

[Chem. Pharm. Bull.]  
34(3)1289—1298(1986)

## Physicochemical Characterization of Oxyphenbutazone and Solid-State Stability of Its Amorphous Form under Various Temperature and Humidity Conditions<sup>1)</sup>

YOSHIHISA MATSUDA\* and SACHIYO KAWAGUCHI

*Kobe Women's College of Pharmacy, Motoyama, Higashinada-ku,  
Kobe 658, Japan*

(Received July 29, 1985)

Four modifications (monohydrate, hemihydrate, anhydrate, and amorphous form) of oxyphenbutazone were prepared and characterized by the use of X-ray powder diffractometry, thermal analysis, infrared spectrophotometry, and elemental analysis. The physicochemical stability of the amorphous form was quantitatively investigated by X-ray diffractometry at three temperatures (25, 40, and 50°C) and three relative humidity levels (0, 50, and 75%). The amorphous form transformed to the anhydrate at low humidity, while it transformed to either the hemihydrate or the monohydrate at moderate or high humidity. These hydrates also converted to the anhydrate *via* the amorphous state at low humidity. The anhydrate did not transform under any storage conditions and showed the highest stability. Increase of temperature greatly accelerated the transformation rate, but the transformation mechanism was not changed.

Among the four modifications the dissolution properties of the hydrates were unexpectedly superior to those of the anhydrate or amorphous form.

**Keywords**—oxyphenbutazone; stability; monohydrate; hemihydrate; anhydrate; amorphous form; characterization; X-ray powder diffractometry; thermal analysis; transformation

### Introduction

In designing solid or semi-solid dosage forms, one major factor that controls their bioavailability is the crystal form of the drug. It is well known that, in general, due to the higher potential energy, an amorphous form has higher solubility than the crystalline forms of drugs and thus shows better bioavailability.<sup>2)</sup> Undesirably, noncrystalline solid converts sooner or later to crystalline forms, *i.e.*, less clinically effective forms, depending on the storage conditions. Although there are several reports on the dissolution properties of the amorphous form of a drug,<sup>3-5)</sup> few studies have appeared on the stability.<sup>3,5,6)</sup> It is therefore essential for more rational dosage design to evaluate the stability of an amorphous drug.

Oxyphenbutazone is one of the longest-serving members of the non-steroidal anti-inflammatory drugs, together with phenylbutazone. Although oxyphenbutazone was designated in Japan as a restricted drug by the Minister of Health and Welfare<sup>7)</sup> and is available only to hospitals, it still holds an important place as a control drug for the judgement of anti-inflammatory or antipyretic actions of new drugs. Its dosage forms commercially available are tablets and suppositories; the release characteristics of the drug from different suppository bases have been reported.<sup>8)</sup> In the present work the preparation of the amorphous form of this drug was attempted and its transformation to crystalline forms under various storage conditions was investigated quantitatively by the use of X-ray powder diffractometry, which is most useful for studying a heat-sensitive reaction.<sup>9)</sup>

### Experimental

**Preparation of Crystalline and Amorphous Forms**—The modifications were prepared as follows: Form I

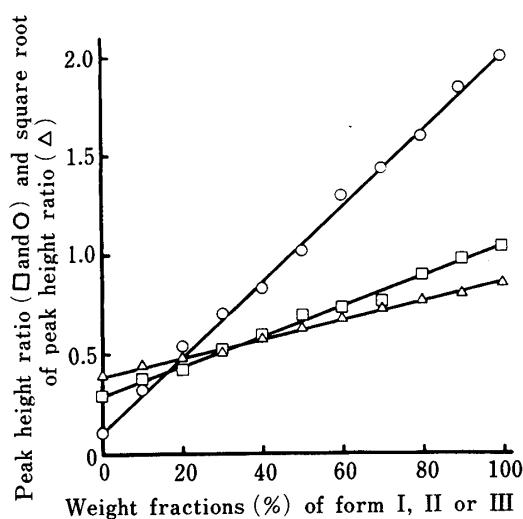


Fig. 1. Calibration Curves for Forms I (Monohydrate), II (Hemihydrate), and III (Anhydrate) by X-Ray Powder Diffractometry  
 $\Delta$ , form I;  $\square$ , form II;  $\circ$ , form III.

