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Polymorphism of Tegafur: Physico-chemical Properties of Four Polymorphs

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Four crystalline forms of tegafur were prepared by recrystallization from different solvents (α-, β-, δ-forms) and by heating (γ-form). They have been characterized using powder X-ray diffraction, thermal analysis, microscopy, density measurements and infrared spectroscopy. From differential scanning calorimetry measurements, it was confirmed that the γ- and δ-forms melted at 175 °C and 165 °C, whereas the α- and β-forms transformed into the γ-form at about 162 °C and 120 °C, respectively. The infrared absorption spectral differences observed between the α- and β-forms were discussed in relation to their intermolecular hydrogen bonding systems. It was also found that the difference in crystal forms significantly altered the dissolution rate of tegafur.

Keywords tegafur; polymorphism; transition; thermal analysis; IR; dissolution

Many papers on the polymorphism of pharmaceuticals have been published during the last 20 years, and many drugs are believed to exist in more than one polymorphic form. Different polymorphic forms are known to possess different properties, including melting point, density, hardness, crystal shape, dissolution rate, solubility and stability.[2)] Polymorphism has particular importance with regard to the bioavailability, stabilization and formulation of medical supplies.[3)]

Tegafur, 5-fluoro-1-(tetrahydro-2-furyl)-uracil, which was synthesized by Hiller *et al.*[4)] as a prodrug of 5-fluorouracil, is an antitumor agent and is widely used in the treatment of various cancers, particularly against gastrointestinal and breast cancers.[5)]

The existence of tegafur in different polymorphic forms was first reported by Machijima *et al.*[6)] In previous papers, we have reported the crystal structures of two crystalline forms of tegafur (α- and β-forms) by single X-ray crystallographic studies.[7,8)]

In the present study, the crystalline forms of tegafur were again investigated, and four crystalline forms (α-, β-, γ-, and δ-forms) were confirmed. The purpose of this report is to demonstrate the methods of preparation and characterization of four tegafur crystal forms using powder X-ray diffraction analysis, thermal analysis and several other physico-chemical measurements.

Experimental

Materials Purified tegafur was supplied from Mitsui Pharmaceutical, Inc. (Tokyo). This sample is colorless and stable at room temperature. Solvents used were of JP XII or of analytical reagent grade.

Preparation of Crystal Forms α-Form: Tegafur was dissolved in warm acetone and permitted to crystallize at room temperature. The colorless columnar crystals were collected by filtration.

β-Form: The colorless prismatic β-form crystals were prepared from a saturated methanol solution by solvent evaporation using a rotary evaporator.

γ-Form: γ-Form crystals were prepared by heating the β-form at 130 °C for 1 h.

δ-Form: δ-Form crystals were obtained by recrystallization from a methanol solution (very slow vaporization of methanol) at room temperature.

Powder X-Ray Diffraction The powder X-ray diffraction patterns were measured with a Rigaku Denki 2027 diffractometer under the following conditions: Cu-K_α radiation, voltage 30 kV, current 5 mA, time constant 0.5 s, scanning speed 2°/min, chart speed 40 mm/min and using a detector scintillation counter.

Thermal Analysis Thermogravimetry (TG): The Shimadzu TGC-20 TG apparatus was used. Each tegafur form (10 mg) was accurately weighed and the temperature was raised from room temperature to the desired temperature (*ca.* 200 °C) at a heating rate of 5 °C/min under a nitrogen gas flow condition. The decomposition temperature was determined from the observed weight loss curves.

Differential Scanning Calorimetry (DSC) A Perkin-Elmer DSC 1B apparatus was used for the measurement of melting point and transition temperature of each form. The measurements were made using liquid sample pans (sample weight was 5 mg) in a nitrogen atomosphere at a heating rate of 4 °C/min, and at a chart speed of 10 mm/min. Transition temperatures and melting points were determined as the point of intersection between the base line and the linear section of the ascending endothermic curve.[9)]

Morphological Observation The transition and the melting properties were observed with a thermomicroscope (Micro melting point apparatus: Yanagimoto, Tokyo). Photomicrograms of the β-form were taken with a photomicrographic system made by Nikon Co. (Tokyo).

