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Dissolution Behavior of Piretanide Polymorphs at Various Temperatures and pHs

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We investigated the dissolution behavior of piretanide polymorphs, forms A and B in buffers from pH 1.0—7.0 at a range of temperatures (30—45 °C) by a dispersed-amount method. These polymorphs were also tested by the stationary-disk method in pH 5 buffer at 30—45 °C. The dissolution of forms A and B compressed into tablets with excipients was also tested in a pH 5 buffer at 37 °C by the paddle method.

The solubility and the initial dissolution rate of forms A and B were temperature dependent at pH 5. Form B showed higher solubility and a faster initial dissolution rate than form A at various temperatures in pH 5. The solubility of form B calculated from the initial dissolution rate determined by the stationary-disk and the conventional dispersed-amount methods agreed well. Tablets of form B dissolved more quickly than those of form A. The solubility of the two forms suggest that a difference in their initial dissolution rates affect the bioavailability of piretanide preparations.

Key words piretanide; polymorph; solubility; initial dissolution rate; stationary disk method

Many polymorphs have been recognized in pharmaceutical preparations and in bulk material, and it is common knowledge that the difference of crystal form affects the bioavailability and stability.[1)] In general, metastable and amorphous forms have higher solubility and faster dissolution rates than the stable form of the drug. Therefore, the absorption rate and/or bioavailability of the metastable form should be higher than the thermodynamically stable form.[2)] Since metastable forms gradually stabilize, however, drug effectiveness may be altered or preparation and storage of pharmaceuticals may be difficult. Knowledge of the transition temperature thus becomes very important from the standpoint of formulating and manufacturing controls. It is also important to know whether polymorphs behave as enantiotropic or monotropic substances, that is, whether the transition from one form to the other is reversible or not.

In this study, the metastable form (form B) of piretanide (3-(aminosulfonyl)-4-phenoxy-5-(1-pyrrolidinyl)-benzoic acid; IUPAC) (Fig. 1) showed higher solubility and a faster initial dissolution rate than the stable form (form A). Furthermore, form B did not change to form A in the conventional solubility study. The transition temperature calculated from the van't Hoff plot using the solubility of the two forms at various temperatures in pH 5 buffer solution by the conventional solubility study corresponded with the value (about 200 °C) obtained by differential scanning calorimetry (DSC).

Experimental

Materials A piretanide bulk sample (lot Nos. L023, L024) was obtained from Hoechst Aktiengesellshaft, Germany. Form B was prepared as described.[3)] The pellets for the stationary disk method were prepared as follows. A powder sample (200 mg) was compressed in a cylindrical die of 13-mm diameter at about 600 kg/cm^2 using an accurate compression/tension testing machine, and the compressed pellet was kept for 1 min in the die at that compression pressure. The ejected pellet was fixed to a dissolution ring holder with beeswax so that only one side of the pellet surface was exposed.

X-Ray Powder Diffraction Analysis X-ray powder diffraction profiles were taken at room temperature with an X-ray powder diffractometer (MXP^3, Mac Science Co.). The operating conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; receiving slit, 0.15 mm; scanning speed, 5° 2θ/min.

Dissolution Study Using the Dispersed Amount Method Various pH dissolution media were prepared:

JP XII first fluid (pH 1.2).

JP XII second fluid (pH 6.8).

pH 1 buffer: KCl–HCl[4)]; 407 ml of 0.2 M HCl and 93 ml of 0.2 M KCl made up to 1 l.

pH 3 buffer: NaCl–glycine–HCl[5)]; 32 ml of 2.5 M NaCl, 31.6 ml of 0.5 M glycine–0.5 M NaCl and 21.0 ml of 0.2 M HCl made up to 1 l.

pH 5 buffer: NaCl–CH_3COONa–CH_3COOH[5)]; 32 ml of 2.5 M NaCl, 20.0 ml of 1.0 M sodium acetate and 40.0 ml of 0.35 M acetic acid made up to 1 l.

pH 7 buffer: NaCl–NaH_2PO_4–Na_2HPO_4[5)]; 32 ml of 2.5 M NaCl, 3.2 ml of 1.0 M NaH_2PO_4 and 22.7 ml of 0.25 M Na_2HPO_4 made up to 1 l.

