

Estimation of Transition Temperature of Pharmaceutical Polymorphs by Measuring Heat of Solution and Solubility

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The transition temperature for enantiotropic polymorphs of pharmaceutical drugs was estimated by measuring the heat of solution and solubility at 25 °C. Instead of the conventional estimation method using van't Hoff plots, a thermodynamic formula was derived with the heat of solution and solubility as variables for calculating the temperature at which the Gibbs free energy difference between two polymorphs in enantiotropic system become zero. The transition temperatures of polymorphic pairs for five model compounds (seratrodast, mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine) calculated by the formula were in good agreement with previous studies. Since this formula requires solubility data at only one arbitrary temperature other than the heat of solution data for both polymorphs in a polymorphic pair, the proposed method is much faster than the conventional method, requiring solubility data at five or more different temperatures for preparing van't Hoff plots.

Polymorphism occurs frequently in drug substances because of the complexity of their chemical structures.[1,2] Polymorphs of a chemical compound are solid crystalline phases which have different internal crystal lattices. The physical properties, such as solubility, melting point, heat of fusion, and molecular density, are also different from each other. In particular, the solubility in aqueous media has been of great interest for the development of polymorphic drug substances, because it may influence the bioavailability.[1,3,4] In addition, the relative thermodynamic stability of polymorphs has also been of great interest. Polymorphs fall into one of two categories: a monotropic system or an enantiotropic system. Although one modification is more stable than the other modification at any temperature in the monotropic system, the stability order is reversed below and above a particular temperature, called the transition temperature, at which the Gibbs free energy difference (ΔG) between two modifications become zero, in the enantiotropic system.

Differential scanning calorimetry (DSC) has been mainly used to evaluate the thermodynamic stability relationship of a polymorphic pair. Burger and Ramberger proposed that if an endothermal solid-solid transition is observed at some temperature during DSC analysis, the polymorphic pair is enantiotropic with a transition temperature below that temperature, and that if an exothermal solid-solid transition is observed at some temperature, the polymorphic pair is monotropic or enantiotropic with a transition temperature above that temperature (Heat of Transition Rule).[5,6] If a polymorphic pair has been determined to be enantiotropic, estimating the transition temperature is very important for drug development.[7] This is because a more stable form suitable for the development of pharmaceuticals should be decided based on the thermodynamic stability. For these reasons, a number of studies on estimating the transition temperature have so far been reported.[8–14] In these studies, the transition temperature was estimated by linear extrapolation of van't Hoff plots (logarithmic solubility versus reciprocal of absolute temperature plots) for each polymorph; the temperature at which these extrapolated lines intersect ($\Delta G = 0$) is the transition temperature.

The purpose of this paper is to demonstrate a novel method for estimating the transition temperature for an enantiotropic polymorphic pair. This method is based on a derived thermodynamic formula with the heat of solution and solubility used as variables, which can indicate the temperature at which ΔG between two modifications is zero.[15] As our model compounds, seratrodast, mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine polymorphic pairs were used; also, the obtained results were compared with those of previous studies. The chemical structures of the model compounds are shown in Fig. 1.

Experimental

Materials. Seratrodast was prepared in-house by Takeda Chemical Industries, Ltd. (Osaka, Japan). Mefenamic acid and carbamazepine were of biochemical grade and obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Sulfathiazole was of reagent grade and obtained from Avocado Research Chemicals Ltd. (Heysham, Lancashire, U. K.). Acetazolamide was a commercial product of JP XIV grade and obtained from Daiich Pharmaceutical Co., Ltd. (Tokyo, Japan). The solvents used to determine the heat of solution and solubility were of analytical reagent grade. Acetonitrile, used as the mobile phase for HPLC, was of HPLC grade.

Preparation of Polymorphic Substance. Seratrodast Polymorphs: The seratrodast prepared in-house was used as Form I. Form II was prepared by melting Form I at 130 °C and cooling it slowly at room temperature.

