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Dissolution Behavior of Solid Drugs. II.[1] Determination of the Transition Temperature of Sulfathiazole Polymorphs by Measuring the Initial Dissolution Rates[2,3]

Motoko Kanke and Keiji Sekiguchi

School of Pharmaceutical Sciences, Kitasato University[4]

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A new method to determine the polymorphic transition temperature was developed by measuring the initial dissolution rates of polymorphic substances automatically, and was applied to α- and β-forms of sulfathiazole (ST). The transition temperature and the heat of transition between both forms were found to be 102.7° and 1.60 kcal/mole, respectively. It was also confirmed that the dissolution processes for both forms are diffusion controlled. Further, the metastable solubilities of β-crystals were estimated from those of the stable α-form and ratios of dissolution rates of α- and β-forms at various temperatures. Since practically "stable" β-crystals could successfully obtain after many trials of crystallization, the solubilities of β-form were also directly measured by solubility equilibrium method. By comparing the solubility data obtained by dissolution rates and solubility equilibrium method, a good agreement was obtained. In addition, thermal methods such as differential thermal analysis and differencial scanning calorimetry will not give accurate transition temperature, because the transition is always suspended by molecular hysteresis. However, the present method will give more correct value, since it utilizes the phenomenon of the delayed transition of the metastable crystals itself. Thus, it will be adopted generally as an universal and less time-consuming one and be applicable even for the determination of the imaginary transition temperature between monotropic polymorphs of organic substances which can not be determined practically by other methods.

Numerous polymorphic crystal forms have been recognized in pharmaceutical preparations and in raw materials. Polymorphic transition may occur rapidly or slowly, or may not occur completely, depending upon the crystal type, various kinds of lattice defect, conditions of exposure, *etc.* Since a metastable form of a drug changes gradually in most cases into a stable one, it may often cause variation in drug effectiveness or difficulties in preparation and storage of pharmaceuticals. On the contrary, it is possible that a thermodynamically metastable form of a drug is practically "stable" from the standpoint of transition kinetics due to extremely slow rate of crystal change or very long induction period. In such a case, the absorption rate and/or bioavailability of a metastable form will be increased relative to the thermodynamically stable one,[5] It is, however, difficult to predict whether transition between polymorphic crystal forms may occur during or after the manufacturing process. Therefore, a knowledge of transition temperatures and transition energies becomes very important from the standpoint of formulation and manufacturing control. It is also important to know whether the polymorphs behave as enantiotropic or monotropic substances: that is, whether transition from one form to the other is reversible or irreversible.

The determinations of transition temperature, transition energy, and solubility of polymorphic crystals have been generally carried out by the conventional solubility determination

1) Part I: M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.* (Tokyo), **21**, 871 (1973).
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3) Presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April, 1972.
4) Location: *9–1, Shirokane 5 chome, Minato-ku, Tokyo.*
5) B.E. Ballard and E. Nelson, *J. Pharmacol. Exptl. Therap.*, **135**, 120 (1962); A.J. Aguiar, J. Krc, Jr., A.W. Kinkel, and J.C. Samyn, *J. Pharm. Sci.*, **56**, 847 (1967); A.J. Aguiar and J.E. Zelmer, *J. Pharm. Sci.*, **58**, 983 (1969).

or various thermal methods of analysis. In the former case, it is difficult or impossible to determine solubility of a metastable polymorph which converts rapidly to the more stable form in solvents, and it takes relatively long exposure time to attain the concentration equilibrium. In the latter ones, the exact determination of transition temperature is usually difficult because of retardation of polymorphic change, especially in organic compounds.

Previously, the authors reported a modified procedure for dissolution rate measurement utilizing a stationary disk, and discussed its application to solubility determinations for slightly soluble drugs in water medium.[1] In the present study, transition temperature, transition energy, and solubility of polymorphs were determined, using the same automatic measurement for initial dissolution rates as developed in the previous work on the hydrate and anhydrous forms of phenobarbital.[2]

The following relationships were utilized in the determination of solubility, transition temperature, and transition energy from dissolution rate measurements, based on the assumption that the Noyes-Whitney's equation is valid.

