Preparation of Piretanide Polymorphs and Their Physicochemical Properties and Dissolution Behaviors

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Piretanide polymorphs were prepared by recrystallization using 27 organic solvents. We identified a new polymorphism, forms A and B, and 6 solvates. They were characterized by X-ray powder diffractometry, differential scanning calorimetry (DSC), thermogravimetry (TG), Fourier-transform infrared (FTIR) spectroscopy, elemental analysis and scanning electron microscopy. After heating, some solvates transformed to the stable form A , and others to form B. X-ray powder diffraction patterns and FTIR spectra of forms A and B were significantly different. However, the X-ray powder diffraction patterns and FTIR spectra of form A and the bulk sample were similar. The DSC curve of form A showed only an endothermic peak at 227 °C corresponding to the melting point. The DSC curve of form B showed endothermic and exothermic peaks at 213 and 216 °C, respectively, as well as a subsequent endothermic peak at 227 °C. The metastable form B transformed to form A. The dissolution profiles of the bulk sample and form B in JP XII, 1st fluid (pH 1.2) at 37 °C were measured by means of the dispersed amount. The solubilities of the bulk sample and form B were estimated to be 8.3 and 13.3 mg/100 ml, respectively.

Keywords piretanide; solvate; X-ray powder diffractometry; solubility; polymorph

Pre-formulation studies are of prime importance in the rational development of dosage forms of labile drugs. To design a dosage form, it is necessary to know the physicochemical properties of the drug, such as solubility, hygroscopicity, dissolution, tabletting compression behavior and others.[1,2]

The polymorphism of drugs affects the physicochemical properties of bulk powders, because metastable crystalline solids have high chemical potential and are unstable. The physicochemical properties of bulk drug powders alter the bioavailability of the preparations by affecting the dissolution rate and/or tablet disintegration. In particular, knowledge of these properties of polymorphic forms of drugs, which are practically insoluble in water, is important for the pharmaceutical design of preparations.[3–5] The stability of polymorphic forms during the manufacturing process is important for the practical application of pharmaceutical preparations. Since the particle size and crystalline form of a drug affect its bioavailability through the dissolution rate[6] depending on the surface area and solubility of the polymorphic forms, mechanical processes such as grinding and tabletting are critical for making high quality pharmaceuticals. Thus, the pharmaceutical design of drugs, especially those of polymorphic forms, is key to producing high quality pharmaceuticals.

Piretanide has widely been used as a diuretic or antihypertensive drug. Since it is practically insoluble in water, especially in an acidic environment, improvement of its dissolution properties is essential, since the solubility of the bulk sample is very low (6.5 mg/100 ml at pH 1), which affects the bioavailability of the pharmaceutical preparation. Kuhnert-Brandstatter and Porche qualitatively reported three piretanide modifications using differential scanning calorimetry (DSC).[7] However, detailed physicochemical properties have not been reported. In this study, we prepared a novel metastable form *via* piretanide solvates, and investigated its physicochemical properties and dissolution behavior.

Experimental

Materials A piretanide bulk sample (lot No.: L023, E024) was obtained from Hoechst Aktiengesellschaft, Germany. Form B was obtained by recrystallization using a hot saturated solution of *tert*-butanol. The saturated solution was allowed to stand for 24 h at room temperature, and the separated crystals were collected by filtration and dried *in vacuo* over silica gel for 24 h at room temperature. These crystals were heated at 140 °C for 1 h.

X-Ray Powder Diffraction Analysis X-ray powder diffraction profiles were taken at room temperature with an X-ray powder diffractometer (MXP3, Mac Science Co.). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; receiving slit, 0.15 mm; scanning speed 5° 2θ/min.

Thermal Analysis DSC and thermogravimetry (TG) were performed with an 8085E2 DSC-TG instrument (Rigaku Denki Co.). The operating conditions in the open-pan system were as follows : sample weight, about 5 mg; heating rate, 2, 5, 10 and 20 °C/min; N_2 gas flow rate, 20 ml/min.

Fourier-Transform Infrared (FTIR) Spectroscopy FTIR spectra were taken by the Nujol mulls method using an FTIR spectrophotometer (JIR5500, JEOL Co.).

Elemental Analysis Elemental analyses of the samples were performed for atoms of C, H, and N with a CHN Corder (Perkin-Elmer 240C) and for S by means of oxygen flask combustion.