Mefenamic Acid Polymorphs: Form I was prepared by re-

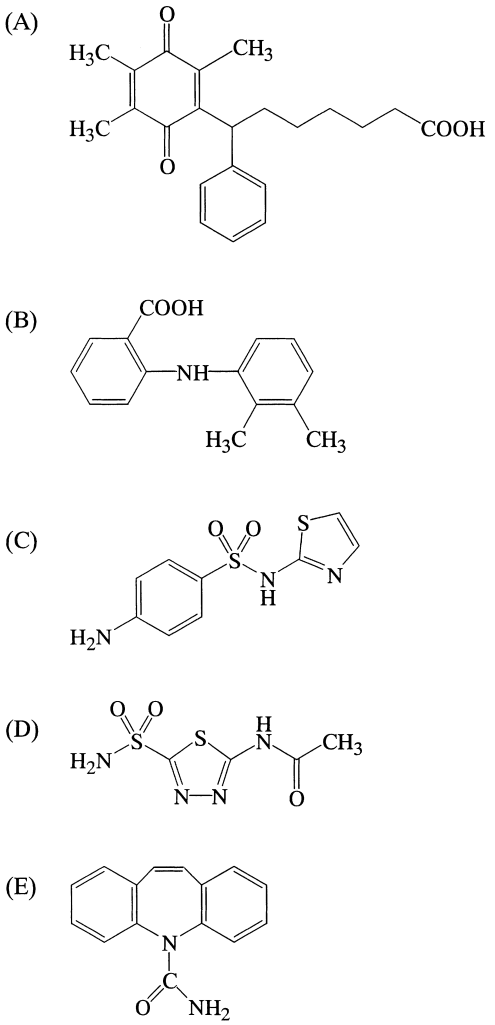

Fig. 1. Chemical structures of model compounds. (A) Seratrodast, (B) mefenamic acid, (C) sulfathiazole, (D) acetazolamide, and (E) carbamazepine.

crystallization from acetone at room temperature. Form II was prepared by heating Form I at 175 °C for 20 min.

Surfathiazole Polymorphs: Form I was prepared by recrystallized from distilled water. Form II was prepared by heating Form I at 180 °C for 20 min.

Acetazolamide Polymorphs: Form A was prepared by the method of Umeda[8] as follows. After aetazolamide (5 g) was dissolved in 700 mL of methanol at 65 °C, the solution was slowly cooled and maintained at 5 °C overnight. The resulting crystals were collected by filtration and dried at 80 °C in vacuo. Form B was prepared by heating Form A at 210 °C for 1 h.

Carbamazepine Polymorphs: Commercially obtained carbamazepine was used as Form III. Form I was prepared by heating Form III at 170 °C for 30 min.

X-ray Powder Diffraction Analysis. The X-ray powder diffraction was measured at room temperature with a RINT 2000 diffractometer (Rigaku Co., Tokyo, Japan) using a scintillation counter, a Cu target X-ray tube with a Ni filter (50 kV, 180 mA) and a symmetrical reflection goniometer scanned at 6° min^{-1} over a 2θ range between 3 and 40°.

Differential Scanning Calorimetry (DSC). The DSC curves were measured with 220CU (Seiko Instruments Inc., Tokyo, Japan) instruments under a nitrogen gas flow at a heating rate of 5 °C min^{-1}. The heating rate was made to correspond with that of previous studies to compare the DSC curves with the previous ones.[8,9,16–18]

Solution Calorimetry. The heat of solution of each sample was determined using an isothermal heat-conduction microcalorimeter system [2277 Thermal Activity Monitor (TAM), Thermometric AB, Järfälla, Sweden] at 25.0 °C. One hundred milligrams of each sample was dissolved in 100 mL of *N,N*-dimethylformamide (DMF), methanol, or acetonitrile as the solvent at 25.0 °C. The dissolution media were stirred at 50 rpm by a paddle.

