A Novel Method for Estimation of Transition Temperature for Polymorphic Pairs in Pharmaceuticals Using Heat of Solution and Solubility Data

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A novel method for thermodynamic stability studies of polymorphic drug substances has been developed. In order to estimate the transition temperature for an enantiotropic polymorphic pair, a formula for calculating the temperature at which the solubilities of each polymorph become equal has been derived with heat of solution and solubility as the variables. This formula is based on the assumption that van't Hoff plots (logarithmic solubility *versus* reciprocal of absolute temperature plots) of each polymorph show a straight line (heat of solution is independent of temperature) whose slope can be expressed as a function of heat of solution. The transition temperatures for seratrodast, acetazolamide and carbamazepine polymorphic pairs calculated by the formula were in good agreement with the results of previous studies. Furthermore, the calculated transition temperature for the indomethacin polymorphic pair was above the melting point, an unrealistic temperature range, suggesting that these polymorphs are monotropically related. Since this formula requires solubility data at only one arbitrary temperature other than 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 the preparation of van't Hoff plots.

Key words thermodynamic stability; drug substance; transition temperature; polymorph; van't Hoff plot

Polymorphism of drug substances now occurs more and more frequently because of the complexity of their chemical structures.[1,2] Polymorphs of a substance are chemically identical; however, they have different physical properties such as solubility, melting point, heat of fusion, molecular density and so on. For the development of polymorphic drug substances, solubility in aqueous media has been of particular interest because it may influence bioavailability.[1,3,4] In addition, the relative thermodynamic stability of the polymorphs has also been of great interest. Polymorphs fall into one of two categories: a monotropic system or an enantiotropic system. Although one polymorphic form is more stable than the other form at any temperature in the monotropic system, the stability order is reversed below and above a particular temperature called the transition temperature, at which their Gibbs free energy are equal, in the enantiotropic system. Therefore, evaluating the thermodynamic stability relationships of polymorphic pairs (monotropic or enantiotropic) and estimating the transition temperatures in the case of enantiotropic polymorphic pairs, is very important for drug development.[5]

In general, the thermodynamic stability relationship of a polymorphic pair has been evaluated based on differential scanning calorimetry (DSC) data. 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).[6,7] They also proposed that if the higher melting form has lower heat of fusion, the polymorphic pair is enantiotropic, otherwise the pair is monotropic (Heat of Fusion Rule).[6—8]

If a polymorphic pair in a pharmaceutical has been determined to be enantiotropic, the transition temperature becomes of great interest. This is because a more stable form suitable for the development of the pharmaceutical should be decided on the basis of the thermodynamic stability. For these reasons, a number of studies on the estimation of transition temperature have been reported until now.[9—15] In these studies, transition temperature has been 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 is the transition temperature.

In this paper, we describe a novel method to determine whether a polymorphic pair is monotropic or enantiotropic and estimate the transition temperature for an enantiotropic polymorphic pair. This method is based on a derived thermodynamic formula, with heat of solution and solubility as the variables, which can indicate the temperature at which the solubilities of each polymorph become equal. For demonstration of the utility of this formula, seratrodast, acetazolamide, carbamazepine and indomethacin polymorphic pairs were used, and the obtained results were compared with those of previous studies.

Experimental

Materials Seratrodast was prepared in-house by Takeda Chemical Industries, Ltd. (Osaka, Japan). Acetazolamide was a commercial product of JP XIV grade and obtained from Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan). Carbamazepine and indomethacin were of biochemical grade and obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Solvents used for the determination of 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.

Acetazolamide Polymorphs: Form A was prepared by the method of Umeda[16] as follows. Acetazolamide (5 g) was dissolved in 700 ml of methanol at 65 °C, and the solution was cooled slowly 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

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1 h.

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

Indomethacin Polymorphs: Form α was prepared by the method of Kaneniwa[10] as follows. Ten grams of indomethacin was dissolved in 10 ml of ethanol at 80 °C; the undissolved indomethacin was filtered off; and 20 ml of distilled water at room temperature was added to the indomethacin-saturated ethanol solution at 80 °C. The precipitated crystals were dried overnight in a P_2O_5 desiccator under a vacuum at room temperature. Form γ was prepared by recrystallization from ethyl ether at room temperature.

X-Ray Powder Diffraction Analysis The X-ray powder diffraction patterns were obtained 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 over a 2θ range between 3 and 40°.

Thermal Analysis A DSC apparatus (model 220CU, Seiko Instruments Inc., Tokyo, Japan) and a thermogravimetry/differential thermal analysis (TG/DTA) apparatus (model 220U, Seiko Instruments Inc.) were used under a nitrogen gas flow at a heating rate of 5 °C/min.

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.