Nuclear Magnetic Resonance (NMR) Spectroscopy The sample was dissolved to a final ratio of 2% in $(CD_3)_2CO$. The proton NMR spectra were recorded at 90 MHz on a NMR instrument (JNM FX90-Q, JEOL Co.).

Scanning Electron Microscopy (SEM) SEM photographs of samples were taken with a scanning electron microscope (model JSM-T20, JEOL Datum Co., Tokyo, Japan) at a magnification of ×350, 500, 1500 or 3500.

Dissolution Study The Dispersed Amount Method: The dissolution profiles of the bulk sample and form B were investigated in JP XII, 1st fluid (pH 1.2). An excess (200 mg) of the sample was introduced into 500 ml of medium in a 1000-ml round-bottomed flask with a plastic cover. The flask was fixed on the 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 appropriate intervals with a syringe through a 0.45-μm membrane. The

concentration of the drug was measured using a spectrophotometer (340, Nihonbunko Co.) at 275 nm.

Results and Discussion

Characterization of Solvates. a) X-Ray Powder Diffractometry Figure 1 shows the X-ray powder diffraction profiles of the bulk sample and six solvates. There were seven main diffraction peaks at 5.4, 8.4, 10.3, 11.1, 19.7, 20.7 and 21.7° (2θ) in the bulk sample, whereas the crystals showed a different profile. The latter were confirmed to be solvates having a different crystal form.

b) Thermal Analysis (DSC and TG) Figures 2 and 3 show the DSC and TG curves of the bulk sample and of six crystal forms which were prepared by recrystallization. All their DSC curves showed an endothermic peak at about 227 °C, corresponding to the melting peak of the bulk sample. Each crystal forms also showed endothermic peaks, causing the individual variations. The DSC curves showed endothermic peaks at 121.0, 89.8, 113.3, 153.3, 132.3 and 165.7 °C with a 15.2, 10.0, 14.5, 7.0, 26.6 and 7.0% loss of weight on TG curves in crystals recrystallized from *tert*-butanol, *n*-propanol, isopropanol, dioxane, propylene glycol and dimetylformamide, respectively. This loss of weight showed that the ratio of solvate to piretanide was 0.9, 0.7, 1.0, 0.3, 1.7 and 0.4 mol/mol for *tert*-butanol, *n*-propanol, isopropanol, dioxane, propylene glycol and dimetylformamide, respectively. Except for propylene glycol and dimethylformamide, the solvates showed a second endothermic peak at about 213 °C and a subsequent exothermic peak at about 216 °C. All crystals had a melting peak at about 227 °C.

The de-solvation of various solvates was analyzed by the Kissinger method (Eq. 1)[8]:

$$d(\ln \phi/T_m^2)/d(1/T) = -E/R \quad (1)$$

where ϕ is the heating rate, T_m is the temperature of the maximum peak, E is activation energy and R is the gas constant.

Dimethylformamide and propylene glycol solvates transformed into form A, but dioxane, *tert*-butanol, isopropanol and *n*-propanol solvates transformed into form B. The results of the activation energy for desolvation, and the DSC peaks, are summarized in Table I. Dioxane solvate had the highest activation energy among the 6 crystalline forms (dioxane > dimethylformamide > *tert*-butanol > isopropanol > propylene glycol > *n*-propanol).

Heating Solvates and Their Characterization The solvates were heated for 1 h at temperatures as much as 15—20 °C higher than that of the first endothermic peak on the DSC curves. The heated crystals were classified into two forms, named A and B, according to the results of X-ray powder diffractometry (Fig. 4) and FTIR spectrophotometry (Fig. 5). Neither of the forms showed an endothermic peak, except for melting point, resulting from crystals on the DSC, nor a loss of weight on the TG curve. Additionally, we identified that the solvent in

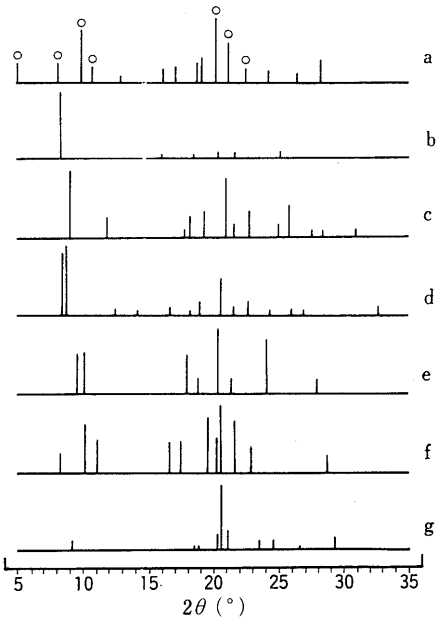

Fig. 1. X-Ray Powder Diffraction Profiles of Piretanide Solvates

(a) Bulk, (b) *tert*-butanol, (c) *n*-propanol, (d) isopropanol, (e) dioxane, (f) propylene glycol, (g) dimethylformamide.