High Performance Liquid Chromatography (HPLC). A Waters model 2690 HPLC system with a 4.6-mm i. d. × 75-mm column containing 5-μm octadecylsilanized silica gel (YMC-Pack Pro C18 AS-307, YMC Co., Ltd.) was used along with a Waters model 996 photodiode array detector to measure the solubility and purity of each sample. The mobile phase was a mixture of 0.02 mol L^{-1} phosphate buffer (pH 7.0) and acetonitrile (3:2), and the flow rate was 1.0 mL min^{-1}. The detection wavelength was set at the maximum of each compound in the mobile phase (seratrodast, 269 nm; mefenamic acid, 290 nm; sulfathiazole, 259 nm; acetazolamide, 266 nm; and carbamazepine, 285 nm). Sample volumes of 20 μL were injected with an automatic injector.

Measurement of Solubility. An excess amount of each sample was added to 100 mL of a dissolving solvent [seratrodast polymorphs, phosphate buffer solution (pH 8.0, 0.05 mol L^{-1}); mefenamic acid polymorphs, dodecyl alcohol; sulfathiazole polymorphs, water; acetazolamide polymorphs, phosphate buffer solution (pH 7.0, 0.1 mol L^{-1}); and carbamazepine polymorphs, 2-propanol] at 25 °C. The suspensions were shaken at 120 strokes min^{-1}. Five milliliter of the suspension was filtered through a membrane filter (0.45 μm). The filtrates were then suitably diluted with the mobile phase and the concentrations of each sample were determined by HPLC, as described above.

Theoretical Section

When a drug substance has a pair of polymorphs, Forms A and B, the Gibbs free energy (G) of each polymorph is expressed using the enthalpy (H) and entropy (S):

$$G_A = -H_A - TS_A, \quad (1)$$

$$G_B = -H_B - TS_B, \quad (2)$$

where T is the absolute temperature. Their relative stability at temperature T is determined by their Gibbs free energy difference, $\Delta G_{A-B} = G_A - G_B$: if $\Delta G_{A-B} < 0$, Form A is more stable; if $\Delta G_{A-B} > 0$, Form B is more stable; if $\Delta G_{A-B} = 0$, Forms A and B are equally stable. ΔG_{A-B} has been widely estimated by the following equation using solubility data:[19–21]

$$\Delta G_{A-B,T} = 2.303RT(\log S_{A,T} - \log S_{B,T}), \quad (3)$$

where R is the gas constant and S is the solubility. Eq. 3 shows that at a given temperature the ratio of the ideal solubilities of two modifications of a substance is always the same. The ratio of the ideal solubilities is independent of the solvent.

On the other hand, the natural logarithmic solubility of Forms A and B at a temperature of T_1 are expressed as a function of the reciprocal of the absolute temperature by the fol-

lowing equations (van't Hoff plots):

$$\log S_{A,T_1} = (-\Delta H_{\text{soln A},T_1}/2.303R)\,(1/T_1) + C_A, \quad (4)$$

$$\log S_{B,T_1} = (-\Delta H_{\text{soln B},T_1}/2.303R)\,(1/T_1) + C_B, \quad (5)$$

where ΔH_{soln} is the heat of solution and C is a constant. When Eqs. 4 and 5 are substituted in Eq. 3, the following equation is obtained:

$$\Delta G_{A\text{–}B,T_1} = -\Delta H_{\text{trans } T_1} + 2.303RT_1\,(C_A - C_B), \quad (6)$$

where $\Delta H_{\text{trans } T_1}$ is the heat of transition corresponding to the difference in the heat of solution ($\Delta H_{\text{soln A},T_1} - \Delta H_{\text{soln B},T_1}$). In the same manner, at a temperature of T_2,

$$\Delta G_{A\text{–}B,T_2} = -\Delta H_{\text{trans } T_2} + 2.303RT_2\,(C_A - C_B). \quad (7)$$