We investigated the dissolution profiles of the bulk sample (form A) and form B in these buffers. An excess (1000 mg) of the sample was introduced into 250 ml of dissolution medium in a 1000-ml round-bottomed flask with a plastic cover. The flask was fixed on a sample holder in a thermostatically regulated water bath maintained at 37 ± 0.5 °C, and stirred by a paddle at 200 rpm. Aliquots (10 ml) of the solution were withdrawn at various intervals with a syringe through a 0.45-μm membrane filter. The filtrate was diluted and the concentration of the drug was measured at 275 nm with a spectrophotometer (Type 430B, JASCO Co.).

Dissolution profiles of the bulk sample and form B were also investigated in pH 5 buffer at various dissolution medium temperatures (30—45 °C), following the procedure described above.

Initial Dissolution Curve Measurement The initial dissolution profiles of bulk sample and form B were investigated after the pellet was fixed on the dissolution ring holder following the conditions and procedure described above, except that 200 ml of dissolution medium was used, and the solution was introduced into a quartz flow-through cell by a peristaltic pump.

Measurement of Contact Angles of Forms A and B Tablets (8 mm in diameter) of forms A and B were produced by tablet machine at about 1000 kg/cm^2 using 500 mg for each one. The contact angle of each tablet was measured by a droplet method using water.

Manufacturing Procedure for Tablets Consisting of Conventional Piretanide Forms A and B Each tablet was produced at a compression pressure of 1000 kg/cm^2 according to our prescription (Table 1) for Arelix® using each crystal fraction from a 150—350 mesh after sieving.

Measurement of Hardness of Piretanide Form A and B Tablets The hardness of each tablet was measured using a hardness testing machine

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(Erweka type TBH28).

Dissolution Behavior of Piretanide Form A and B Tablets The dissolution profile of each tablet was determined in the pH 5 buffer solution. We used the experiment described to determine the profiles of the bulk sample, except for the dissolution medium volume (500 ml) and temperature, and the rotation speed (50 rpm).

DSC DSC was performed with an 8085E2 DSC-TG instrument (Rigaku Denki Co.). The operating conditions in the open-pan system were: sample weight, about 5 mg; heating rate, 10 °C/min; N_2 gas flow rate, 20 ml/min.

Results and Discussion

Dissolution Profiles of Forms A and B Obtained by the Dispersed-Amount Method Figure 2 (a, b) shows the dissolution profiles of forms A and B at 37 °C in buffers at various pH. Both forms showed normal dissolution curves.

Figure 3 shows that the solubilities of forms A and B depended on the pH of the buffer. The pK_a of piretanide at 1.3 and 3.8 is attributable to the pyrrolidinyl group and to the carboxy group, respectively. As these groups are both changeable depending on pH, respectively, the discrepancy of solubilities was due to the difference in pH.

Table 1. Prescription of Piretanide Tablet

	Piretanide bulk (form A or B)	6.0 mg
Diluent	Corn starch	49.0 mg
Diluent and binder	Crystalline cellulose	104.8 mg
Lubricant	Magnesium stearate	0.2 mg
Total		160.0 mg

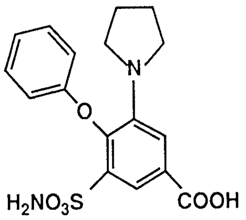

Fig. 1. Structure of Piretanide

Figure 4 also shows that the solubilities of forms A and B in pH 5 buffer depended upon the temperature.

The van't Hoff plots for the two forms (Fig. 5) showed a linear relationship within the temperature range studied, indicating that the two extrapolated straight lines meet at 216 °C. The transition temperature of form B to form A was close to that of form B measured by DSC.[3] The heat of solution was estimated from the slope of the line. These slopes were extremely close to each other, although, the heat of solution of form A (11.6 kcal/mol) was slightly higher than that of form B (10.9 kcal/mol).

X-Xay Powder Diffraction Analysis of Forms A and B The X-ray powder diffraction profile of form A showed the major characteristic peaks at 5.4, 8.4, 10.3, 11.1, 19.7, 20.7 and 21.7° (2θ), whereas that of form B showed peaks at 10.4, 13.3, 15.7, 18.4, 20.1, 23.2 and 24.3° (2θ), indicating that the two modifications significantly differed, as described elsewhere.[3] After compression at about 600 kg/cm^2, pellets of the forms were carefully ground with an agate mortar and pestle, and the X-ray powder diffraction profiles were recorded. The profiles of compressed forms A and B were identical to those of the original samples for every crystal form (Fig. 6). Moreover, after the dissolution experiment, the X-ray powder diffraction profiles of the crystallized precipitate coincided with that of each intact form. These results suggest that no crystallographic change occurred in these crystal forms during the compression process or the dissolution test under our experimental conditions.