(monohydrate): A single batch of commercial oxyphenbutazone (Dolder Ltd., Lot No. 30662; Switzerland) was used; the drug (6.0 g) was dissolved in a mixed hot solvent (100 ml) of methanol and water (1 : 1) and allowed to recrystallize at room temperature. Form II (hemihydrate): The drug (6.0 g) was dissolved in 100 ml of methanol, water was added to this solution until the cloud point was reached, and then recrystallization was allowed to occur. Form III (anhydrate): The drug (6.0 g) was dissolved in 100 ml of methylene chloride, then anhydrous magnesium sulfate as a dehydrating agent was added, and the solution was evaporated to dryness at 40 °C under reduced pressure. Form IV (amorphous form): This form was prepared by the same method as for form III except that the evaporation temperature was 15 °C. The separated crystals of these modifications were collected by filtration through a sintered-glass funnel and dried under reduced pressure. They were triturated in a mortar, and the sieve fraction of < 150 mesh was used for dissolution and stability studies. The solvents used were all of reagent grade. No other modifications could be found.

**Identification of Modifications**—The modifications were identified by using X-ray powder diffractometry (Rigaku Denki, Geigerflex model 2011; Ni-filtered Cu- $K_{\alpha}$  radiation, 35 kV, 5 mA; scanning speed, 4°/min; count range, 1000 cps), differential scanning calorimetry (DSC, Shimadzu Corporation, model DSC-30; open pan system in nitrogen gas flow; heating rate, 10 °C/min; sensitivity,  $\pm 5$  mJ/s), thermogravimetry (TG, Shimadzu Corporation, model TG-30; sensitivity,  $\pm 0.5$  mg), infrared (IR) spectrophotometry by the KBr disc method (Hitachi, model 295), and elemental analysis.

**Dissolution Studies**—The solubilities of the sample powders were determined in simulated intestinal fluid (USP XX), pH 7.5, at 37 °C. The sampling procedures were the same as used in a previous investigation.<sup>9</sup> The concentrations of drugs were determined by measurement of the absorbance at 253 nm using a ultraviolet (UV) spectrophotometer (Shimadzu Corporation, UV-140). The dissolution rate was also determined in accordance with the stationary disc method reported previously.<sup>10</sup> In the present investigation the dissolution medium withdrawn from the dissolution system was continuously fed into a flow cell of the spectrophotometer through a peristaltic pump, and the absorbance was recorded automatically. The rate was determined five times for each sample.

**Measurement of Contact Angles**—Each sample powder (100 mg) was filled into a single set of flat-faced punches and die, which was fitted on a compression-tension testing machine (Shimadzu Corporation, Autograph IS-5000). Pellets of 8-mm diameter were prepared at a constant compression force of 1000 kg. About 13.5  $\mu$ l of the dissolution medium was deposited on the pellet surface on a contact angle meter (Kyowa Kaimenkagaku, model CA-D). The droplet was then built up with a further increment of liquid and the photographs of the droplet were taken after 5 and 15 s. The contact angle,  $\theta$ , was calculated from the following equation:

$$\theta = 2 \tan^{-1} \left( \frac{h}{r} \right)$$

where  $h$  and  $r$  are the height and radius of the droplet, respectively. The measurements were taken on five pellets at 25 °C for each sample.

**Preparation of Calibration Curves and Determination of Transformation Rate**—Known quantities of forms I, II, or III were thoroughly mixed with form IV in various ratios in a mortar. Lithium fluoride as an internal standard was added to each mixture in a constant weight ratio of 1 : 2, and mixed thoroughly. The trinary mixture was subjected to X-ray powder diffractometry. As is evident from Fig. 1, the plots of the ratio of diffraction peak heights of form II (21.5°) or form III (8.5°) to that of lithium fluoride (38.8°) against the weight fractions of forms II or III gave good linear correlations ( $r = 0.994$  and  $0.998$  for form II and III systems, respectively), as did the plots of square

root of the diffraction peak height ratio of form I ( $15.2^\circ$ ) to lithium fluoride ( $38.8^\circ$ ) ( $r=0.997$ ). The peak height ratio was determined in triplicate for each system and weight fraction. These plots were always reproducible. The determination of the single peak height of lithium fluoride at  $38.8^\circ$  was not disturbed by any diffraction peaks attributable to forms I, II, or III. Hence, these three calibration curves were used to determine the transformation rate of form IV to forms I, II, or III.

**Storage Conditions and Sampling of Modifications**—The designated amount of a sample was placed in a vial as gently as possible and stored over saturated solutions of various salts placed in laboratory desiccators. The desiccators were kept in a thermostated cabinet. Phosphorus pentoxide was used to provide a limiting humidity of 0% relative humidity (RH). The amorphous sample was stored in the form of a binary mixture with lithium fluoride. From the results of a preliminary control stability study without lithium fluoride, it was confirmed that the addition of lithium fluoride to the sample did not significantly affect the transformation rate during storage. The storage conditions for form IV were as follows: 25, 40, and  $50^\circ\text{C}$ ; 0, 50, and 75% RH. The stored sample was withdrawn from each vial at various time intervals for X-ray powder diffractometry. After the measurement, the sample was returned to the vial for further storage.