Infrared Absorption Spectroscopy (IR) A Hitachi 295 IR spectrophotometer was used, and samples were prepared as KBr disks.

Density Measurement The density of each form was measured by the floatation method at 20 °C. Cyclohexane and carbon tetrachloride were mixed to obtain solvents with visible density.

Dissolution Rate Measurement The dissolution rates were determined according to the stationary disk method. A disk (diameter: 10 mm) was prepared by compressing 250 mg of the sample under a pressure of 250 kg cm^{-2} in a hydraulic press. It was confirmed by powder X-ray diffraction that no polymorphic transition took place during the compression. The compressed disk was fixed in the dissolution cell and put into a 500 ml beaker. Distilled water, 500 ml, which was preheated at 37 °C, was added to the beaker and the beaker was immersed in a thermostated water bath at 37 °C. The dissolution medium was stirred with a two-bladed glass propeller at a rate of 32 rpm. The concentration of dissolved drug was measured at 271 nm with a spectrophotometer (Shimadzu model 200). Each point on the profile represents the average of five determinations.

Results and Discussion

Identification of the Four Polymorphs The powder X-ray diffraction patterns of different crystal preparations are shown in Fig. 1. The powder X-ray diffraction patterns of each crystal form showed different patterns which revealed the presence of four different crystal structures of tegafur. For the α- and β-forms, the calculated interplanar spacings from the single crystal data reported previously were in good agreement with the observed values.[7,8)] The characteristic diffraction peaks of other polymorphic forms were observed at $2\theta = 22.0°$ and at 9.8° for the γ- and δ-forms, respectively. The TG curve of each form

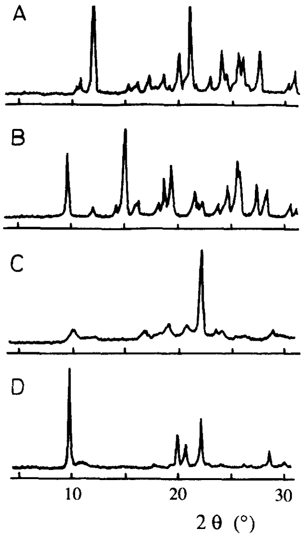

Fig. 1. Powder X-Ray Diffraction Patterns of Polymorphic Forms of Tegafur

A, α-form; B, β-form; C, γ-form; D, δ-form.

Table I. Elemental Analysis of $C_8H_9FN_2O_3$ (Tegafur)

	C (%)	H (%)	N (%)
Calcd	48.00	4.53	14.00
α-Form	47.96	4.54	14.01
β-Form	48.02	4.54	13.97
γ-Form	48.00	4.51	13.88
δ-Form	47.70	4.44	14.24

showed no weight loss until 176 °C, at which temperature the decomposition began.

To determine the level of impurities, elemental analysis and HPLC were conducted. From the HPLC measurements which were performed using an ODS column and a 25% methanol aqueous solution as the elution solvent, only one peak due to tegafur was observed, and no other peaks were detected. The observed values in elemental ayalysis were coincident with the theoretical values as shown in Table I. These results suggest that the four preparations did not contain solvents of crystallization or impurities. Therefore, we confirmed that the four crystal forms were different polymorphic forms of tegafur (α-, β-, γ- and δ-forms).

Crystal Shapes of Polymorphs Photomicrograms of the single crystals of the α- and β- forms are shown in Fig. 2. Until now, single crystals of other polymorphs have not been obtained. The crystals of the α-form differ completely from the crystals of the β-form with regard to crystal shape. Single crystals of the α-form are colorless and columnar, while those of the β-form are colorless and prismatic.