Dissolution Profiles of Forms A and B Obtained by the Stationary Disk Method Figure 7 (a, b) shows the initial dissolution curves of forms A and B, respectively, in pH 5 buffer at 30—45 °C obtained by the stationary disk method. Straight lines were obtained under each condition, and both were estimated to be under sink condition for 0—10 min. This shows the effect of temperature on the initial dissolution rate of forms A and B. The values increased with a rise in temperature (Table 2). The

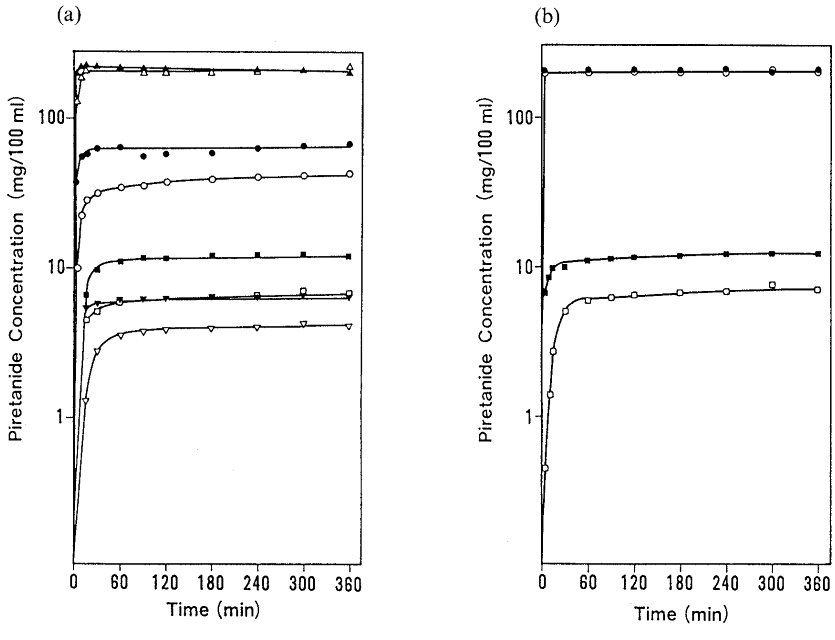

Fig. 2. Solubility of Piretanide Forms A (Open Symbols) and B (Closed Symbols) at 37 °C in Various Buffer Solutions

(a) (□, ■), pH 1; (▽, ▼), pH 3; (○, ●), pH 5; (△, ▲), pH 7. (b) (□, ■), 1st fluid; (○, ●), 2nd fluid.

apparent initial dissolution rate of form B, which was calculated from the slope of the line was 1.5 times higher than that of form A.

The dissolution process of the two forms followed the Noyes–Whitney–Nernst equation. Kanke and Sekiguchi[6] derived Eq. 1 from this equation under sink conditions, assuming the apparent dissolution rate constants of the metastable and stable forms to be shown by:

$$C_{sa}=C_{sh}(J_a/J_h) \tag{1}$$

where C_{sa} is the solubility of form B, C_{sh} is the solubility of form A, J_a is dissolution rate of form B and J_h is the dissolution rate of form A.

Table 3 shows the solubility of form B obtained by the initial dissolution rate and that of both forms obtained by the dispersed amount method. The solubility of form

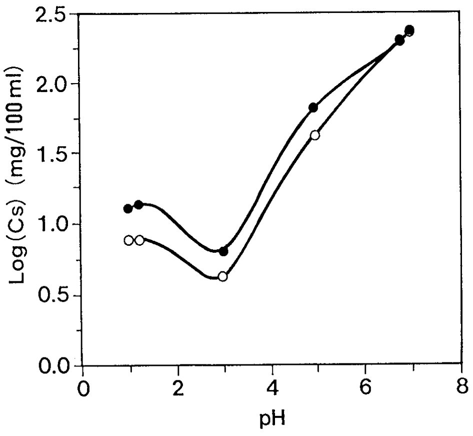

Fig. 3. Effect of pH on the Solubility of Forms A and B
○, form A; ●, form B.