## Results and Discussion

### Characterization of Modifications

Figure 2 shows the X-ray powder diffraction patterns of forms I, II, III, and IV. Distinct differences in the profiles among forms I, II, and III were evident; form I displayed two characteristic peaks at  $9.0$  and  $15.2^\circ$ , whereas the diffraction intensity of form II was the strongest at  $19.2^\circ$ . Form III showed the maximal diffraction peak at  $8.5^\circ$  in close vicinity to that of form I, but the discrimination of the two forms was possible in the region of higher diffraction angles. Form IV did not show any diffraction peak, but gave a halo pattern.

Figure 3 depicts the DSC thermograms of the same forms as those in Fig. 2. Form I showed a broad endothermic peak at about  $80^\circ\text{C}$ , but it showed no other endothermic or exothermic peaks at higher temperatures, suggesting that no transformation to any other form occurred. A similar result was obtained for form II, which showed an endotherm at

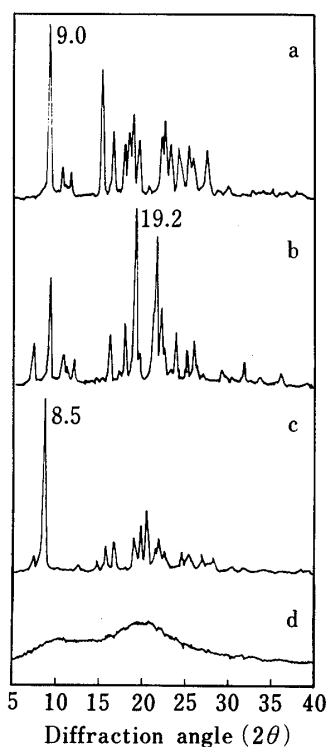


Fig. 2. X-Ray Powder Diffraction Patterns of Forms I (a), II (b), III (c), and IV (d)

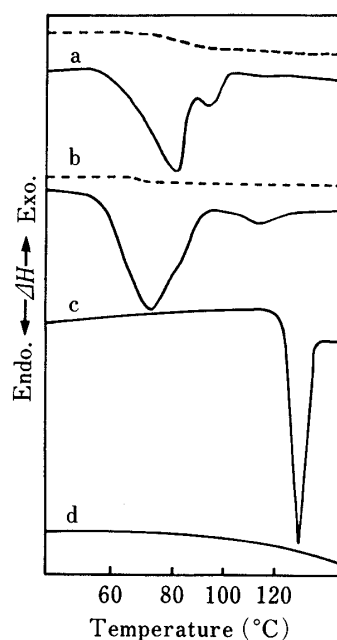


Fig. 3. DSC (—) and TG (----) Curves of Forms I (a), II (b), III (c), and IV (d)

Sample weight: 9.59 (form I), 10.62 (form II), 11.44 (form III), and 7.18 mg (form IV).

76 °C. The thermogravimetric analysis patterns for forms I and II showed losses in weight which began at 70 °C and were complete at about 130 °C. The losses for forms I and II represented about 5.0 and 2.4% of the total, which are very close to the theoretical values of 5.26 and 2.70% for a 1 : 1 and a 2 : 1 hydrate, respectively. Form III showed only one sharp endothermic peak at 126 °C, which was well above the melting points of forms I and II. Form IV showed only a diffuse endotherm, thus proving it to be in an amorphous state.

The infrared (IR) spectra of the four forms are shown in Fig. 4. There were significant

TABLE I. Elemental Analyses of Oxyphenbutazone Modifications

Modification	Formula	Elemental analysis (%)			H <sub>2</sub> O (%)	
		Calcd (Found)			Calcd	Found <sup>a)</sup>
		C	H	N		
Form I (Monohydrate)	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> · H <sub>2</sub> O	66.65 (66.57)	6.48 (6.47)	8.18 (8.25)	5.26	5.0
Form II (Hemihydrate)	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> · 1/2 H <sub>2</sub> O	68.45 (68.58)	6.35 (6.34)	8.40 (8.32)	2.70	2.4
Form III (Anhydrate)	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	70.35 (69.97)	6.22 (6.19)	8.64 (8.63)	0	—
Form IV (Amorphous form)	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	70.35 (69.75)	6.22 (6.22)	8.64 (8.53)	0	—

a) Thermogravimetry.