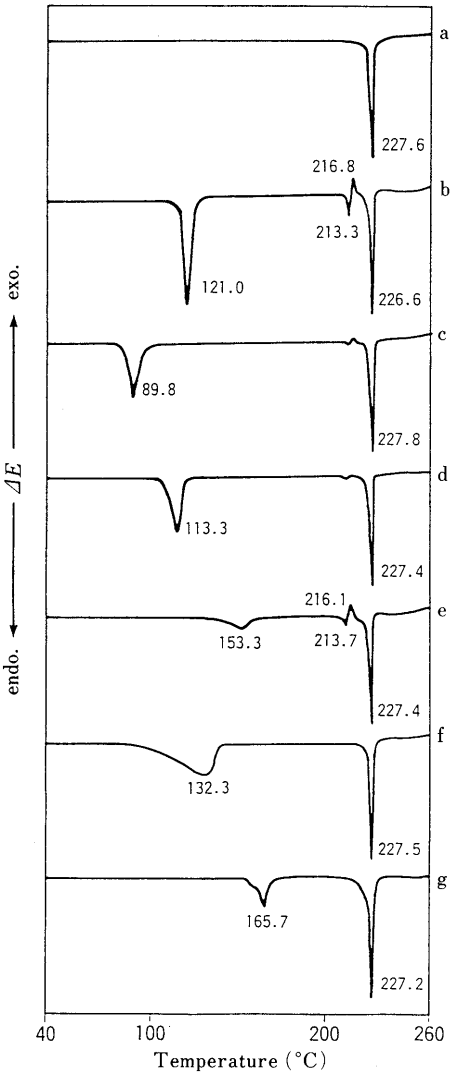

Fig. 2. DSC Thermograms of Piretanide Solvates

(a) Bulk, (b) *tert*-butanol, (c) *n*-propanol, (d) isopropanol, (e) dioxane, (f) propylene glycol, (g) dimethylformamide.

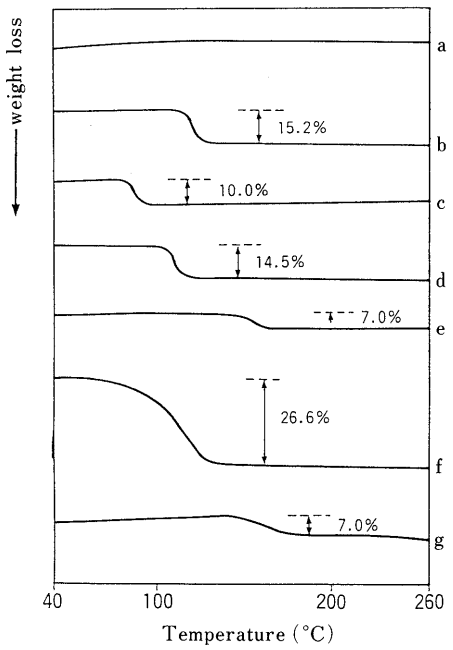

Fig. 3. TG Thermograms of Piretanide Solvates

(a) Bulk, (b) *tert*-butanol, (c) *n*-propanol, (d) isopropanol, (e) dioxane, (f) propylene glycol, (g) dimethylformamide.

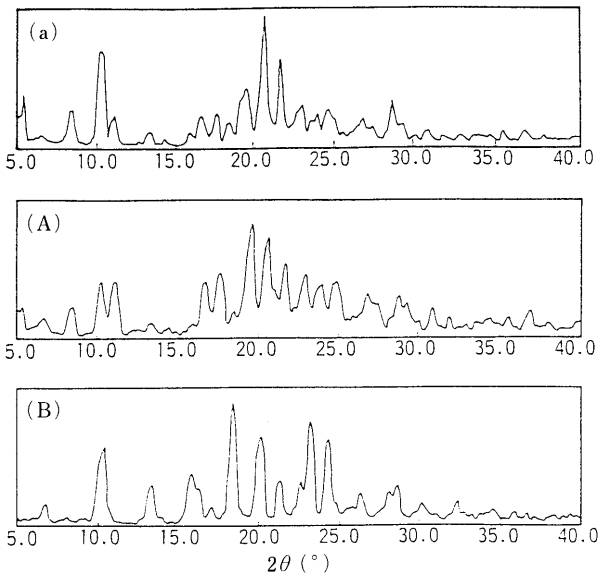

Fig. 4. X-Ray Powder Diffraction Patterns of Piretanide Bulk Sample (a), Forms A (A) and B (B)