Thermal Behaviour of the Four Polymorphs Figure 3 shows the DSC curves of the four polymorphs. The γ- and δ-forms had only one endothermic peak corresponding to their melting at 175 °C and 165 °C, respectively. The curve of the α-form showed two endothermic peaks at 162 °C and 174 °C. The first endothermic peak is attributed to the polymorphic transition and the second peak is due to melting. The β-form also gave two endothermic peaks, a broad peak from 90—120 °C and one at 175 °C. From the comparison of powder X-ray diffraction patterns and DSC curves before and after heating the β-form crystals at 120 °C, the broad peak from 90 °C to 120 °C was determined to be due to the transition from the β-form to the γ-form. The second endothermic peak at 175°C corresponded to the melting of the γ-form. The morphological changes involved in the transition from the β-form to the γ-form were examined using thermomicroscopy and photomicrograms.

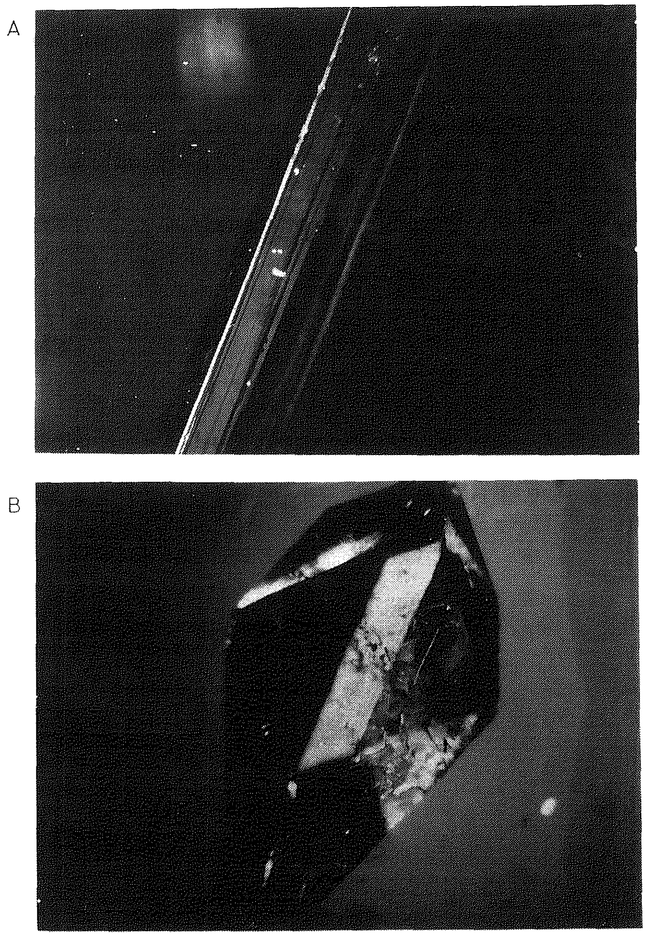

Fig. 2. Photomicrograms of Single Crystals of α- and β-Forms

A, α-form; B, β-form.

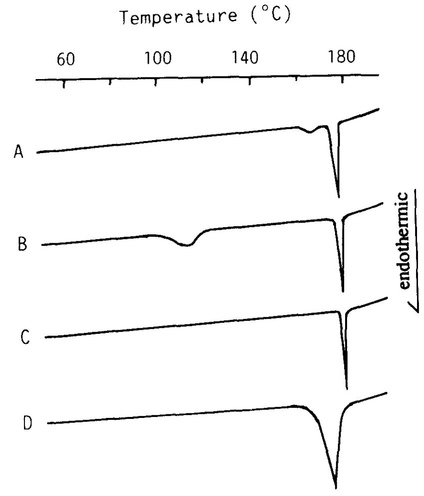

Fig. 3. DSC Curves of Polymorphic Forms of Tegafur

A, α-form; B, β-form; C, γ-form; D, δ-form.

Figure 4 shows photomicrographs before the transition (β-form) and after the transition (γ-form). Prismatic crystals of the β-form (Fig. 4A) melted at about 115 °C, then they immediately solidified to needle-shaped crystals (Fig. 4B). In morphological observation by thermomicrosocpy, the β-form melted at about 150 °C, and then instantly solidified to needle-shaped crystals (γ-form).