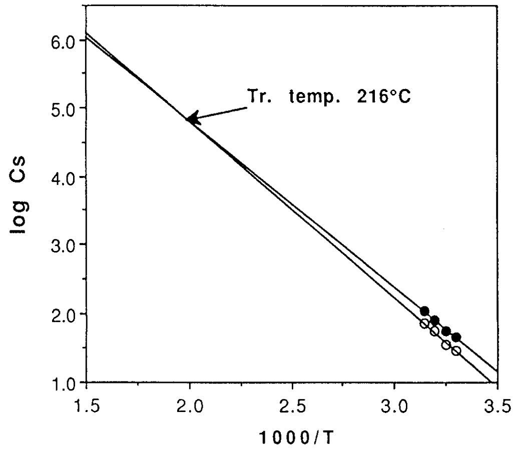

Fig. 5. van't Hoff Plots for Piretanide Forms A and B at pH 5
○, form A; ●, form B.

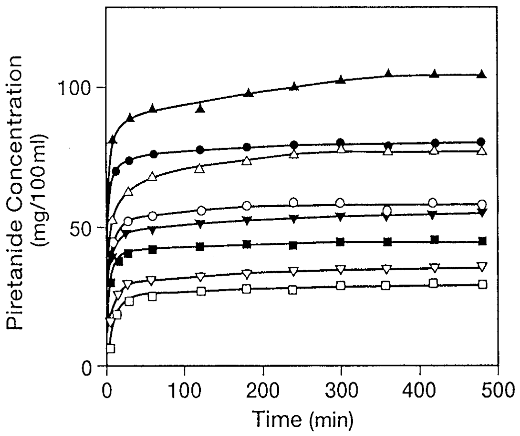

Fig. 4. Solubility of Piretanide Forms A (Open Symbols) and B (Closed Symbols) at Varied Temperatures at pH 5
(□, ■), 30 °C; (▽, ▼), 35 °C; (○, ●), 40 °C; (△, ▲), 45 °C.

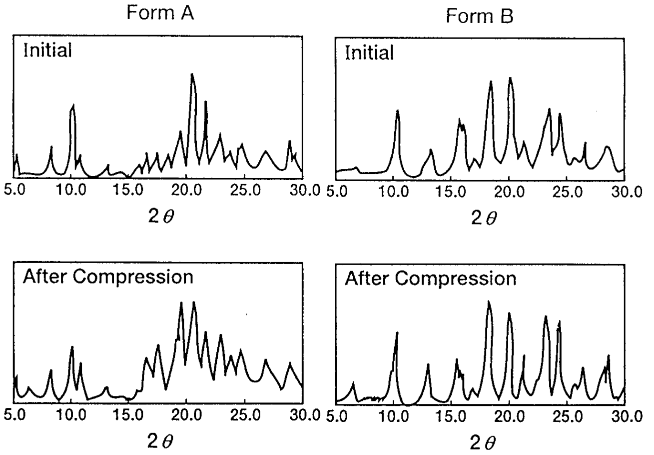

Fig. 6. X-Ray Powder Diffraction Profiles of Piretanide Forms A and B before and after Compression

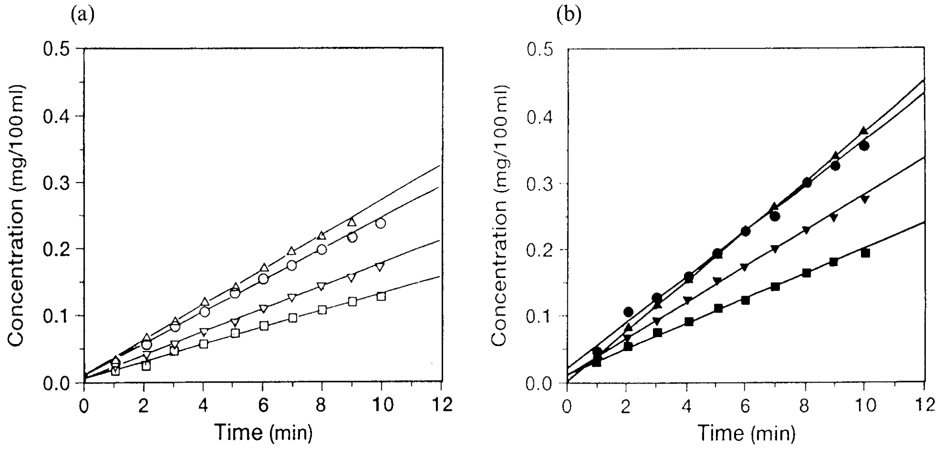

Fig. 7. Initial Dissolution Rate of Piretanide Forms A (Open Symbols) and B (Closed Symbols) at Varied Temperatures at pH 5
(a) □, 30 °C; ▽, 35 °C; ○, 40 °C; △, 45 °C. (b) ■, 30 °C; ▼, 35 °C; ●, 40 °C; ▲, 45 °C.