the solvate was removed by heating during NMR and elemental analysis. Form A was obtained by recrystallization and heating from hot saturated solutions of propylene glycol or dimethylformamide. The saturated solutions were allowed to stand at 5 °C or at room temperature. On the other hand, form B was obtained by recrystallization and heating from *n*-propanol, isopropanol, *tert*-butanol, propylene glycol or dioxane, respectively. Isopropanol is non-toxic in these solvents. Therefore, it can be used for practical therapy without toxicity resulting from the remaining solvate.

Characterization of Forms A and B. a) X-Ray Powder Diffractometry Figure 4 shows the X-ray powder diffraction profiles of forms A and B. The diffraction angles and the characteristic diffraction intensities are also summarized in Table II. Form B showed major diffraction peaks at 10.4, 13.3, 15.7, 18.4, 20.1, 23.2 and 24.3° (2θ), whereas form A showed the same profile as the bulk sample, with a slight difference in characteristic diffraction intensity, suggesting that both modifications are significantly different in crystal structure. The results of the elemental analysis of these forms are summarized in Table III. The observed and calculated values were in good agreement. It was therefore confirmed that no residual solvent or impurities were present in the form A and B crystals. Additional supporting data were provided by the NMR spectra. These results indicated that the bulk sample was the same as form A, with a slight difference in characteristic diffraction intensity.

b) IR Spectra Figure 5 shows the IR spectra of forms A and B. The IR spectrum of piretanide has been explained by Matsubara, *et al.*[9] as follows: The absorption band at 3415 cm^{-1} is attributable to the OH group in carboxylic acid, the bands at 3360 and 3265 cm^{-1} to the NH_2 group in sulfonic acid, and those at 1694 and 1679 cm^{-1} to the C=O group in carboxylic acid. The IR spectrum of form A was the same as that of the bulk sample (3411, 3358, 3259, 1695, 1678 cm^{-1}). Form B exhibited an absorption band at 3406 cm^{-1} attributable to the OH group in carboxylic acid; the new bands that appeared at 3295 and 3251 cm^{-1} were attributable to the NH_2 group in sulfonic acid, and that at 1696 cm^{-1} was attributable to the C=O group in carboxylic acid. The results of the IR spectra suggested that form A had a different crystal structure from that of form B. Therefore, form A is probably the same as the bulk sample, according to the results of the IR spectrum and the X-ray diffraction profile.

TABLE I. Comparison of Activation Energy for De-solvation and DSC Peaks on Piretanide Solvates

Solvates	Peak of DSC (°C)		Crystal form after transformation	Activation energy for de-solvation (kJ/mol)
	Endothermic	Exothermic		
Bulk	227.6	—	—	—
tert-Butanol	121.0, 213.3, 226.6	216.8	B	680.3
n-Propanol	89.8, 213.5, 227.8	216.5	B	1025.5
Isopropanol	113.3, 213.1, 227.4	215.3	B	611.3
Dioxane	153.3, 213.7, 227.4	216.1	B	2425.9
Propylene glycol	132.3, 227.5	—	A	136.0
Dimetylformamide	165.7, 227.2	—	A	1913.8
Form B	213.9, 226.6	215.6	—	6996.9

Table II. X-Ray Powder Diffraction Angle and Relative Diffraction Intensities of Piretanide Forms A and B

