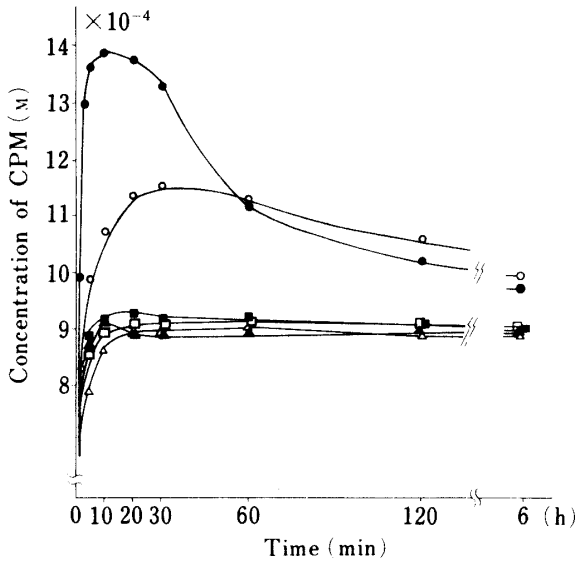

Fig. 1. Dissolution Curves of CPM Polymorphs in 50 ml of pH 2.0 KCl–HCl Buffer at 30 °C by the Dispersed Amount Method

□, form A; ■, form B; ○, form C; ●, form II; △, form III; ▲, form V. Each value is the mean of three experimental runs.

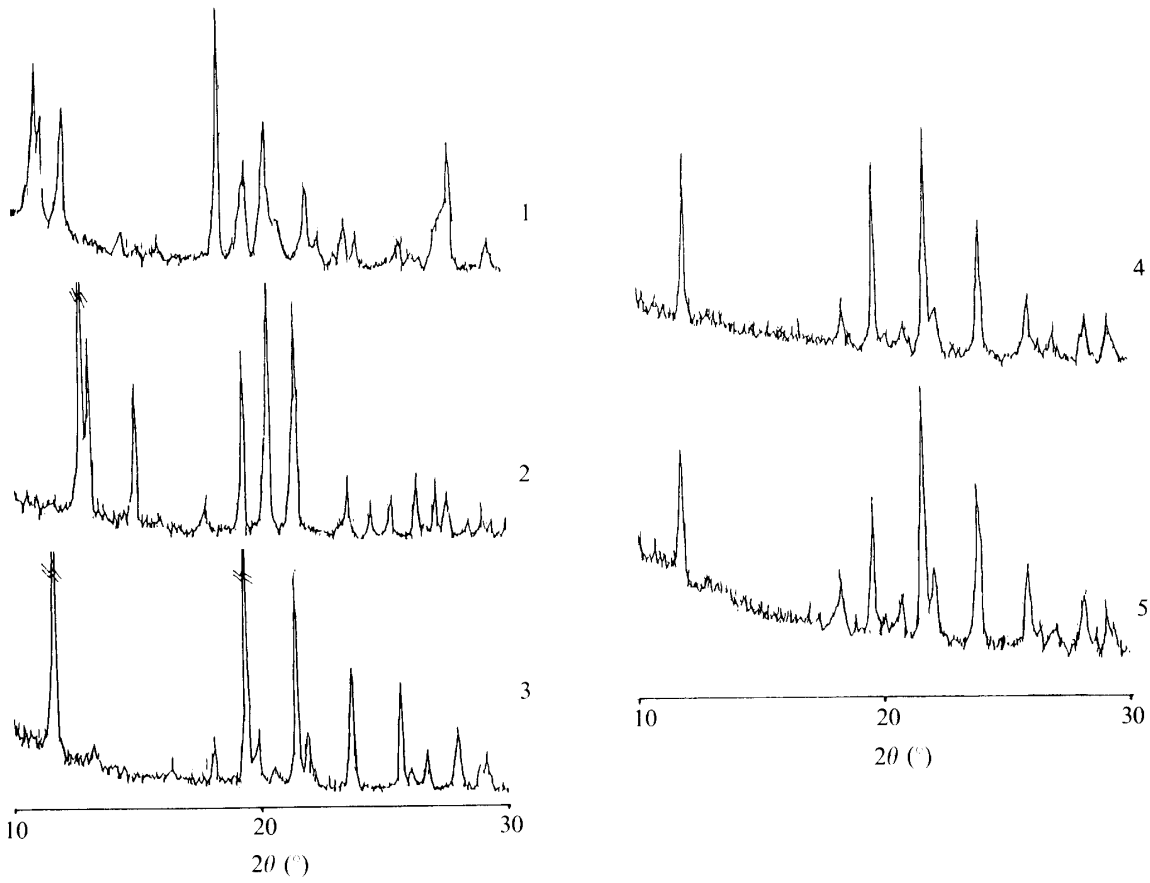

Fig. 2. X-Ray Diffraction Patterns of Form II and Form C before and after Dissolution by the Dispersed Amount Method