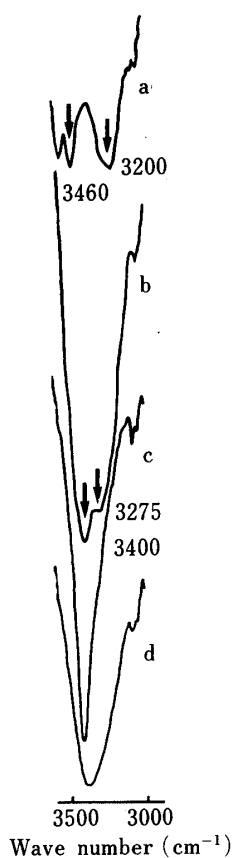


Fig. 4. IR Spectra of Forms I (a), II (b), III (c), and IV (d)

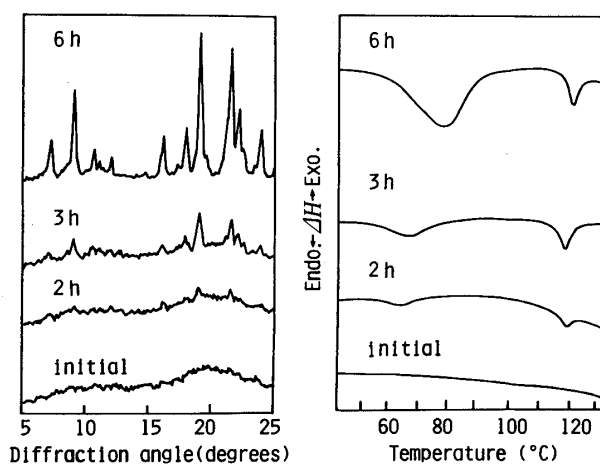


Fig. 5. Changes in X-Ray Diffraction Pattern (Left) and DSC Thermogram (Right) of the Amorphous Form Owing to Transformation at 40 °C and 75% RH

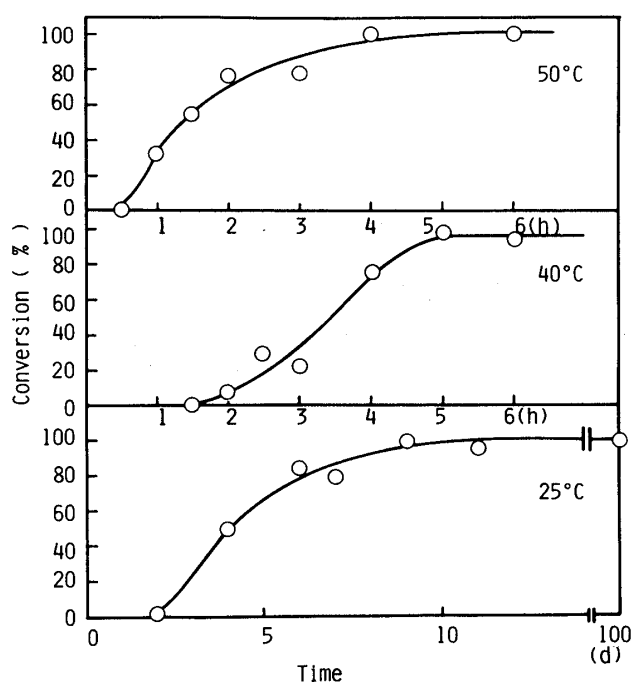


Fig. 6. Time-Course of Transformation of the Amorphous Form to the Hemihydrate at 75% RH

differences among these modifications in the absorption bands due to hydroxyl groups; forms I and II each showed a further absorption band (at  $3460$  and  $3400\text{ cm}^{-1}$ , respectively) due to the hydroxyl group in the water of crystallization, in addition to that (at  $3200$  and  $3275\text{ cm}^{-1}$ , respectively) due to the phenolic hydroxyl group. On the other hand, forms III and IV each showed only one absorption band (at  $3420$  and  $3380\text{ cm}^{-1}$ , respectively) due to the phenolic hydroxyl group. In addition, form III gave a strong and sharp absorption curve in this wave number region, while that of form IV was broad and medium. These results may be due to a difference in the molecular association in the crystal lattice. The results of X-ray diffractometry, thermal analysis, IR spectroscopy, and elemental analysis (Table I) prove conclusively that forms I, II, III, and IV are the monohydrate, hemihydrate, anhydrate, and amorphous form, respectively. Thus the general nature of these modifications was established to provide a firm basis for the subsequent discussion.