Form A			Form B		
2θ (°)	d (Å)	I/I_0	2θ (°)	d (Å)	I/I_0
5.36[a]	16.47	0.21	6.70	13.18	0.14
6.62	13.34	0.13	10.44[a]	8.47	0.68
8.40[a]	10.52	0.32	13.26[a]	6.67	0.33
10.28[a]	8.60	0.59	15.74[a]	5.63	0.39
11.08[a]	7.98	0.59	16.26	5.45	0.23
13.26	6.67	0.10	18.36[a]	4.83	1.00
16.62	5.33	0.48	20.14[a]	4.41	0.70
17.64	5.02	0.56	21.26	4.18	0.32
19.66[a]	4.51	1.00	22.60	3.93	0.28
20.66[a]	4.30	0.82	23.20[a]	3.83	0.79
21.74[a]	4.08	0.56	24.28[a]	3.66	0.65
22.66	3.92	0.21	26.30	3.39	0.19
22.96	3.87	0.44	28.14	3.17	0.21
23.94	3.71	0.32	28.66	3.11	0.27
24.86	3.58	0.42	30.14	2.96	0.13
26.84	3.32	0.31	32.32	2.77	0.16
27.52	3.24	0.20			
28.84	3.09	0.32			
29.26	3.05	0.24			
30.82	2.90	0.23			
31.84	2.81	0.12			
35.52	2.53	0.12			
36.88	2.44	0.21			

a) Main peak.

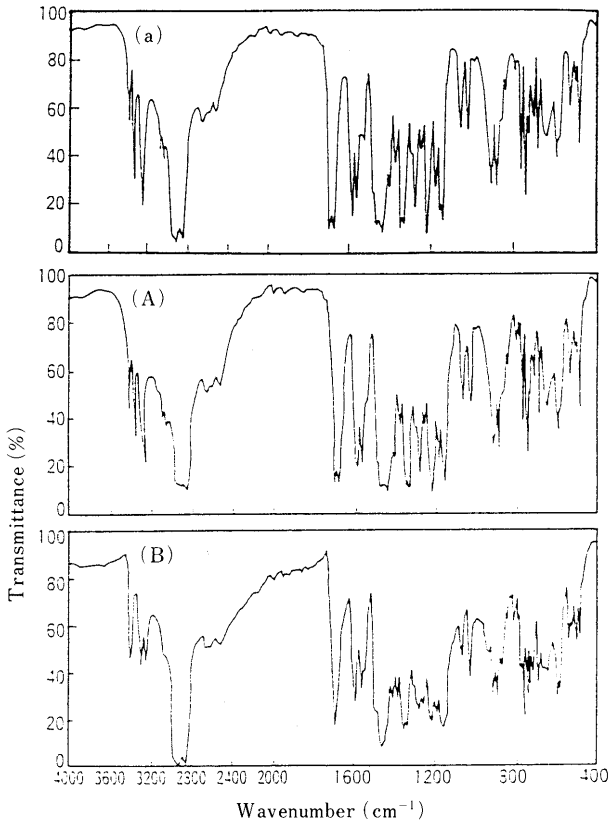

Fig. 5. FTIR Spectra of Piretanide Bulk Sample (a), Forms A (A) and B (B) Using the Nujol Mull Technique

Table III. Elemental Analysis of Forms A and B

Modification	Formula		Elemental analysis (%)			
			C	H	N	S
Form A (Bulk)	$C_{17}H_{18}N_2O_5S$	Calcd	56.35	5.01	7.73	8.85
		Found	56.37	4.99	7.70	8.74
Form B	$C_{17}H_{18}N_2O_5S$	Calcd	56.35	5.01	7.73	8.85
		Found	56.28	4.97	7.67	8.84

c) Thermal Analysis Figure 6 shows the DSC and TG curves of forms A and B. The DSC curve of form A showed only an endothermic peak at about 227 °C without a loss of weight, which is the same as that of the bulk sample. In contrast, form B showed an endothermic peak at about 213 °C, a subsequent exothermic peak at about 216 °C, and a melting peak at about 227 °C. These results confirmed that form B, after the melting at 213 °C, transformed into form A at 216 °C, and then form A was melted at 227 °C.

d) SEM Observation Figure 7 shows SEM photographs of forms A and B. Distinct morphological differences were evident among these samples. Form A consisted of aggregated secondary particles of about 120 μm in diameter with the primary columnar particles being less than 10 μm in length and 2—3 μm in width. Form B had smooth platy crystals with a particle width distribution between 10 and 100 μm.