The first endothermic peak of the α-form may be due to a transition into one of the other polymorphic forms. As melting took place immediately after the first peak, it is difficult to isolate the transformed powder sample. The melting point of the transformed sample agreed well with that of γ-form, therefore, it might be reasonable to consider that the transition to the γ-form occurred at 162 °C.

Infrared Spectra IR spectra of the polymorphs of tegafur are shown in Fig. 5. Yamagami *et al.* reported the assignment of IR absorption bands of tegafur in the solid state.[10] Their assignments are as follows: ν_{NH}, ν_{CH}: 3000 cm^{-1}, $\nu_{C=O}$: 1710, 1675 cm^{-1}, $\nu_{C=C}$: 1650 cm^{-1}, δ_{CH}: 1465 cm^{-1}, δ_{CH}: 1265 cm^{-1}, ν_{C-O-C}: 1065 cm^{-1}, ν_{CH_2}: 915 cm^{-1}.

IR patterns were slightly different, particularly in the 1600—1800 cm^{-1} region. The differences in absorption for carbonyl stretching ($\nu_{C=O}$) near 1700 cm^{-1} are noteworthy. The α-form has three absorption bands, while the β-, γ- and δ-forms have two absorptions. Nakai *et al.* reported the determination of the crystal structures of tegafur polymorphs (α- and β-forms).[7,8] They reported that the α-form consisted of two conformationally different molecules, A and B. In the α-form, N(2) is hydrogen-bonded to O(1) of the adjacent enantiomeric molecule (molecule A to A, molecule B to B). In the β-form, on the other hand, N(2) is hydrogen bonded to O(2) of the adjacent enantiomeric molecule. Table II shows the hydrogen bonding parameters for each hydrogen bonding system. In the α-form crystal, the length of the hydrogen bonding in the A molecules was 0.15 Å shorter than that in the B molecules, and good linearity of hydrogen bonding in the A molecules was observed. It was estimated that the hydrogen bonding in A molecules was stronger than that in B molecules; therefore, the absorption band at 1665 cm^{-1} could be assigned to the C(1)=O(1) (in A molecules) carbonyl stretching, the band at 1698 cm^{-1} to the C(1)=O(1) (in B molecules) carbonyl stretching, and the band at 1729 cm^{-1} to the C(2)=O(2), which was free from hydrogen bonding. In the β-form crystal, one kind of hydrogen bonding was present and the IR absorption band at 1678 cm^{-1} could be assigned to the hydrogen-bonded carbonyl stretching, and the band at 1712 cm^{-1} to the free carbonyl stretching. Accordingly, the differences of the molecular conformation and the