#### Stability of Amorphous Form at High Humidity

Figure 5 shows typical time-courses of the X-ray powder diffraction pattern and DSC thermogram of the amorphous form stored at  $40^\circ\text{C}$  and 75% RH. The X-ray diffraction patterns obtained after more than 2 h did not coincide with any pattern of anhydrate or monohydrate. A marked increase of the diffraction intensities at  $19.2$  and  $21.5^\circ$  and the occurrence of a broad endotherm at about  $80^\circ\text{C}$  on the DSC curve strongly suggest hemihydration. This reasoning is well supported by the fact that the X-ray diffraction pattern and DSC curve obtained after 6 h were in good agreement with those of the intact sample prepared by the recrystallization method. Figure 6 illustrates the quantitative time course of the percent conversion to hemihydrate at three temperature levels and at 75% RH. The best-fitting curves at the three temperatures were all sigmoidal in shape. The transformation rate was affected by temperature and was remarkably accelerated with elevation of temperature; at  $25^\circ\text{C}$  the transformation began after an induction period of about 2 d and was complete within 10 d. The time-course of the percent conversion was in good correspondence to that of weight loss obtained from the TG curves (not presented in this paper); the weight loss reached about 2.1% after 7 d, which was a little lower than the theoretical value (2.70%), and was thereafter equilibrated. The fact that even after 100 d of storage the hemihydrate did not transform to any other modification proves it to be sufficiently stable under these conditions.

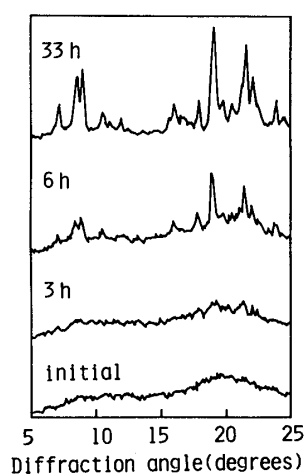


Fig. 7. Changes in X-Ray Diffraction Pattern (Left) and DSC Thermogram (Right) of the Amorphous Form Owing to Transformation at 40°C and 50% RH

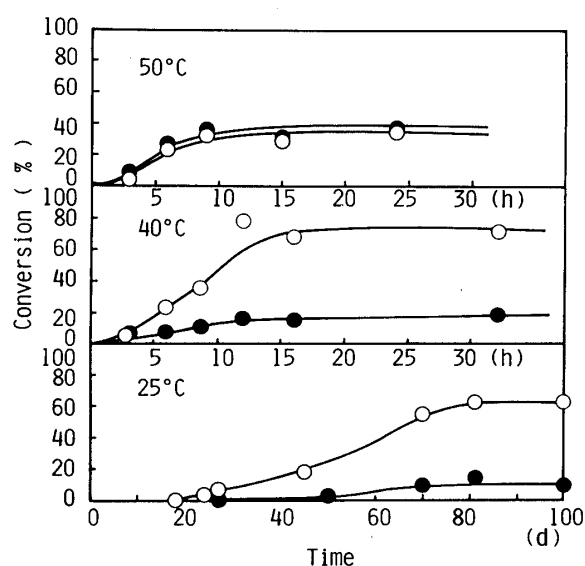


Fig. 8. Time-Course of Transformation of the Amorphous Form to the Hemihydrate (○) and Anhydrate (●) at 50% RH

However, at 40 and 50°C, the transformations began within only 1.5 and 0.5 h, respectively, and progressed more rapidly. Although hemihydration was complete in a few hours, the results obtained after prolonged storage (100 d and 1 year) revealed that the hemihydrate partially converted to the monohydrate, suggesting that consecutive transformation would occur at higher temperatures; the conversions to the monohydrate after these storage times at 40°C were 20 and 38%, respectively. This result suggests that the transformation of the hemihydrate to the monohydrate is the rate-determining step in the crystallization process of the amorphous form.

#### Stability of Amorphous Form at Moderate Humidity

Figure 7 shows the time-courses of X-ray diffraction pattern and DSC curve of the amorphous form stored at 40°C and 50% RH. The diffraction intensities at 8.5, 9.0, 19.2, and 21.5° increased markedly with increasing storage time. The DSC thermogram also showed both a broad endotherm at about 80°C and a sharp endothermic peak at 120–126°C, which were assigned to the hemihydrate and anhydrate, respectively. These results indicate that the anhydrate and hemihydrate were formed simultaneously during the transformation process. Figure 8 shows the time-course of transformation of the amorphous form stored at the same temperatures as in Fig. 6 at 50% RH. At 25°C the amorphous form began to transform with an induction period of about 20 d, and the percent remaining decreased to 30% after 100 d; the conversions to the hemihydrate and anhydrate were 61 and 9%, respectively. The higher the temperature, the more rapidly the transformation progressed, with a shorter induction period. The relative conversions of the hemihydrate to the anhydrate in the equilibrium state at 25, 40, and 50°C were 6.8, 3.5, and 0.9, respectively, so that a lower relative conversion of the hemihydrate occurred at higher temperature. This result suggests that sufficient entrapping of water molecules in the crystal entity is more difficult at higher temperature. In addition, the fact that the equilibrium states obtained at 40 and 50°C were maintained during prolonged storage (10 d) confirms that no further transformations of these modifications occurred.