The equation states that

$$\frac{dC}{dt} = K(C_s - C) \tag{1}$$

where dC/dt is the dissolution rate, C_S is saturated concentration (solubility), C is the concentration of drug in the bulk solution at time t, and K is an apparent rate constant. When any kind of pure solvent such as distilled water is used as dissolution medium, the relationship between the concentration of bulk solution and the absorbance at beginning stages of dissolution experiment satisfies the Beer's law, although the law can not often applied to concentrated solution. Thus, the following equation is valid,

$$\frac{dE}{dt} = \varepsilon \cdot \frac{dC}{dt} \tag{2}$$

where ε is the molar extinction coefficient, and E is the absorbance of the solution. Combining equations (1) and (2),

$$\frac{dE}{dt} = \varepsilon K(C_s - C) \tag{3}$$

As the concentration of the solution at starting time is zero and concentration in early stages of dissolution is negligible in comparison to C_S, equation (3) may be reduced to,

$$\frac{dE}{dt} = \varepsilon K C_s \tag{4}$$

and,

$$\log\left(\frac{dE}{dt}\right) = \log K + \log C_s + \log \varepsilon \tag{5}$$

The Arrhenius equation can be applied for dissolution process, and equation (6) is given as,

$$\log K = -\frac{E_a}{2.303R} \cdot \frac{1}{T} + \log A \tag{6}$$

where E_a is activation energy for dissolution, R is the gas constant, and A is a frequency factor. Also from temperature dependency of solubility, equation (7) is yielded,

$$\log C_s = -\frac{\Delta H}{2.303R} \cdot \frac{1}{T} + \text{const.} \tag{7}$$

where ΔH is the heat of solution. Substituting equations (6) and (7) into (5),

$$\log\left(\frac{dE}{dt}\right) = -\frac{(\Delta H+E_a)}{2.303R}\cdot\frac{1}{T} + \text{const.} \tag{8}$$

The quantity $(\Delta H+E_a)$ can be readily calculated from the slope of equation (8). Assuming E_a to be equal for polymorphic forms of a same substance, the transition energy, or the difference in ΔH, can be readily determined.

It is often difficult or impossible to determine solubility of metastable form (C'_S) by direct solubility measurement, since the polymorphic transition during the relatively long exposure to the solvent may easily occur. However, the data obtained from the dissolution rate measurement may be applied to the estimation of C'_S, using the solubility of the stable form (C_S) obtained experimentally.

Rewriting equation (4) for both stable and metastable forms,

$$\left(\frac{dE}{dt}\right) = \varepsilon K C_S \tag{9}$$

$$\left(\frac{dE'}{dt}\right) = \varepsilon K' C_S' \tag{10}$$

where (dE/dt) and (dE'/dt) are dissolution rates for the stable and the metastable forms, respectively, and K and K' are apparent dissolution rate constants for the stable and the metastable forms. Since the apparent dissolution rate constant K can be assumed to be equal to K', the following relationship is obtained by dividing equation (9) by equation (10)

$$C_S' = C_S \times \frac{(dE'/dt)}{(dE/dt)} \tag{11}$$

The assumption adopted in deriving the above equations will be reasonably accepted if the dissolution processes for polymorphs are diffusion controlled, since both crystal forms will take the same molecular dispersion state in solution.

It is known that sulfathiazole is enantiotropic and exists in at least two distinct crystal forms, the α-form, or form I, being stable at lower ranges of temperature, and the β-form, or form II, being stable at high temperatures. Higuchi *et al.*[6] and Milosovich[7] observed the rapid conversion from the metastable to the stable form in aqueous solution. In the present study, therefore, sulfathiazole was chosen as a model substance to determine the transition temperature between its polymorphs from the dissolution rates obtained by the present measurement technique. No evidence of transition to the α-form was detected during every run of measurement. Therefore, each dissolution rate thus obtained represents that for the original polymorphic forms. By introducing the data into the above equations, transition temperature, heat of transition, and solubility of the β-form were calculated. In order to make comparison, these physicochemical constants were also measured or calculated by conventional solubility determination method, utilizing powdered ST samples. Results obtained from both methods, together with transition temperature and energy determined from thermal analysis are given below.