HPLC A Waters model 2690 HPLC system with a 4.6-mm i.d.×75-mm column that contains 5-μm octadecylsilanized silica gel (YMC-Pack Pro C18 AS-307, YMC Co., Ltd., Kyoto, Japan) was used along with a Waters model 996 photodiode array detector. The mobile phase was a mixture of 0.02 mol/l phosphate buffer (pH 7.0) and acetonitrile (3 : 2), and the flow rate was 1.0 ml/min. The detection wavelength was set at the maximum of each compound in the mobile phase (seratrodast: 269 nm, acetazolamide: 266 nm, carbamazepine: 285 nm and indomethacin: 268 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), acetazolamide polymorphs: phosphate buffer solution (pH 7.0, 0.1 mol/l), carbamazepine polymorphs: 2-propanol and indomethacin polymorphs: 2nd Fluid used as the test fluid in the disintegration test (JP XIV)] at 25 °C, and the suspensions were shaken at 120 strokes/min. Five milliliters 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

Logarithmic solubility of a polymorphic compound is expressed as a function of the reciprocal of absolute temperature by the following equation (van't Hoff plots):

$$\log S=(-\Delta H_{\mathrm{soln}}/2.303R)(1/T)+C \tag{1}$$

where S is the solubility, ΔH_{soln} is the heat of solution, R is the gas constant and C is a constant. In previous studies,[9—15] this equation has been widely applied for the estimation of transition temperature for the enantiotropic polymorphic pairs. At a temperature of T_1, the logarithmic solubilities of Form A and B in a polymorphic pair are written as Eqs. 2 and 3.

$$\log S_{\mathrm{A},T_1}=(-\Delta H_{\mathrm{soln\,A},T_1}/2.303R)(1/T_1)+C_{\mathrm{A}} \tag{2}$$

$$\log S_{\mathrm{B},T_1}=(-\Delta H_{\mathrm{soln\,B},T_1}/2.303R)(1/T_1)+C_{\mathrm{B}} \tag{3}$$

Subtracting Eq. 3 from Eq. 2, the difference in the logarithmic solubility for the two polymorphs can be expressed by Eq. 4:

$$\log S_{\mathrm{A},T_1}-\log S_{\mathrm{B},T_1}=(-\Delta H_{\mathrm{trans}\,T_1}/2.303R)(1/T_1)+(C_{\mathrm{A}}-C_{\mathrm{B}}) \tag{4}$$

where $\Delta H_{\mathrm{trans\,T_1}}$ is the heat of transition corresponding to the difference in the heat of solution ($\Delta H_{\mathrm{soln\,A},T_1}-\Delta H_{\mathrm{soln\,B},T_1}$). In the same manner, Eq. 5 is obtained at a temperature of T_2.

$$\log S_{\mathrm{A},T_2}-\log S_{\mathrm{B},T_2}=(-\Delta H_{\mathrm{trans}\,T_2}/2.303R)(1/T_2)+(C_{\mathrm{A}}-C_{\mathrm{B}}) \tag{5}$$

Subtraction of Eq. 5 from Eq. 4 eliminates the intercept ($C_{\mathrm{A}}-C_{\mathrm{B}}$), and Eq. 6 is yielded.

$$(\log S_{\mathrm{A},T_1}-\log S_{\mathrm{B},T_1})-(\log S_{\mathrm{A},T_2}-\log S_{\mathrm{B},T_2})=(-\Delta H_{\mathrm{trans}\,T_1}/2.303R)(1/T_1)-(-\Delta H_{\mathrm{trans}\,T_2}/2.303R)(1/T_2) \tag{6}$$

Provided heat of solution is assumed to be independent of temperature in a narrow temperature range between T_1 and T_2, the values of $\Delta H_{\mathrm{trans}\,T_1}$ and $\Delta H_{\mathrm{trans}\,T_2}$ can be treated to be equal. Therefore, Eq. 6 becomes:

$$(\log S_{\mathrm{A},T_1}-\log S_{\mathrm{B},T_1})-(\log S_{\mathrm{A},T_2}-\log S_{\mathrm{B},T_2})=(-\Delta H_{\mathrm{trans}}/2.303R)(1/T_1-1/T_2) \tag{7}$$

In the case that T_2 is the transition temperature (T_{trans}), $\log S_{\mathrm{A},T_2}-\log S_{\mathrm{B},T_2}=0$, therefore:

$$(\log S_{\mathrm{A},T_1}-\log S_{\mathrm{B},T_1})=(-\Delta H_{\mathrm{trans}}/2.303R)(1/T_1-1/T_{\mathrm{trans}}) \tag{8}$$

Finally, the transition temperature can be expressed as Eq. 9.

$$T_{\mathrm{trans}}=[2.303R(\log S_{\mathrm{A},T_1}-\log S_{\mathrm{B},T_1})/\Delta H_{\mathrm{trans}}+1/T_1]^{-1} \tag{9}$$