1: form II before the dissolution experiment. 2: form C before the dissolution experiment. 3: form A (stable form). 4: form II at 6 h after the start of the dissolution experiment. 5: form C at 6 h after the start of the dissolution experiment. Rigaku Denki Geigerflex D-2 diffractometer; Ni-filtered Cu-K_α radiation.

accompanying the crystallization was almost the same as that of form A. Therefore, this result might be due to the transformation from form II to form A in the initial dissolution stage. Considering that the diffusion constant of form II is almost the same as that of form A, the following equations for dissolution in the initial stage can be obtained in the same way as described in the previous paper.[11]

$$dC/dt = K_t\{C_{sm} \cdot \exp(-K_r \cdot t) + C_{so}[1 - \exp(-K_r \cdot t)]\} \quad (1)$$

$$C = K_t(C_{sm} - C_{so})[1 - \exp(-K_r \cdot t)]/K_r + K_t \cdot C_{so} \cdot t \quad (2)$$

C_{sm} is the saturated concentration of form II, C_{so} the concentration at time t which corresponds to the concentration of form A in the bulk liquid at equilibrium, K_t the dissolution rate constant, and K_r the rate constant of the crystallization process.

On the other hand, the dissolution rate of form C in water was represented by the Noyes–Nernst equation, and it was slightly larger than that of form A. As shown in Fig. 4, this result seemed to be due to phase transformation when the sample was compressed to make a disk. In this study form C was gradually transformed to form A when it was compressed under 2 ton/cm^2 pressure in a manner similar to that reported for barbital polymorphs.[12] Therefore, it was difficult to get a compressed disk of pure form C. Consequently, the dissolution parameters of form II were determined quantitatively only by the stationary disk method.

a) Effect of Stirring Conditions on the Dissolution Behavior of Form II——Figure 5

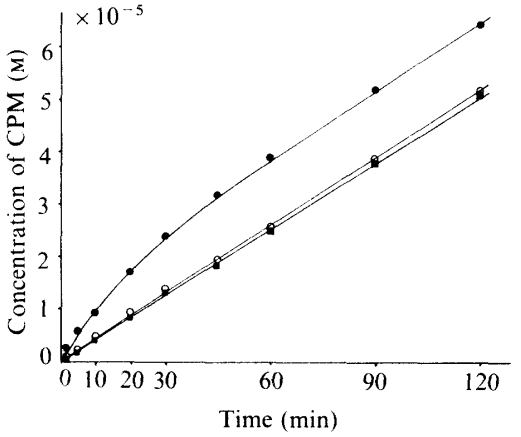

Fig. 3. Initial Dissolution Curves of Form II, Form A and Form C in 250 ml of Deionized Water by the Stationary Disk Method (30 °C, 100 rpm)

●, form II; ○, form C; ■, form A. Each value is the mean of five experimental runs.

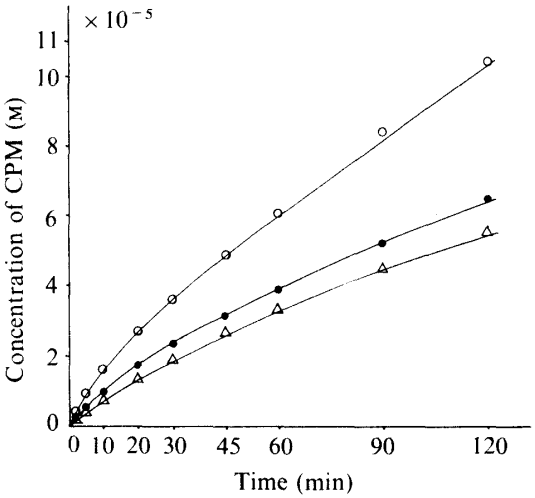

Fig. 5. Initial Dissolution Curves of Form II in 250 ml of Deionized Water under Various Stirring Conditions at 30 °C by the Stationary Disk Method

○, 300 rpm; ●, 100 rpm; △, 50 rpm. Each value is the mean of five experimental runs.

