

## Preparation and Identification of Crystal Modification of Piroxicam

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Data obtained from X-ray diffractometry, thermal analysis, IR spectroscopy and microscopic observation were used for the identification and characterization of four crystalline modifications of piroxicam. Form a was crystallized from sodium hydroxide-hydrochloric acid and from c was obtained by crystallization from toluene. Form b and d was crystallized from methanol under the different temperature conditions.

Relative rates of dissolution and solubility of four crystal forms of piroxicam in distilled water were measured.

During the past few years, there have been frequent demonstrations of the fact that the appropriate selection of the most suitable crystalline modification, polymorph, amorphous form, or crystalline solvate can influence significantly the medicinal value of a given chemical agent.<sup>1-5)</sup> Although polymorphic forms of a compound dissolve to give identical solutions, these forms differ with respect to their thermodynamic activities, equilibrium solubilities, and rates of dissolution. Therefore, the rate of release of a polymorph from a solid dosage form, whether *in vivo* or *in vitro*, should depend on which form is present.

Given the possible consequences of an injudicious choice of a particular polymorphic form employed in the formulation of a medicinal agent, and given the estimate that almost one-third of all organic compounds are likely to exhibit polymorphism,<sup>6-8)</sup> it seems reasonable to propose that some kind of screening procedure should be used routinely to detect this phenomenon in potential pharmaceuticals.

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Piroxicam, 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2 benzothiazine-3-carboxamide-1,1-dioxide, nonsteroidal anti-inflammatory agent, is an example of water-insoluble drugs.<sup>9~10</sup> *In vitro* absorption of the drug from a solid dosage form is thus expected to be dissolution rate limited. Of biopharmaceutical interest is the difference in solubility commonly exhibited by crystal modifications. Enhanced therapeutic activity may be achieved with the use of the higher energetic form. Thus, attempts were made in this study to prepare the drug in a crystalline form with a higher free energy content, usually meaning a higher solubility.

## Experimental

**Materials**—Piroxicam (YuHan Corporation, Korea) were used. The reagents and solvents used were reagent grade.

**Preparation of Crystal Forms**—Form a; piroxicam (10gm) was dissolved in 0.5M NaOH (70ml) at 40°, dilute HCl was slowly added dropwise with stirring until adjusted pH 4, and the resulting solution permitted to crystallize at room temperature. The crystals were filtered, carefully washed with distilled water and dried at 50°. Form b; piroxicam (10gm) was added in methyl alcohol (100ml), suspended for 2 hours at 40°, refluxed for 3 hours, and then permitted to crystallize with cooling. The crystals were dried at 50°. Form c; piroxicam (10gm) was dissolved in toluene (60ml), cooled on ice bath. The resulting precipitate was dried at 50°. Form d; piroxicam (10gm) was dissolved in hot methyl alcohol (500ml), and the resulting solution permitted to be crystallized, at room temperature. The crystals were filtered and dried at 50°.

**X-Ray Diffraction**—Powder diffractograms were obtained using powder samples of piroxicam polymorphs. The powder was packed into a planchet, 1mm deep, 20mm long and 10mm wide. X-ray diffractograms were obtained using a Rigaku 2028 diffractometer. The instrument variables were set as follows: (a) scanning speed 4°/mm, chart speed 20mm/min, time constant 1sec, range 2000cps. (b) Cu K $\alpha$  radiation, 30Kv 15mA, Ni filtered, wavelength 1.5405Å.

**Differential Thermal Analysis**—Shimadzu DT-30B differential thermal analyzer, equipped with a standard cell, was employed to detect transition and melting temperature of the crystal forms of piroxicam. In all determinations the heating rate was 10°C/min, DTA range was 50 $\mu$ V. Temperature range 25—250°, chart speed 5mm/min.

**Infrared Spectroscopy**—The infrared spectra of the four forms of piroxicam were

recorded on a Perkin-Elmer M-467 infrared spectrophotometer

**Microscopic Observation**—The crystal forms were identified with microscope.

**Solubility Studies**—The concentration attained in distilled water for each polymorphic forms was monitored by following the increase in absorbance at a fixed wavelength as a function of time in the presence of an excess of the solid phase and under essentially constant agitation at 27°.