Thus, the transition temperature for an enantiotropic polymorphic pair can be calculated from heat of transition and solubility at only one arbitrary temperature. When the calculated transition temperature falls in an unrealistic temperature range, above the melting point or below 0 K, the polymorphic pair is monotropic. 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 form from that of other. However, it is reasonable that heat of transition of a polymorphic pair is estimated by solution calorimetry as the difference in heat of solution of each polymorph rather than by DSC. This is because heat of transition cannot be measured by DCS if solid–solid transition does not occur or 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 in the determination of heat of solution and solubility because heat of transition corresponding to the difference in the heat of solution is theoretically independent of solvent used; therefore, we can freely choose any kind of solvent. A highly solubilizing solvent should be used for a precise measurement of heat of solution, whereas a moderately solubilizing solvent should be used for a reasonable measurement of solubility.

Results and Discussions

Identification of Polymorphic Form Seratrodast, acetazolamide, carbamazepine and indomethacin polymorphs were identified by X-ray powder diffraction analysis and DSC. The X-ray powder diffraction patterns (Fig. 1) and the DSC curves (Fig. 2) were identical to those reported previously.[9,10,16,17] The results of TG and HPLC suggested that each of the polymorphs was not solvated and did not decompose.

Since the DSC curve of seratrodast Form II showed an exothermal solid–solid transition at 89 °C (Fig. 2A), the polymorphic pair was considered to be monotropic or enantiotropic with a transition temperature above 89 °C according

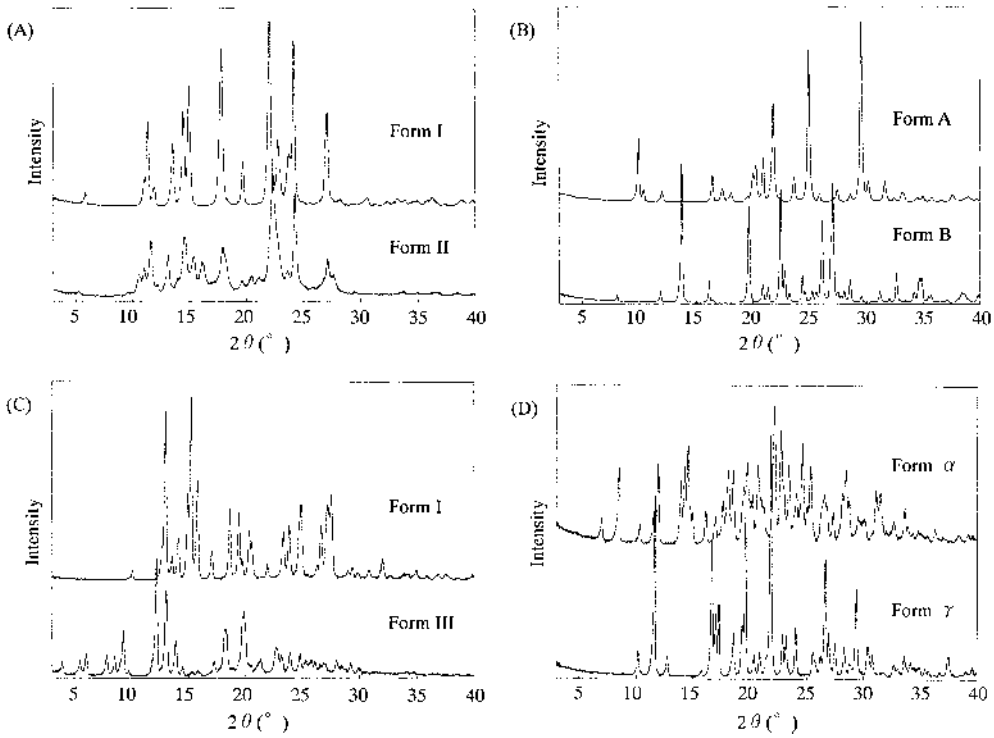

Fig. 1. X-Ray Powder Diffraction Patterns of Polymorphic Forms of Various Drug Substances
(A) Seratrodast, (B) acetazolamide, (C) carbamazepine, and (D) indomethacin.