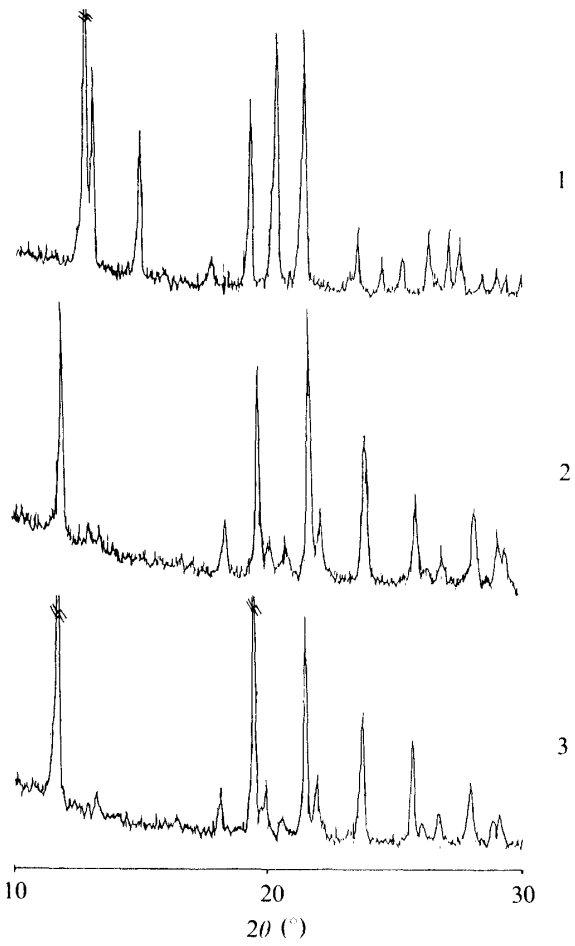

Fig. 4. X-Ray Diffraction Patterns of Form C before and after Compression into a Disk

1: form C before compression. 2: form C after compression. 3: intact form A (stable form).

TABLE I. Saturated Concentrations, C_{sm} and C_{so}, and Rate Constants of Crystallization and Dissolution, K_r and K_t, under Various Stirring Conditions at 30 °C

Sample	Stirring condition (rpm)	$C_{sm} \times 10^3$ (M)	$C_{so} \times 10^4$ (M)	$K_r \times 10^2$ (min^{-1})	$K_t \times 10^4$ (min^{-1})
Form II	300	2.52	9.44	9.95	8.37
	100	2.54	9.44	4.56	4.38
	50	2.53	9.44	2.12	3.02

shows the results obtained for the dissolution of form II under various stirring conditions. All the parameters in Eq. (1) and (2) for the dissolution process were calculated,[13,14] and are summarized in Table I. The values of C_{sm} of form II were two or three times greater than that of C_{so} of form A, indicating that form II showed a greatly enhanced dissolution rate in the initial dissolution stage. These K_r values indicate that the transformation from form II to form A took place in the initial dissolution stage. Thus, it seemed hardly possible to determine the solubility of polymorphs by the usual equilibrium method. Therefore, the stationary disk method employed in this study was used. However, the K_r values were affected by the stirring conditions. This result, therefore, is in conflict with the general concept that the crystallization process takes place in the Volmer layer on the surface of the solid.[11,15] It may be considered that the crystallization process also took place in the diffusion layer; nevertheless, it seems difficult to explain exactly the change of K_r values with stirring conditions.

b) Effect of Temperature on the Dissolution Behavior of Form II——Figure 6 shows the results obtained for form II at various temperatures. The values of dissolution rate after the phase change were in good agreement with those obtained for form A at all temperatures. The dissolution parameters obtained are shown in Table II. These values increased more or less with increase of the bulk liquid temperature.

By plotting the saturated concentration of each form according to the van't Hoff's equation as shown in Fig. 7, the transition temperature was estimated from the intersection point of the two straight lines, and the heat of transition was estimated from the difference in

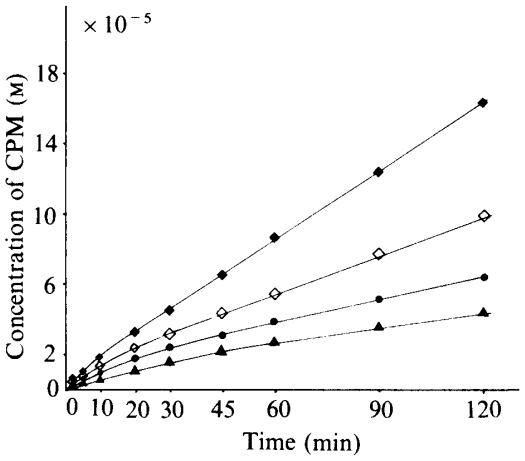

Fig. 6. Initial Dissolution Curves of Form II in 250 ml of Deionized Water at 20, 30, 40 and 50 °C under Stirring (100 rpm) by the Stationary Disk Method

◆, 50 °C; ◇, 40 °C; ●, 30 °C; ▲, 20 °C. Each value is the mean of five experimental runs.