## Results and Discussion

**Identification of Crystal Modifications of Piroxicam**—A polymorph is a solid crystalline phase of a compound resulting from the possibility of at least two different arrangements of the molecules of the compound. The temperature, solvent chosen for crystallization, and rate of cooling are important factors in determining the type of polymorph obtained.<sup>11-12</sup> The general procedure for the preparation of the different crystal forms was adopted for the crystallization from specific solvents. For this purpose, the material was obtained under the solvent recrystallization techniques.

The methods for studying polymorphism are X-ray powder diffractometry, infrared spectroscopy, differential thermal analysis, dilatometry, proton magnetic resonance spectroscopy, polarizing microscopic observation and magnetic anisotropy. Four crystalline modifications of piroxicam were obtained by the crystallization technique described above and identified using data from X-ray diffractometry, thermal analysis, infrared spectroscopy and microscopy. Figure 1 shows the powder diffractograms for each crystal modification. The forms are distinguished by peak differences in the region of  $2\theta$  values of 10 to 50. Crystalline materials in powder form give characteristic X-ray diffraction patterns made up peaks in certain positions with varying intensities. Figure 2 shows the DTA thermogram patterns of crystalline form a, b, c and d. In differential thermal analysis, enthalpic changes, both ~~exo and~~ endothermic, are caused by phase transitions. The thermograms of form b, c and d give an essentially straight base line with a single endothermic peak corresponding to fusion at 205°, 203° and 190°, respectively. It can be seen that forms b and c have identical DTA patterns, but differences in the IR spectra, X-ray diffractograms and microscopic observations of these two modifications can be seen. There are two endothermic peaks in the DTA thermogram of form a. The peaks occur at 125° and 200°. The first endothermic peak corresponds to loss