Experimental

Materials——α-Sulfathiazole (α-ST): Commercial product of JP VII grade was recrystallized from distilled water. β-Sulfathiazole (β-ST): mp 200—202°, was recrystallized from *n*-propanol. As have been reported in the previous paper, practically "stable" crystals of β-form were obtained in some crops of recrystallizations.

6) W.I. Higuchi, P.D. Bernardo, and S.C. Mehta, *J. Pharm. Sci.*, **56**, 200 (1967).
7) G. Milosovich, *J. Pharm. Sci.*, **53**, 484 (1964).

Preparation of Sample Disks——Preparation of disks was the same as described in the previous paper[1] except that pure sample powder of both forms of ST were used. Particle size of ST used for disk preparation and for conventional solubility measurement was in the range of 63—149 μ.

Characterization of Polymorphic Forms——ST powder and disks before and after dissolution rate experiments and solubility determinations were characterized by X-ray diffraction analysis, infrared (IR) absorption, and/or differential scanning calorimetry (DSC). The apparatus used for the X-ray diffraction analysis was a Rigaku Geigerflex 2030, Cu-Kα, IR absorption was measured by a Jasco IRA-1 Grating Infrared Spectrophotometer, and the DSC apparatus used was a Perkin–Elmer DSC-1B Differential Scanning Calorimeter. The X-ray patterns, the IR spectra and the DSC curves of both ST forms were reported previously.[1]

Dissolution Rate Measurement——The apparatus used in conducting the dissolution rate measurement experiments is shown in Fig. 1. The dissolution measurement cell was similar to that used in the previous study.[1] 250 ml of distilled water were placed in the water jacketed cell, and agitated by magnetic stirrer at the speed of 300 rpm. The solution medium was circulated by means of a pump at a flow rate of 440 ml/min. The temperature of the solution medium was monitored until it stabilized at the desired value. The sample disk was fixed on the disk holder and then placed into the dissolution medium. Zero time for each experiment was the time of placement of the sample into the cell. The amount of sample dissolved as a function of time was measured automatically by a log converter (TOA PB-70A) equipped recorder (TOA

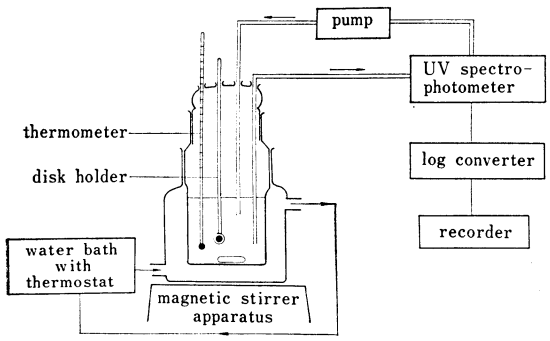

Fig. 1. Schematic Diagram showing the Apparatus used for the Dissolution Rate Measurements

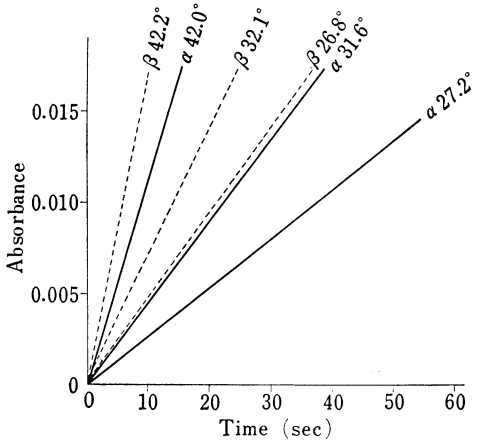

Fig. 2. Curves representing the Initial Dissolution Rates of Sulfathiazole Polymorphs at Various Temperatures by Automatic Recording

solid lines: α-ST
dotted lines: β-ST

EPR-3T) attached to a spectrophotometer (Hitachi Perkin–Elmer 139, 283 mμ wave length) through which the dissolution medium was continuously circulated. The exposed disk surface was wiped with lens paper on withdrawal from the solution at the termination of the experiments, and then examined by X-ray diffractometry, DSC and/or IR. Identical characteristic patterns before and after measurements were obtained.