To eliminates ($C_A - C_B$), Eq. 7 is substituted in Eq. 6, yielding

$$T_1/T_2 = (\Delta G_{A\text{–}B,T_1} + \Delta H_{\text{trans } T_1})\,/\,(\Delta G_{A\text{–}B,T_2} + \Delta H_{\text{trans } T_2}). \quad (8)$$

Provided that the influence of the temperature on the heat capacity of Forms A and B is similar (i.e., the graphs of H versus T are reasonably parallel) in a narrow temperature range between T_1 and T_2, ΔH_{trans} is a constant and can be estimated at any temperature. Therefore, Eq. 8 becomes

$$T_1/T_2 = (\Delta G_{A\text{–}B,T_1} + \Delta H_{\text{trans}})\,/\,(\Delta G_{A\text{–}B,T_2} + \Delta H_{\text{trans}}). \quad (9)$$

In the case that T_2 is the transition temperature (T_{trans}), $\Delta G_{A\text{–}B,T_2} = 0$; therefore

$$T_{\text{trans}} = (\Delta G_{A\text{–}B,T_1}/(H_{\text{trans}} \cdot T_1) + 1/T_1)^{-1}. \quad (10)$$

Finally, substituting Eq. 3 in Eq. 10 yields

$$T_{\text{trans}} = [\,2.303\,R\,(\log S_{A,T_1} - \log S_{B,T_1})/ \Delta H_{\text{trans}} + 1/T_1\,]^{-1}. \quad (11)$$

Thus, the transition temperature for an enantiotropic polymorphic pair can be calculated from the heat of transition and the solubility at only one arbitrary temperature. The heat of transition can usually be estimated from DSC data directly by integrating a solid–solid transition peak or subtracting the heat of fusion of one polymorph from that of the other. However, it is reasonable that heat of transition of a polymorphic pair is estimated by solution calorimetry as the difference in heats of solution of each polymorph rather than by DSC. This is because the heat of transition cannot be measured by DSC if a solid-solid transition does not occur, or the heat of fusion of a polymorph cannot be obtained due to associated decomposition. In the proposed method, there is no need to use the same solvent when determining the heat of solution and the solubility because the heat of transition corresponding to the difference in the heat of solution is theoretically independent of the solvent used; therefore, we can freely choose any kind of solvent. A highly solubilizing solvent should be used for a precise measurement of the heat of solution, whereas a moderately solubilizing solvent should be used for a reasonable measurement of the solubility.

Results and Discussions

Identification of Polymorphic Form. The polymorphic forms of seratrodast, mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine used in the present studies were identified by an X-ray powder diffraction analysis and DSC. The X-ray powder diffraction patters and the DSC curves of each polymorph were identical to those of previous studies.[8–10,16–18,22] The results of HPLC suggested that each of the polymorphs did not decompose. The polymorphs of each compound were obviously identified from these results.

Heat of Solution. For evaluating the precision of the measurement, the heats of solution of the seratrodast polymorphs were measured in three different solvents (DMF, methanol, and acetonitrile) at 25.0 °C. Though the heats of solution varied with the kind of solvent, the heats of transition corresponding to the differences in the heats of solution were almost equal for each solvent (6.05, 6.03, and 6.05 kJ mol^{-1}), as shown in Table 1, suggesting that the measurements had been accomplished with great precision.

Table 2 gives the heats of solution of the mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine polymorphs in DMF. The heat of transition of each polymorphic pair, estimated as the differences in their heats of solution, was 3.67, 5.28, 2.02, and −2.93 kJ mol^{-1}, respectively.