Dissolution Behavior of Forms A and B Figure 8 shows the dissolution profiles of form A (the bulk sample) and form B by the dispersed amount method. These two

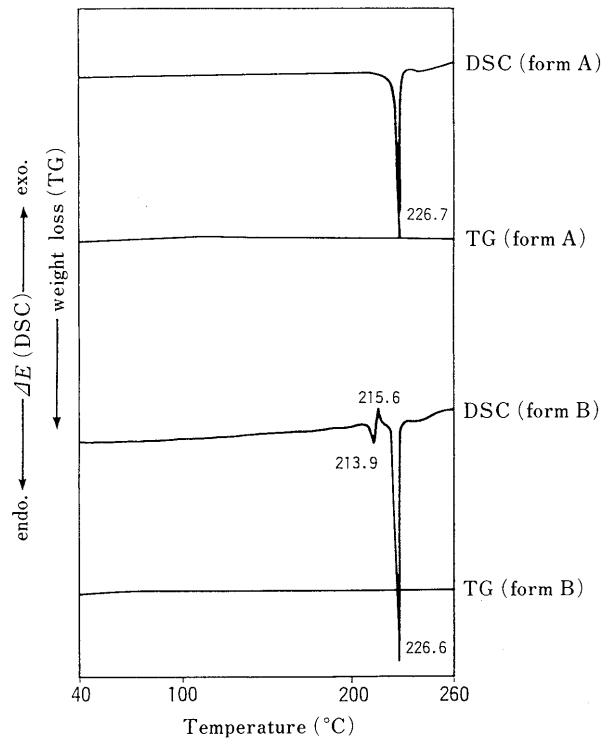

Fig. 6. DSC and TG Thermograms of Piretanide Forms A and B

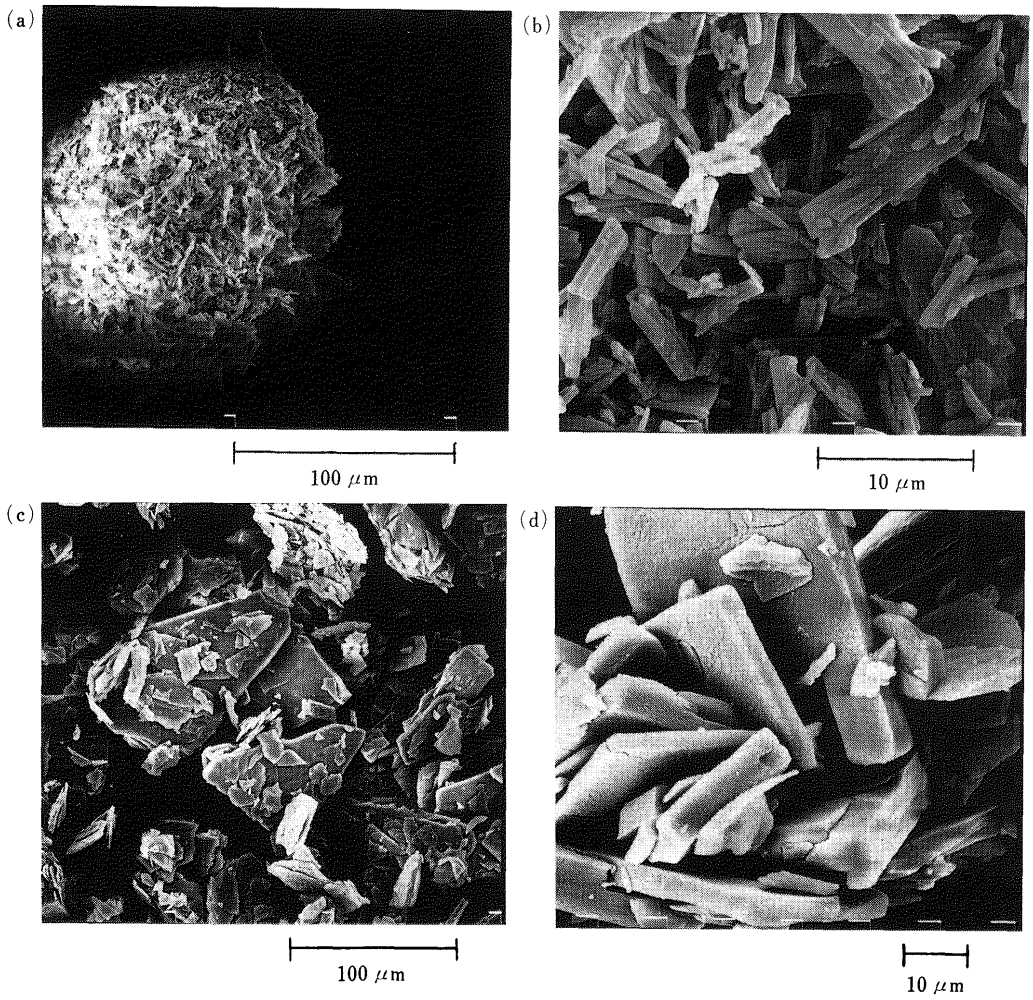

Fig. 7. Scanning Electron Photomicrographs of Piretanide Forms A and B
(a) Form A (× 500), (b) form A (× 3500), (c) form B (× 350), (d) form B (× 1500).