Conventional Solubility Determinations——About 1.5 g of sample powder (63—149 μ) were placed in 100 ml of water in the same type of cell used in the dissolution measurements, and agitated at 600 rpm at temperatures of 25°, 30°, 35°, 40°, 45°, and 49°. Solution samples were taken by glass syringe at short time intervals during the early stages of each experiment, and then at approximately hourly intervals until the concentration completely attained equilibrium. The solution samples were then immediately filtered through a 0.45 μ membrane filter (Millipore HAWP 01300), and a carefully measured aliquot was diluted for spectrophotometric assay.

Determination of Transition Temperature and Heat of Transition by Differential Scanning Calorimetry (DSC)——A Perkin–Elmer DSC-1B Differencial Scanning Calorimeter was used.

(1) Transition Temperature Measurements: Sample: α-ST, finely powdered; sample weight: 8.5—13.2 mg; sample pan: solid aluminum pan; sensitivity: 8 mcal/sec; heating rate: variable 1° to 64°/min; chart speed: variable, from 5 to 80 mm/min. Temperature corrections were made by Indium, a sample kit provided by the manufacturer.

(2) Heat of Transition Measurements: Sample: α-ST, finely powdered; sample weight: 5.8—9.3 mg; sensitivity: 8 mcal/sec; heating rate: 4° and 8°/min; chart speed: variable, from 10 to 80 mm/min.

Areas under the transition peaks were measured both with a planimeter, and by weighing the peak area cut from photocopies of the recorder charts.

Result and Discussion

Transition Temperature and Heat of Transition obtained by Dissolution Rate Measurement

The initial dissolution curves of α- and β-ST at various temperatures are shown in Fig. 2. The relationship between log (dE/dt) and $1/T$ obtained by the initial dissolution curves are depicted in Fig. 3. The transition temperature indicated by the intersection

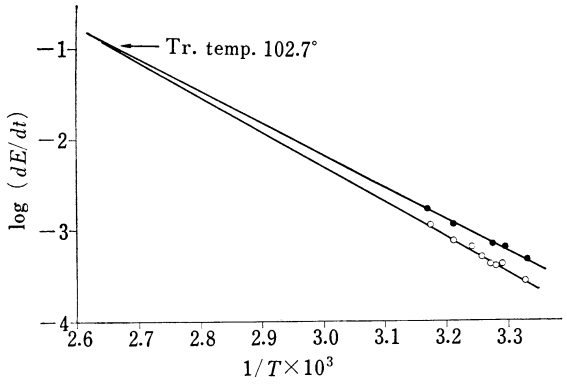

Fig. 3. Plots of log (dE/dt) against $1/T$ for α- and β-forms of Sulfathiazole in Water