Solubility. The dissolution behaviors of the seratrodast polymorphs in a phosphate buffer solution (pH 8.0, 0.05 mol

Table 1. Heats of Solution in Various Solvents Measured at 25.0 °C and Heats of Transition for Seratrodast Polymorphs

Solvent	ΔH_{soln}/kJ mol^{-1}		ΔH_{trans}/kJ mol^{-1}
	Form I	Form II	
DMF	22.66	16.61	6.05
Methanol	39.12	33.09	6.03
Acetonitrile	39.82	33.77	6.05

Table 2. Heats of Solution in DMF Measured at 25.0 °C and Heats of Transition for Various Polymorphic Drug Substances

Compound	Crystal form	ΔH_{soln} kJ mol^{-1}	ΔH_{trans} kJ mol^{-1}	Direction of transition
Seratrodast	Form I	22.66	6.05	II → I
	Form II	16.61		
Mefenamic acid	Form I	17.75	3.67	II → I
	Form II	14.08		
Sulfathiazole	Form I	−6.30	5.28	II → I
	Form II	−11.58		
Acetazolamide	Form A	−4.35	2.02	B → A
	Form B	−6.37		
Carbamazepine	Form I	4.50	−2.93	III → I
	Form III	7.43		

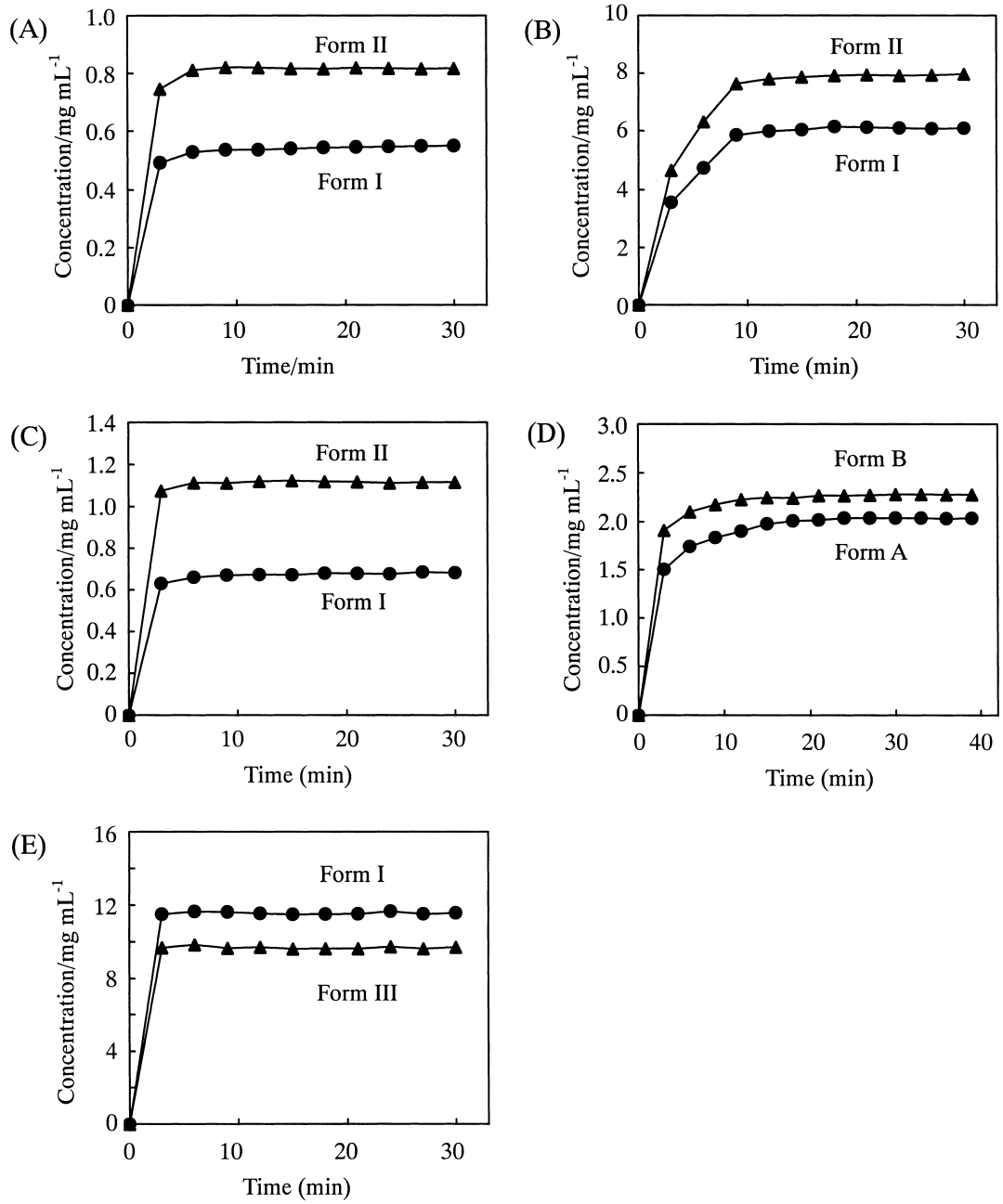

Fig. 2. Dissolution profiles of polymorphic forms of various drug substances at 25 °C.
(A) Seratrodast in phosphate buffer solution (pH 8.0, 0.05 mol L^{-1}), (B) mefenamic acid in dodecyl alcohol, (C) sulfathiazole in water, (D) acetazolamide in phosphate buffer solution (pH 7.0, 0.1 mol L^{-1}), and (E) carbamazepine in 2-propanol.

L^{-1}), mefenamic acid polymorphs in dodecyl alcohol, sulfathiazole polymorphs in water, acetazolamide polymorphs in phosphate buffer solution (pH 7.0, 0.1 mol L^{-1}), and carbamazepine polymorphs in 2-propanol, measured at 25 °C, are shown in Fig. 2. These dissolving solvents were chosen to correspond with those used in previous studies.[8–12] These plots show the concentration attained in solution for each polymorphic pair as a function of time in the presence of an excess of the solid phase. The measurements were completed within 40 min for each polymorphic pair. The solubilities were estimated by averaging the concentrations at equilibrium. It was confirmed by an X-ray diffraction analysis in all cases that neither of the polymorphic forms was transformed to the other.