Table 2. A Comparison of the Initial Dissolution Rate of Piretanide between Forms A and B at Varied Temperatures at pH 5

Temp. (°C)	Initial dissolution rate (μg/ml/min)	
	Form A	Form B
30	0.129	0.189
35	0.174	0.272
40	0.239	0.346
45	0.267	0.372

Table 3. A Comparison of the Solubility of Piretanide Form B between Saturated Solubility and the Initial Dissolution Rate at pH 5

Temp. (°C)	Solubility (mg/100 ml)		
	Form A	Form B	
	Exptl.	Exptl.	Calcd[a]
30	29.7	45.7	43.6
35	35.6	54.6	55.6
40	55.0	81.4	79.4
45	72.1	105.7	100.5

a) Values calculated from equation, $C_{\mathrm{sa}}=C_{\mathrm{sh}}\times J_{\mathrm{a}}/J_{\mathrm{h}}$.

Table 4. A Comparison of the Contact Angles between Piretanide Forms A and B

	Form A	Form B
Contact angle (°)	54.6±1.3	46.7±2.1

Mean±S.D. (n=6).

Table 5. A Comparison of Hardness of Piretanide between Form A and B Tablets

	Form A	Form B
Hardness (kg)	9.14±0.46	9.22±0.31

Mean±S.D. (n=5).

B calculated by Eq. 1 using the initial dissolution rates of forms A and B and using the solubility of form A by the dispersed amount method almost corresponded with that of form B by the dispersed amount method.

Contact Angles of Forms A and B Table 4 shows the contact angles of forms A and B, with that of form B being about 10° smaller than that of form A. This indicated that form B was superior to form A in wettability. Therefore, the dissolution of form B was significantly faster than that of form A.

Hardness of Piretanide Forms A and B Tablets Table 5 shows hardness of tablets of the two forms. No difference was observed between them, because they both contained only 4% bulk material and diluents (cornstarch, crystalline cellulose) accounted for 96%. Therefore, neither of the bulk materials significantly influenced hardness.

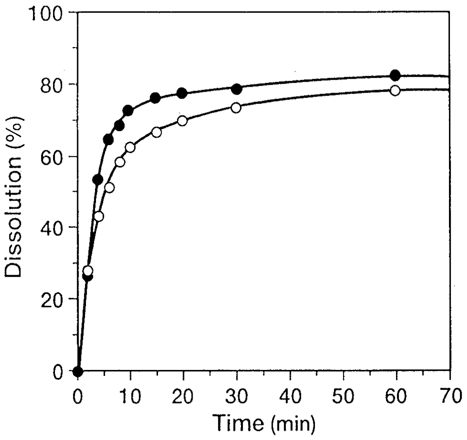

Fig. 8. Dissolution Profiles of Piretanide Form A or B Tablets (6 mg) at 37 °C and 50 rpm at pH 5

○, form A (n=4); ●, form B (n=4).

Dissolution Behavior of Piretanide Forms A and B Tablets Figure 8 shows the dissolution behavior of piretanide tablets using form A or B. The dissolution profiles were similar, although the form B tablet was faster at the beginning. These findings, along with the difference in contact angle, solubility and initial dissolution rate suggested that form B crystals were more hydrophilic, more soluble and had a higher dissolution rate than form A.

Conclusion

In this study, form B obtained by desolvation after recrystallization was about 1.5—1.6-fold more soluble than the stable form A in acidic buffers (pH 1—5) at various temperatures (30—45 °C). In spite of its metastable form, form B was stable without polymorphic transformation into form A in various pH buffer solutions. Tablets produced according to the prescription for our commercial preparation Arelix® using form B crystals exhibited better dissolution than form A. These results suggested that form B would be more bioavailable than form A.

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