#### Stability of Amorphous Form at Low Humidity

As expected from the results of Figs. 6 and 8, the anhydrate was the only transformation

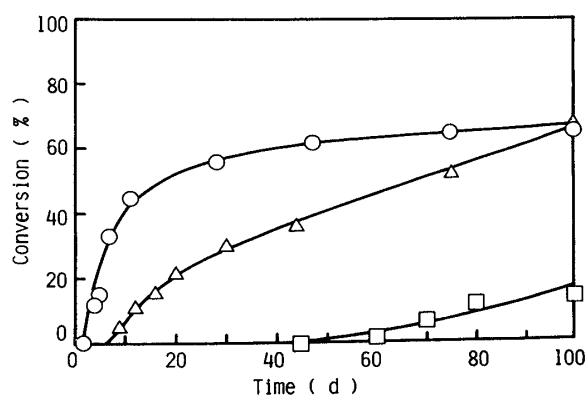


Fig. 9. Time-Course of Transformation of the Amorphous Form to the Anhydrate at 0% RH

□, 25°C; △, 40°C; ○, 50°C.

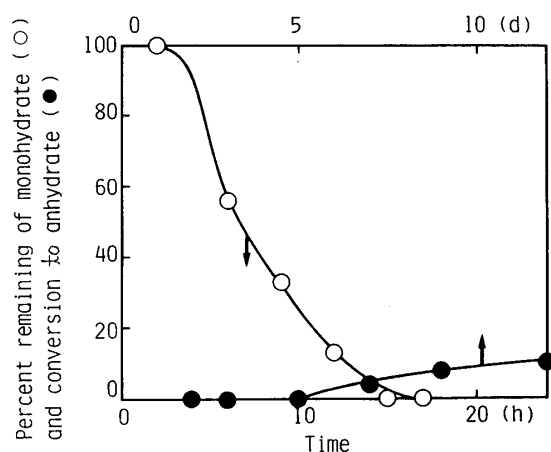


Fig. 10. Time-Course of Transformation of the Monohydrate (○) to the Anhydrate (●) via the Amorphous Form at 40°C and 0% RH

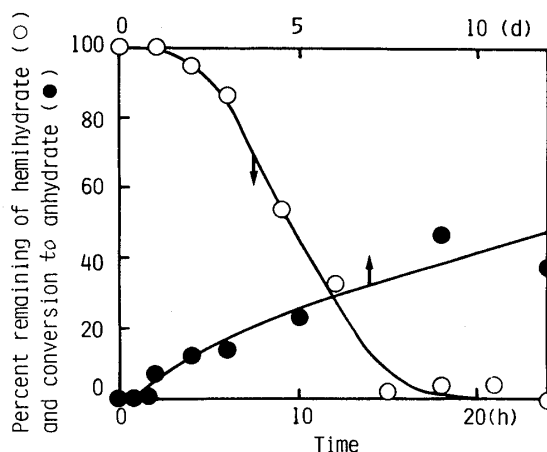


Fig. 11. Time-Course of Transformation of the Hemihydrate (○) to the Anhydrate (●) via the Amorphous Form at 40°C and 0% RH

product of the amorphous form at every temperature under the condition of 0% RH (Fig. 9). It took more than 45 d at 25°C for the transformation to start, and the conversion was only 14% even after storage for 100 d. Although the effect of temperature was also remarkable at this extreme relative humidity, the transformation was by far the slowest among the three relative humidities. This finding suggests that water molecules adsorbed on the surface of the amorphous powder contribute to the transformation. Judging from the water-absorbing power of phosphorus pentoxide, as well as the environmental temperature and atmospheric pressure, complete desorption of water molecules from the sites of potential nuclei formation seems to be difficult under this humidity condition. Therefore, even though the amount of water is very small, it may serve as a nucleation catalyst in the anhydration process.<sup>9)</sup>

### Stabilities of Monohydrate, Hemihydrate, and Anhydrate

To investigate the possibility of transformation of the monohydrate and hemihydrate at low humidity, intact samples of these modifications were stored at 40°C and 0% RH. Figure 10 shows the time-course of percent remaining of the monohydrate and of the conversion to the anhydrate. The percent remaining of the monohydrate gradually decreased as dehydration progressed, and the monohydrate transformed completely to an amorphous form within 15 h. The amorphous state persisted for more than 5 d, and then a further transformation to the anhydrate started. The escape of water molecules from the crystal entity might give rise to the disorder of the crystal structure. It is noteworthy that the monohydrate transformed not directly but consecutively to the anhydrate via a transition state which was relatively stable.