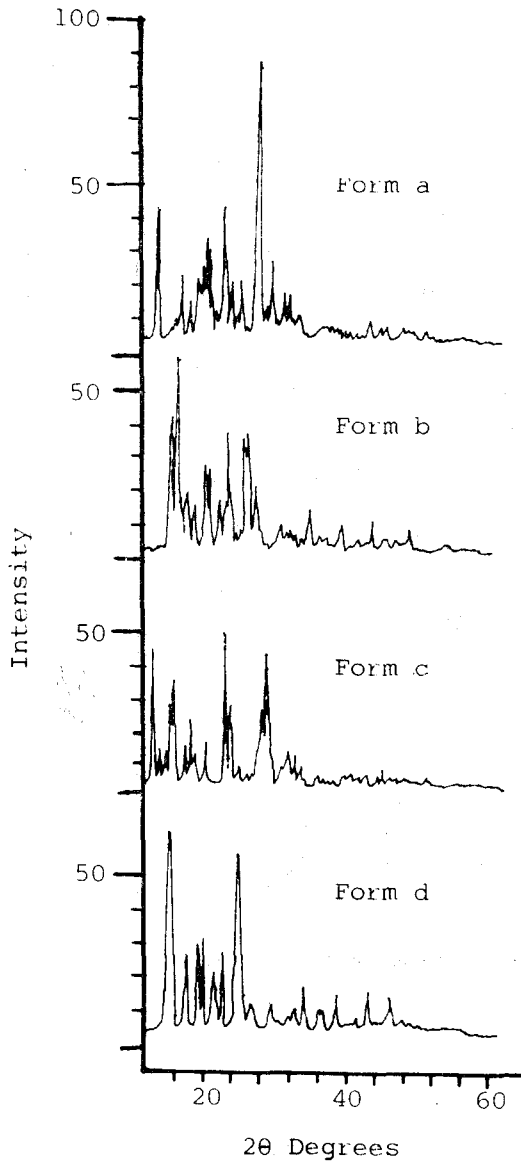


Figure 1—X-ray diffractograms of crystal forms of piroxicam

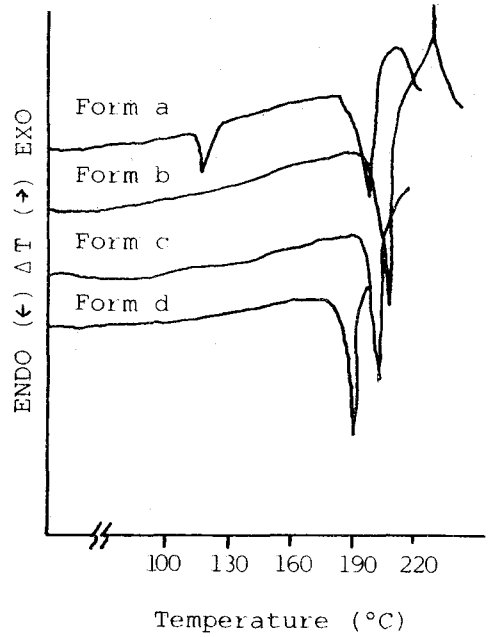


Figure 2—D.T.A. thermograms of crystal forms of piroxicam

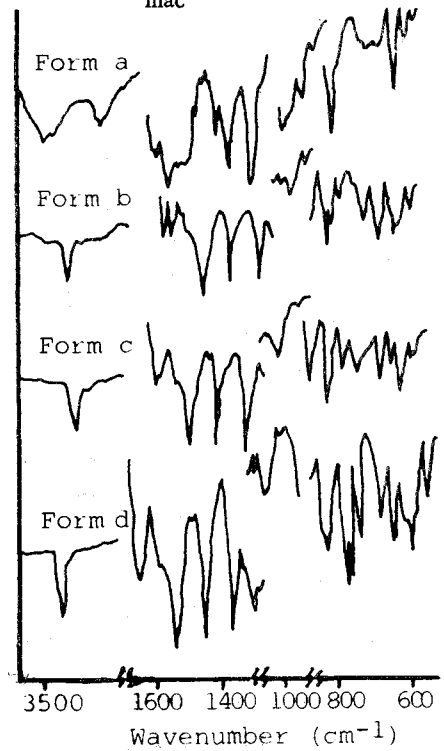


Figure 3—Infrared spectra of crystal forms of piroxicam

of hydrate from the crystal structure, and the second peak corresponds to fusion with melting point at  $200^{\circ}$ . The IR spectra of form a, b, c and d were showed in figure 3. Hydrate form of form a exhibits at  $3,440\text{ cm}^{-1}$  broadly. Differences in the spectra are found at  $3,400$ ,  $1,300$ ,  $1,100$ ,  $800$  and  $600\text{ cm}^{-1}$ . The  $3,400\text{ cm}^{-1}$  band is due to an N-H stretching vibration, and the  $1,300$  and  $1,100\text{ cm}^{-1}$  bands have been assigned to asymmetrical and symmetrical  $\text{SO}_2$  stretching vibrations. It is observed in this study that the major differences in the IR spectra of different modifications of the compounds are in the regions of  $\text{—NH}$  stretching vibrations and asymmetric and symmetric  $\text{—SO}_2$  stretching vibrations. Figure 4 shows the photomicrographs for each crystal modification. Form a exhibits non-homogenous crystals and form b and c showed polyhedric crystals. Otherwise, form d exhibits thin needle shaped crystals.

**Determination of Solubility Profiles of Crystal Forms**—The progress of dissolution was monitored by following the increase in absorbance at a fixed wavelength as a function of time. The calibration curve of piroxicam is shown in Figure 5.