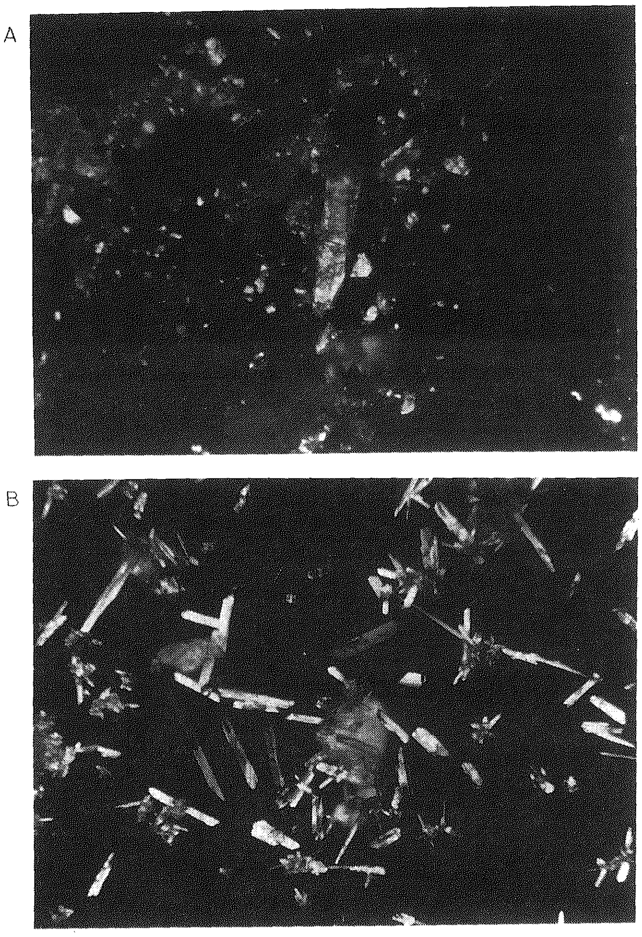

Fig. 4. Micrographs of Tegafur Crystals (β-Form) before and after Heat Transition

A, before transition (β-form); B, after transition (γ-form).

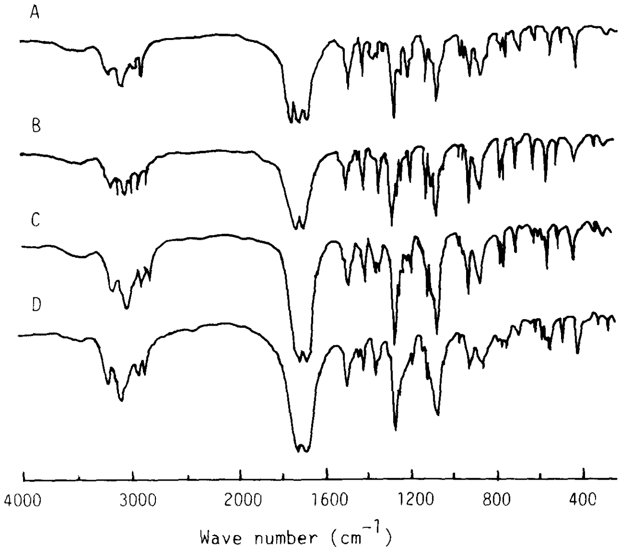

Fig. 5. IR Spectra of Polymorphic Forms of Tegafur

A, α-form; B, β-form; C, γ-form; D, δ-form.

TABLE II. Hydrogen Bond Parameters

α-Form	Distance (Å) N(2)···O(1)	Distance (Å) H(N2)···O(1)	Angle (°) N(2)–H(N2)···O(1)	β-Form	Distance (Å) N(2)···O(2)	Distance (Å) H(N2)···O(2)	Angle (°) N(2)–H(N2)···O(2)
N(2)–H(N2)···O(1)[a]	2.884 (4)	1.91 (4)	170 (3)	N(2)–H(N2)···O(2)	2.840 (3)	2.00 (3)	170 (3)
N(2)–H(N2)···O(1)[b]	2.835 (4)	2.06 (4)	162 (3)				

[a] Hydrogen bond between molecule A and its enantiomer. [b] Hydrogen bond between molecule B and its enantiomer.

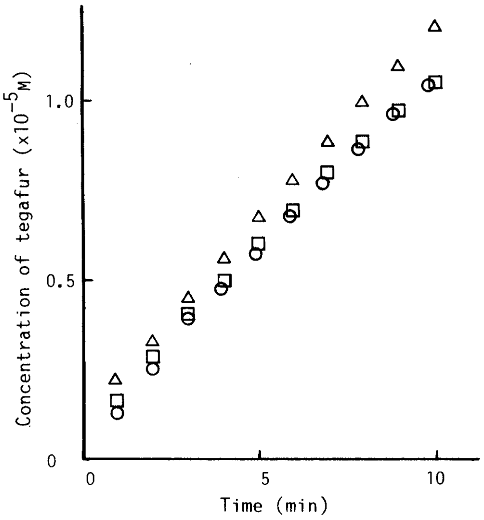

Fig. 6. Dissolution Profiles of Polymorphic Forms of Tegafur in Water at 37 °C

□, α-form; △, β-form; ○, γ-form. Each value is the mean of five experimental runs.

hydrogen bond system between α- and β-forms may have a great influence on the packing of tegafur molecules. The IR patterns of the γ- and δ-forms are analogous to that of the β-form. It is suggested that the hydrogen bond systems of the γ- and δ-forms are similar to that of the β-form.