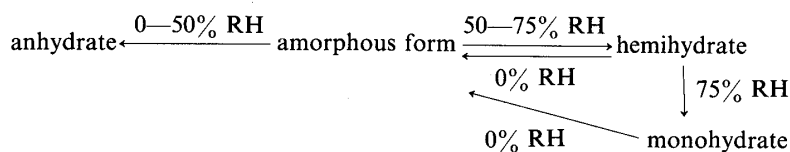


Chart 1. Postulated Mechanism for Transformations of the Amorphous Form under Various Storage Conditions

TABLE II. Product(s) during the Transformation of the Amorphous Form under Various Storage Conditions

Temperature (°C)	Relative humidity		
	0%	50%	75%
25	Anh <sup>a)</sup>	Anh + Hemi <sup>b)</sup> ↑	Hemi
40	Anh	Anh + Hemi	Hemi → Mono <sup>c)</sup>
50	Anh	Anh + Hemi ↓	Hemi → Mono

a) Anhydrate. b) Hemihydrate. c) Monohydrate. The downward and upward arrows represent increase of conversion to the anhydrate and hemihydrate, respectively.

TABLE III. Contact Angles of Oxyphenbutazone Modifications<sup>a)</sup>

Modification	Contact angle (°)	
	After 5 s	After 10 s
Monohydrate	67.6	63.4
Hemihydrate	66.2	62.6
Anhydrate	78.6	76.4

a) The contact angle of the amorphous form could not be determined because of the poor compressibility. Each value represents the mean of five determinations.

The rate-determining step in this transformation is therefore the anhydration process. This result suggests that the crystal structure differs considerably between the monohydrate and the anhydrate, and that consequently the molecules cannot easily rearrange after once becoming randomly oriented. Figure 11 shows the stability of the hemihydrate under the same conditions as for the monohydrate. The mode of transformation was quite similar except that anhydration of the hemihydrate was more rapid than that of the monohydrate. This may be attributed to the difference in the amount of water molecules entrapped in the crystal lattice. The stability of the resultant anhydrate was evaluated at 40 °C and 75% RH. The X-ray diffraction pattern and thermogram of the sample stored for 1 year did not show any change, thus proving that no hydration accompanied the production of the hemihydrate or monohydrate. Based on the above results and discussion, a possible transformation mechanism of the amorphous form and the products under various storage conditions is summarized in Chart 1 and Table II. Chart 1 clearly demonstrates that the anhydrate is the most stable form under all storage conditions tested, and that the amorphous form converts to either the anhydrate or the hydrates, depending on the relative humidity.

### Dissolution Properties

The dissolution properties of the four modifications are depicted in Fig. 12. The apparent equilibrium solubilities were almost the same for the monohydrate, hemihydrate, and amorphous form. It is generally believed that anhydrous forms show higher solubilities than hydrated materials.<sup>11-16)</sup> The reason for this has been assumed to be that as the hydrate has already interacted with water, the energy released for crystal break-up, on interaction of the hydrate with water, is less than that for the anhydrate.<sup>15)</sup> However, the anhydrate in the present investigation unexpectedly gave much lower equilibrium solubility than the other forms without showing a solubility maximum, due to the transformation in the solution; the hemihydrate was thus about 1.8 times more soluble than the anhydrate. The discrepant behavior of the anhydrate can be explained in terms of the foregoing result that the anhydrate was the most thermodynamically stable form and did not transform to any other forms. The dissolution rate in the unequilibrated dissolution process was in the sequence hemihydrate >