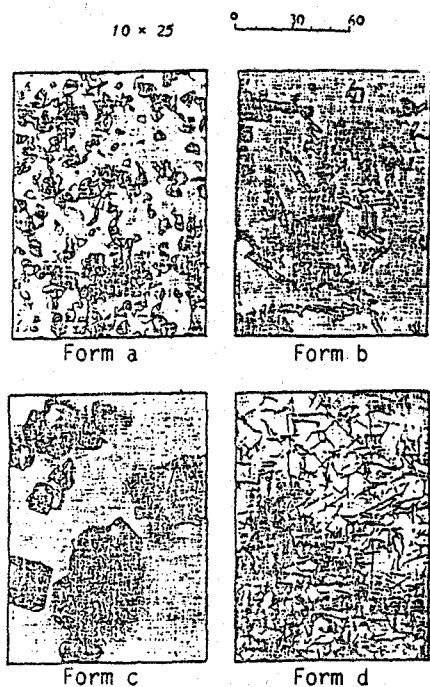


Figure 4—Photomicrographs of crystal forms of piroxicam

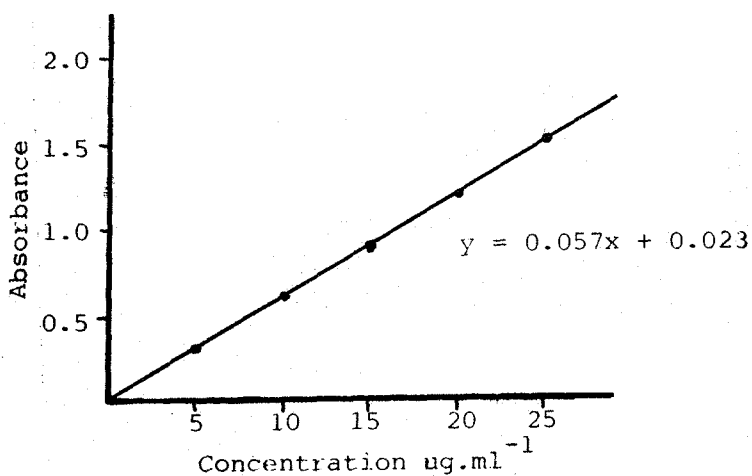


Figure 5—The calibration curve of piroxicam

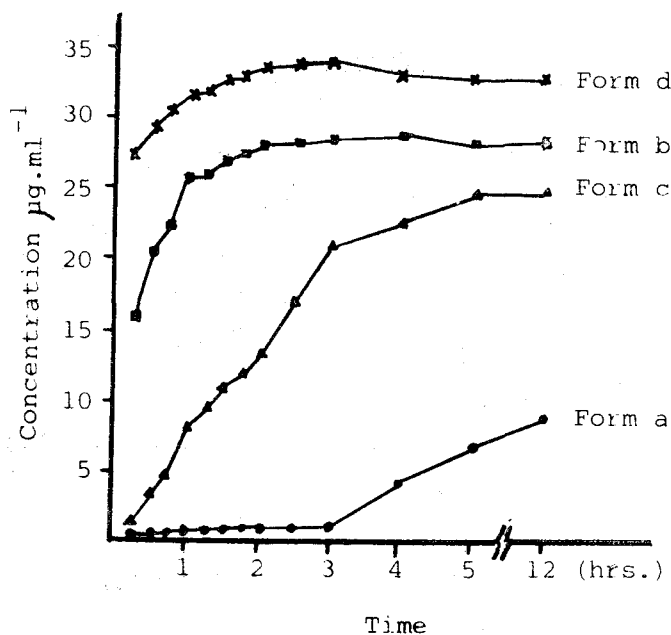


Figure 6—Solubility profile of piroxicam polymorphs in water at 27°C

The results for dissolution of the crystal forms of piroxicam in distilled water at 27° are shown in Figure 6. These plots show the concentration attained in solution for each polymorphic forms with function of time in the presence of an excess of the solid phase and under essentially constant agitation. It is apparent from the data that form d has faster dissolution rate and more water solubility than the other forms, b and c. Particularly form a is extremely insoluble in distilled water. This difference could not be due to differences in the crystal size as the same sieve fraction used for each form, but is attributed to the higher free energy state of form d.<sup>4,5)</sup>

## Conclusion

The piroxicam can exist in different polymorphs and four crystalline forms of piroxicam were identified by X-ray powder diffractometry, differential thermal analysis infrared spectroscopy, and microscopic observation.

As a result of the solubility and relative rates of dissolution of four crystal forms, form d was found to be significantly more soluble than the others, and the aqueous solubility of form a was extremely low.

### References

- 1) A.J. Aguiar and J.E. Zelmer, *J. Pharm. Sci.*, **58**, 983(1969)
- 2) J.W. Poole and C.K. Bahal, *ibid.*, **57**, 1945(1968)
- 3) W.I. Higuchi, P.D. Barnardo and S.C. Mehta, *ibid.*, **56**, 200(1967)
- 4) J.W. Poole and C.K. Bahal, *ibid.*, **59**, 1265(1970)
- 5) J.A. Clements and S.D. Popli, *Can. J. Pharm. Sci.*, **8**, 89(1973)
- 6) S.S. Yang and J.K. Guillory, *J. Pharm. Sci.*, **61**, 26(1972)
- 7) T. Higuchi and R. Kuramoto, *ibid.*, **43**, 393(1954)
- 8) D. Guttman and T. Higuchi, *ibid.*, **45**, 659(1956)
- 9) E.H. Wiseman, Y.H. Chang and J.G. Lombardino, *Arzneim Forsch. (Drug Res.)* **26**, Nr. 7(1976)
- 10) K.P. Biserka and R.T. Ziva, *Acta Cryst.* **B38**, 2948(1982)
- 11) J. Haleblan and W. McCrone, *J. Pharm. Sci.*, **58**, 911(1969)
- 12) D.C. Monkhouse and J.L. Lach, *Can. J. Pharm. Sci.*, **7**, 29(1972).