○ : α-ST
● : β-ST

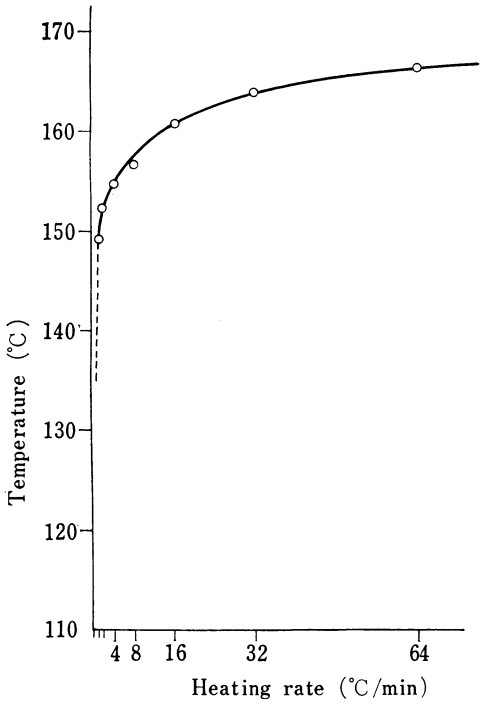

Fig. 4. Effect of Heating Rate of DSC on Transition Temperature of Sulfathiazole (α→β)

of the two curves is 102.7°, and the transition energy was calculated to be 1.60 kal/mole by taking the difference between the heats of dissolution for the two forms, which were calculated from the slopes of equation (8). Curves shown in Fig. 3 were determined by the least squares method. The crystal structure of the exposed disk surface showed identical characteristic X-ray diffraction patterns before and after the dissolution rate measurements. Therefore, it can be concluded that no polymorphic form conversions occurred during the experiments, and the results obtained can be considered reliable in this regard. It is interesting to note that practically "stable" β crystals showed the identical X-ray patterns with of β-crystals which converted rapidly into stable α-form in water medium.

Transition Temperature and Heat of Transition obtained by DSC

A plot of transition initiation temperatures versus heating rates for a series of heating rates is shown in Fig. 4. The transition initiation temperature is defined here as the tempera-

ture at which endothermic heat effect due to polymorphic transition begins to occur. Although in principle the transition temperature should be obtained by extrapolating the curve of Fig. 4 to a heating rate of 0°/min, but it is obviously difficult in this case to determine the accurate transition point by extrapolation. However, calculation of the average heat of transition, based on 20 separate runs, indicated a transition energy value of 1.63±0.07 kcal/mole.

Solubility Determination

Solubility curves for sulfathiazole polymorphs obtained by the equilibrium method at various temperatures are shown in Fig. 5. Solubility values obtained are given in columns 2 and 3 of Table I. Fig. 6 shows the van't Hoff plots for these data with the curves determined by the least squares method. Analysis of these curves indicates a transition temperature of 112.6° and a transition energy of 1.64 kcal/mole. The solid sample phase was examined

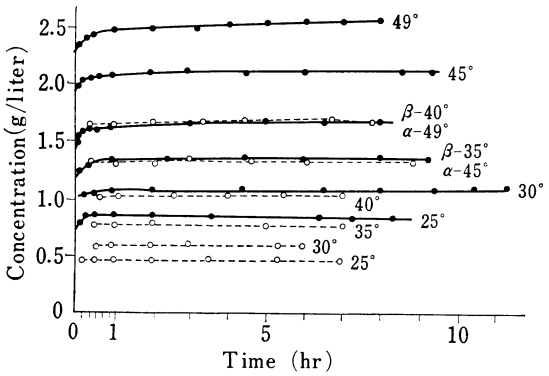

Fig. 5. Dissolution Curves for α- and β-forms of Sulfathiazole in Water at Temperatures ranging from 25° and 49°

···○···: α-ST
—●—: β-ST

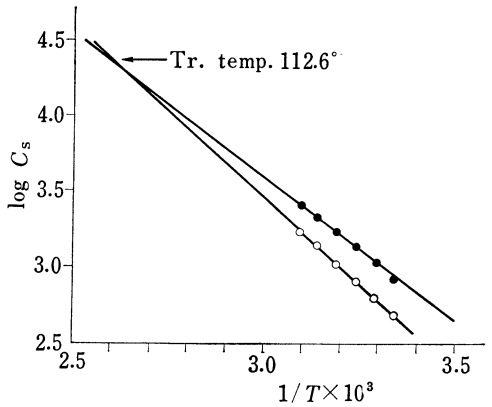

Fig. 6. The van't Hoff Plots for α- and β-forms of Sulfathiazole in Water

○ : α-ST
● : β-ST

by X-ray diffraction analysis, DSC, and/or IR both before and after each solubility measurement. No conversion of β-form was observed even after 6 to 11 hours of measurement time when the practically "stable" β-crystals were used. Usually, however, some conversion from metastable to stable form would occur during long measurement times. The authors did experience such conversions several times during the early stages of this work when using ordinally metastable β-form crystals obtained by heat transition or by recrystallization. Even in such cases, solubility of the metastable form can be calculated from equation (11) by