Calculation of the Transition Temperature. The transition temperatures for each polymorphic pair were calculated by the proposed formula using the heat of transition and solubility data described above. The results are given in Table 3. The transition temperatures for the seratrodast, mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine polymorphic pairs were 84.9, 89.6, 116.8, 72.1, and 77.6 °C, respectively, which were in good agreement with those reported (83.4,[9] 89,[10] 112.6,[11] 78.4,[8] and 73 °C[12]). The differences between these values could be due to such factors as the equipment, chemical purity, polymorphic purity, and degree of crys-

Table 3. Transition Temperatures Calculated by Heat of Transition and Solubility Results for Various Polymorphic Drug Substances

Compound	Crystal form	ΔH_{trans}	Solubility at 25 °C	T_{trans}/°C	
		kJ mol^{-1}	mg mol^{-1}	Calculated value	Literature value
Seratrodast	Form I	6.05	0.543	84.9	83.4
	Form II		0.817		
Mefenamic acid	Form I	3.67	6.09	89.6	89
	Form II		7.93		
Sulfathiazole	Form I	5.28	0.677	116.8	112.6
	Form II		1.118		
Acetazolamide	Form A	2.02	2.04	72.1	78.4
	Form B		2.28		
Carbamazepine	Form I	−2.93	11.56	77.6	73
	Form III		9.68		

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Conclusions

A thermodynamic formula for estimating a transition temperature for an enantiotropic polymorphic pair was derived using the heat of solution and solubility. The transition temperatures for the polymorphic pairs of five model compounds (seratrodast, mefenamic acid, sulfathiazole, acetazolamide, and carbamazepine), calculated by the formula, were 84.9, 89.6, 116.8, 72.1, and 77.6 °C, respectively, which are in good agreement with the results of previous studies. This formula requires solubility data at only one arbitrary temperature other than the heats of solution data for each polymorph; therefore, the proposed method is much faster than the conventional method, which requires solubility data at five or more different temperatures for preparing van't Hoff plots. These results demonstrate that the proposed formula would be very useful for polymorphic studies on drug substances.

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