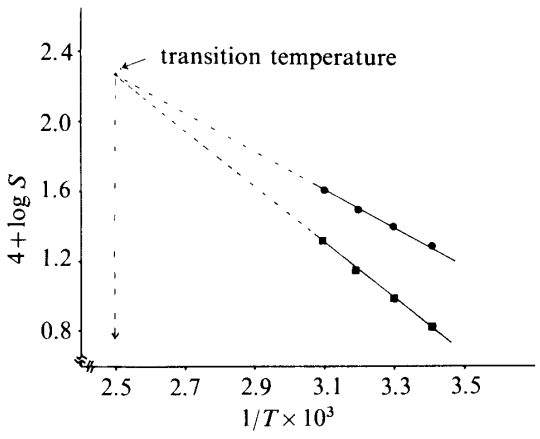

Fig. 7. The van't Hoff Plots for CPM Polymorphs II and A in Deionized Water

S, solubility; ●, form II; ■, form A.

TABLE II. Saturated Concentrations, C_{sm} and C_{so}, and Rate Constants of Crystallization and Dissolution, K_r and K_t, at Various Temperatures under Stirring at 100 rpm

Sample	Temperature (°C)	$C_{sm} \times 10^3$	$C_{so} \times 10^4$	$K_r \times 10^2$	$K_t \times 10^4$
Form II	20	1.79	6.69	2.36	3.49
	30	2.54	9.44	4.56	4.38
	40	3.12	13.90	10.03	5.43
	50	4.15	20.77	20.33	6.31

TABLE III. Thermodynamic Values Calculated for CPM Polymorphs II and A

Sample	Transition temperature (°C)	Heat of solution (kcal/mol)	Heat of transition (kcal/mol)	ΔG_{30} (cal/mol)
Form II	127	4.58	−2.38	−575
Form A		6.96		

TABLE IV. Activation Energies, E_a, of Crystallization and Dissolution in Deionized Water (kcal/mol)

Sample	Crystallization process	Dissolution process
Form II	13.73	3.89

slope between these two straight lines. The results are shown in Table III.

The transition temperature was estimated to be 127 °C and the heat of transition was −2.38 kcal/mol. These values of transition temperature and heat of transition from form II to form A were not confirmed by DSC because the transition temperature is close to the melting point. ΔG for the two polymorphs of chlorpropamide in the present study was about 600 cal/mol. An enhancement of bioavailability by using form II can be expected on the basis of this ΔG if it is possible to prevent the transformation of polymorphs by mean of addition of a protective colloid such as gelatin or gum arabic.[4,16,17] The temperature dependence of K_r and K_t at 100 rpm stirring gave the apparent activation energies, E_a, of crystallization and dissolution, as summarized in Table IV. The value of E_a of crystallization is similar to the data reported for a crystallization process involving a phase change from anhydrate to hydrate.[11] This result also supports the view that transformation of polymorphs took place in the initial dissolution stage. The values of E_a of the dissolution process obtained seem reasonable in comparison with reported data on organic medicinals.[12]

The above results show that the dissolution kinetics of these polymorphs could be analyzed in the same way as described for the anhydrate-to-hydrate conversion reported in a previous paper.[11]

Acknowledgement A part of this study was supported by an Otani Research Grant. The authors are very grateful to Mr. Y. Kimura and Miss C. Takizawa for their assistance in the experimental work. Thanks are also due to Dr. K. Takayama for making his computer programs available for the calculations.

References and Notes

1) This paper forms Part XL of "Physico-chemical Approach to Biopharmaceutical Phenomena." The preceding paper, Part XXXIX: H. Ueda, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 2618 (1982).
2) A part of this work was presented at the 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1983.
3) Formerly, Hoshi Institute of Pharmaceutical Sciences.
4) H. Ueda, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 2618 (1982).
5) D. L. Simmons, R. J. Ranz and N. D. Gyanchandani, *Can. J. Pharm. Sci.*, **8**, 125 (1973).
6) A. Burger, *Sci. Pharm.*, **43**, 152 (1975).
7) S. S. Al-Saieq and G. S. Riley, *Pharm. Acta Helv.*, **57**, 8 (1982).
8) K. Takayama, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **25**, 2608 (1977).
9) K. Sekiguchi, E. Owada and K. Ito, *Chem. Pharm. Bull.*, **15**, 873 (1967).

10) Y. Hamada, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **23**, 1205 (1975).
11) H. Nogami, T. Nagai and T. Yotsuyanagi, *Chem. Pharm. Bull.*, **17**, 499 (1969).
12) H. Nogami, T. Nagai, E. Fukuoka and T. Yotsuyanagi, *Chem. Pharm. Bull.*, **17**, 23 (1969).
13) This calculation was carried out on a Toshiba PASOPIA microcomputer with the "MULTI" program.
14) "MULTI": Y. Tanaka and K. Yamaoka, "Kagakusha no Tame no Maicon Gaido," Nankodo, Ltd., Tokyo, 1981.
15) M. Volmer, *Physick. Z.*, **22**, 646 (1921).
16) A. J. Aguiar and J. E. Zelmer, *J. Pharm. Sci.*, **58**, 983 (1969).
17) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).