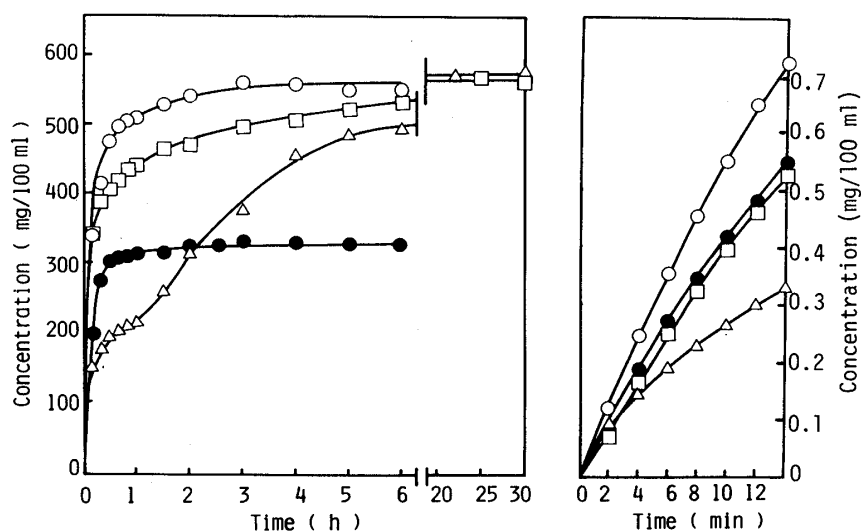


Fig. 12. Solubility Profiles (Left) and Dissolution Rates (Right) of the Monohydrate (□), Hemihydrate (○), Anhydrate (●), and Amorphous Form (△) in Simulated Intestinal Fluid at 37°C

monohydrate > anhydrate. This result agreed with the logic of Shefter and Higuchi<sup>11)</sup> that the dissolution rate of hydrated material would theoretically decrease with increase in the amount of water of crystallization. The abnormal behavior of the anhydrate in dissolution may be attributable to much higher hydrophobicity of the crystal surfaces than in any other form (Table III). The difference of wettability among the crystal forms depends on the surface energy. Therefore, it is likely that different crystal forms of a drug have different contact angles. Poorer dissolution properties of the anhydrate as compared with hydrates have also been observed for erythromycin.<sup>17)</sup> The dissolution profiles almost entirely reflected the dissolution rates except for the anhydrate. In these two figures the amorphous form unexpectedly showed the poorest dissolution properties. This is certainly ascribable both to rapid hydration, which obstructs the diffusion of drug molecules into the bulk solution, and to lowering of the effective surface area due to the subsequent rigid agglomeration of crystals. Such hydration could be confirmed by X-ray diffractometry for amorphous sample remaining undissolved.

In conclusion, the amorphous form of oxyphenbutazone was unstable under all storage conditions tested, and was transformed to the anhydrate, hemihydrate, or monohydrate depending sensitively on the environmental relative humidity. The transformation rate was markedly accelerated with an elevation of temperature. This is the first report to propose a quantitative interpretation of the different transformations of an amorphous material. It was also of interest that dehydration or hydration between the anhydrate and hydrates was not reversible. The *in vitro* availability of the amorphous form was inferior to those of the two hydrates. On the basis of these properties, the monohydrate, which is specified in the Japanese Pharmacopeia (JP X), may be the most suitable form for the preparation of pharmaceuticals.

#### References and Notes

- 1) This study was presented in part at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982.
- 2) J. D. Mullins and T. J. Macek, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 245 (1960).
- 3) H. Imaizumi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **28**, 2565 (1980).
- 4) Y. Fukumori, T. Fukuda, Y. Yamamoto, Y. Shigitani, Y. Hanyu, Y. Takeuchi, and N. Sato, *Chem. Pharm. Bull.*, **31**, 4029 (1983).

- 5) M. Otsuka and N. Kaneniwa, *Chem. Pharm. Bull.*, **31**, 230 (1983).
- 6) T. Macek, *Am. J. Pharm.*, **137**, 217 (1965).
- 7) Notification No. 109 of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Dated February 21st, 1984.
- 8) S. A. Ibrahim, A. Abd Elbary, H. Elsorady, and H. Abd Elmonem, *Pharmazie*, **35**, 170 (1980).
- 9) Y. Matsuda, E. Tatsumi, E. Chiba, and Y. Miwa, *J. Pharm. Sci.*, **73**, 1453 (1984).
- 10) Y. Matsuda, S. Kawaguchi, H. Kobayashi, and J. Nishijo, *J. Pharm. Sci.*, **73**, 173 (1984).
- 11) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).
- 12) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.*, **14**, 339 (1966).
- 13) A. J. Aguiar and J. E. Zelmer, *J. Pharm. Sci.*, **58**, 983 (1969).
- 14) M. A. Moustafa, A. R. Ebian, S. A. Khalil, and M. M. Motawi, *J. Pharm. Pharmacol.*, **23**, 868 (1971).
- 15) A. T. Florence and D. Attwood, "Physicochemical Principles of Pharmacy," Macmillan Press Ltd., London, 1981, p. 17.
- 16) M. Otsuka and N. Kaneniwa, *Yakugaku Zasshi*, **102**, 967 (1982).
- 17) P. V. Allen, P. D. Rahn, A. C. Sarapu, and A. J. Vanderwielen, *J. Pharm. Sci.*, **67**, 1087 (1978).