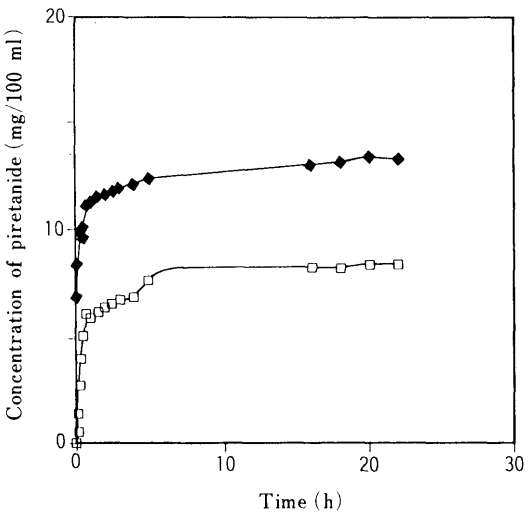

Fig. 8. Dissolution Profiles of Bulk Piretanide (Form A) and Form B at pH 1.2 at 37°C
□—□, bulk; ◆—◆, form B.

samples showed normal dissolution curves without any maximum value. The solubilities were 8.3 and 13.3 mg/100 ml for the bulk sample and form B, respectively. The initial dissolution rate for Form B was higher than that of the bulk sample. The X-ray powder diffraction patterns of the crystallized precipitate after dissolution coincided with those of the intact bulk sample and form B, as shown in Fig. 9. This result indicated that no transformation had occurred in the dissolution medium, and form B was about 1.6-fold more soluble than the bulk sample. Form B was stable in JP XII, 1st fluid at 37 °C without a phase change.

Conculusion

In this study, we identified a novel polymorphic form B of piretanide by means of de-solvation of 4 solvates. Form B was confirmed by X-ray powder diffractometry, DSC, TG, FTIR spectroscopy, elemental analysis and SEM. It was 1.6-fold more soluble than the stable form A in JP XII, 1st fluid at 37 °C. Therefore, form B may be used as the bulk powder since it has greater bioavailability than form A.

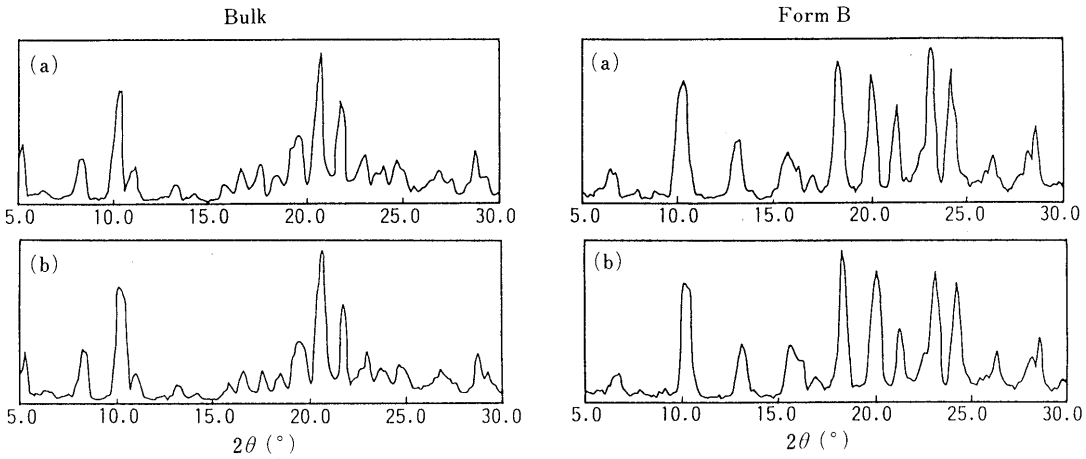

Fig. 9. Changes in the X-Ray Powder Diffraction Profiles of Bulk Piretanide (Form A) and Form B before and after the Dissolution Test
(a) Initial, (b) after dissolution.

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