Table I. Solubility Data for α- and β-forms of Sulfathiazole in Water

Temp. (°C)	α-ST Exptl. g/liter	β-ST Exptl. g/liter	β-ST Calcd.[a] g/liter
25	0.465	0.840	0.813
30	0.594	1.100	0.993
35	0.790	1.367	1.266
40	1.040	1.690	1.598
45	1.350	2.115	1.993
49	1.683	2.544	2.408

a) values calculated from equation, $C_s' = C_s \times \frac{dE'/dt}{dE/dt}$

utilizing the experimentally determined solubility for the stable form and the ratio of dissolution rates for both forms. These data are given in column 4 of Table I. It is seen that the calculated solubility values of β-form are in good agreement with the experimental values given in column 3. Therefore, the validity of the assumption that the apparent dissolution rate constant K for the α-form is equal to K′ for the β-form in equation (11) was confirmed experimentally. It can be concluded that transition temperature determination by dissolution rate measurements could be used practically.

Activation Energy of Dissolution

The activation energy of dissolution for each α- and β-forms of sulfathiazole was obtained by the difference between the heat of dissolution, or the slope of curve in Fig. 3, and the heat of solution, or the slope of curve in Fig. 6 for each form. The values of 7.18 kcal/mole and 7.22 kcal/mole were calculated for α- and β-forms, respectively. These values of activation energy for both forms are considered to coincide within experimental error. Therefore, the assumption that E_a is equal for α- and β-forms was confirmed experimentally.

Thickness of Diffusion Layer

Thickness of diffusion layer, δ was calculated by the following equations,

$$D = \frac{\kappa T}{6\pi\mu r} \text{(Stokes–Einstein Eq.)} \tag{12}$$

$$K = \frac{SD}{V\delta} \tag{13}$$

where D is the diffusion constant, k is the Boltzmann constant, T is the absolute temperature, μ is viscosity, r is the radius of a solute molecule, S is the surface area of the solid, and V is the volume of dissolution medium.

If the molecules of both forms of ST are assumed to be spherical, the molecular radius r is obtained from the weight and volume of the disk. By introducing the values of various constants into equation (12), D became 5.8×10^{-6} cm^2/sec at 25°. From the value of K experimentally determined, the δ was found to be 5.7×10^{-3} cm.

Conclusion

As is shown above, the transition temperature and the heat of transition between α- and β-forms of ST were found to be 102.7° and 1.60 kcal/mole, respectively, which are in good agreement with values obtained by solubility equilibrium method and with energy obtained by DSC. Further, by the present method the values of the metastable solubility of the β-form are easily estimated and they almost coincide with those determined by solubility method. In addition, it was found that the dissolution processes for α- and β-forms of ST are thought to be diffusion controlled from the thickness of diffusion layer, and the magnitude and equality of activation energies of both forms.

Hitherto, the determination of transition temperature or the heat of transition of polymorphic substances were done either by various methods of thermal analysis or by the solubility equilibrium method. In the former ones, the accurate determination of transition temperature is difficult because transition is often delayed greatly, especially in organic chemicals. Also solubility method is often inapplicable to the metastable polymorphs by the fact that they are easily converted to the more stable forms when they are exposed to the solvent, and as well the method requires much longer experimental time. In the method described here, however, the time of exposure to the dissolution medium was so short that the rate can be measured before the transition of the metastable form is occurred.

Further, it is anticipated that the method is applicable not only to enantiotropic substances, but also even to the estimation of transition temperature between monotropic polymorphs of organic compounds which can not be determined practically by other methods.