Densities of the Four Polymorphs Densities of the four polymorphs measured by the flotation method are as follows: α-form: 1.52 gcm^{-3}, β-form: 1.54 gcm^{-3}, γ-form: 1.52 gcm^{-3} and δ-form: 1.53 gcm^{-3}. Densities of the single crystals of the α- and β-forms are reported as 1.52 and 1.54 gcm^{-3}, respectively. Density data in this work is reliable because the observed values of α- and β-forms coincide perfectly with their calculated values. It was found that the β-form is packed more efficiently than the other polymorphic forms.

Dissolution Rates of α-, β-, and γ-Forms The dissolution rates were determined for three crystal forms of tegafur at 37°C. Milosovich reported that sulfathiazole undergoes a polymorphic transition during dissolution.[11] The powder X-ray patterns were compared before and after the dissolution tests. Changes in the crystal forms of tegafur were not observed in this experiment.

The dissolution profiles measured by the stationary disk method are shown in Fig. 6. The difference in crystal forms significantly altered the dissolution rate of tegafur. The dissolution rate constants of the α-, β-, and γ-forms were calculated as 9.46, 11.0 and 9.58 × 10^{-7} M/min, respectively. The dissolution rate of the β-form was 1.16 times greater than that of the α-form. Lim reported a good correlation between the dissolution rates and solubility of polymorphic forms.[12] The solubility of the β-form might be higher than that of the α-form or the γ-form.

References and Notes

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2) S. Srčič, J. Kerč, U. Urleb, I. Zupančič, G. Lahajnar, B. Kofler, J. Smid-Korbar, *Int. J. Pharm.*, **87**, 1 (1992); R. J. Behme, D. Brooke, R. F. Farney, T. T. Kensler, *J. Pharm. Sci.*, **74**, 1041 (1985); Y. Matsuda, S. Kawaguchi, H. Kobayashi, J. Nishijo, *ibid.*, **73**, 173 (1984); M. Shibata, H. Kokubo, K. Morimoto, K. Morisaka, T. Ishida, *ibid.*, **72**, 1436 (1986); W. C. Stagner, J. K. Guillory, *ibid.*, **68**, 1005 (1979).

3) J. K. Haleblian, *J. Pharm. Sci.*, **64**, 1269 (1975).

4) S. A. Hiller, R. A. Zhak, M. J. Lidak, Brit. Patent 1 168 391 (1969) [*Chem. Abstr.*, **68**, 29664*j* (1968).

5) N. I. Karev, N. G. Blokhina, E. K. Vozny, M. P. Pershin, *Neoplasma*, **19**, 347 (1972).

6) K. Machijima, S. Nakajima, S. Sato, The 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, April 1979.

7) Y. Nakai, K. Yamamoto, K. Terada, T. Uchida, N. Shimizu, S. Nishigaki, *Chem. Pharm. Bull.*, **30**, 2629 (1982).

8) Y. Nakai, K. Yamamoto, K. Terada, T. Uchida, N. Shimizu, K. Yamaguchi, *Chem. Pharm. Bull.*, **34**, 1242 (1986).

9) W. W. Wendlant, "Thermal Analysis," 3rd ed., John Wiley and Sons, Inc., New York, 1986, p. 213.

10) K. Yamagami, K. Yoshisue, T. Masaki, A. Akazawa, K. Harima, T. Suzue, *Iyakuhin Kenkyu*, **5**, 165 (1974).

11) G. Milosovich, *J. Pharm. Sci.*, **53**, 484 (1964).

12) S.-L. Lim, *J. Pharm. Sci.*, **61**, 1423 (1972).