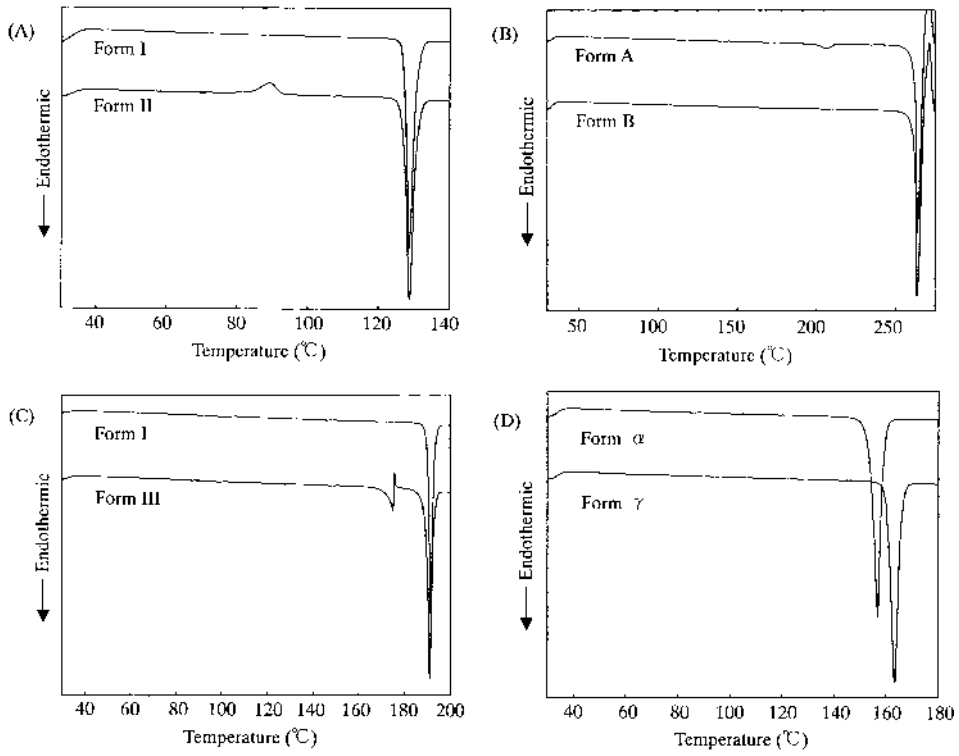

Fig. 2. DSC Curves of Polymorphic Forms of Various Drug Substances
(A) Seratrodast, (B) acetazolamide, (C) carbamazepine, and (D) indomethacin.

to the Heat of Transition Rule. Form A of acetazolamide and Form III of carbamazepine showed endothermic solid–solid transitions at 206 and 175 °C (Figs. 2B, C), respectively, indicating they are enantiotropically related to the other forms. On the other hand, indomethacin polymorphs showed no solid–solid transition (Fig. 2D). Form α and Form γ melted at 157 and 163 °C, and the heats of fusion were 35.4 and 36.5 kJ/mol, respectively. Since the higher melting form

(Form γ) has higher heat of fusion, the indomethacin polymorphic pair was considered to be monotropic according to the Heat of Fusion Rule.

Heat of Solution Though the heat of solution varies with the kind of solvent, the heat of transition corresponding to the difference in the heat of solution is theoretically equal. The heats of solution of the seratrodast polymorphs measured in three different solvents, DMF, methanol and acetonitrile, at 25.0 °C are shown in Table 1. The heats of transition for each solvent were 6.05, 6.03 and 6.05 kJ/mol, suggesting that the measurements had been accomplished with great precision.

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)		ΔH_{trans} (kJ/mol)
	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)	ΔH_{trans} (kJ/mol)	Direction of transition
Seratrodast	Form I	22.66	6.05	II→I
	Form II	16.61		
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		
Indomethacin	Form α	5.46	−1.13	$\gamma\rightarrow\alpha$
	Form γ	6.59		

The heats of solution of the acetazolamide, carbamazepine and indomethacin polymorphs in DMF are shown in Table 2. The heat of transition of each polymorphic pair, estimated as the differences in their heats of solution, was 2.02, −2.93 and −1.13 kJ/mol, respectively.

Solubility The dissolution behaviors of the seratrodast polymorphs in phosphate buffer solution (pH 8.0, 0.05 mol/l), acetazolamide polymorphs in phosphate buffer solution (pH 7.0, 0.1 mol/l), carbamazepine polymorphs in 2-propanol and indomethacin polymorphs in 2nd Fluid used as the test fluid in the disintegration test (JP XIV), measured at 25 °C, are shown in Fig. 3. These dissolving solvents were chosen to correspond with those used in previous studies.[9—12] The plots in Fig. 3 show the concentrations 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 seratrodast, acetazolamide and carbamazepine polymorphs due to fast dissolution rates. However, the measurements for the indomethacin polymorphs were allowed to continue for more than 2 h because of slow dissolution rates. The solubilities were estimated by averaging the concentrations at equilibrium. It was confirmed by X-ray diffraction analysis in all cases that neither of the polymorphic forms was transformed to the other.

Calculation of Transition Temperature Transition temperatures for each polymorphic pair were calculated by the proposed formula [Eq. (9)] using heat of transition and solubility data. The results are given in Table 3. The transition temperatures for the seratrodast, acetazolamide and carbamazepine polymorphic pairs were 84.9, 72.1 and 77.6 °C,

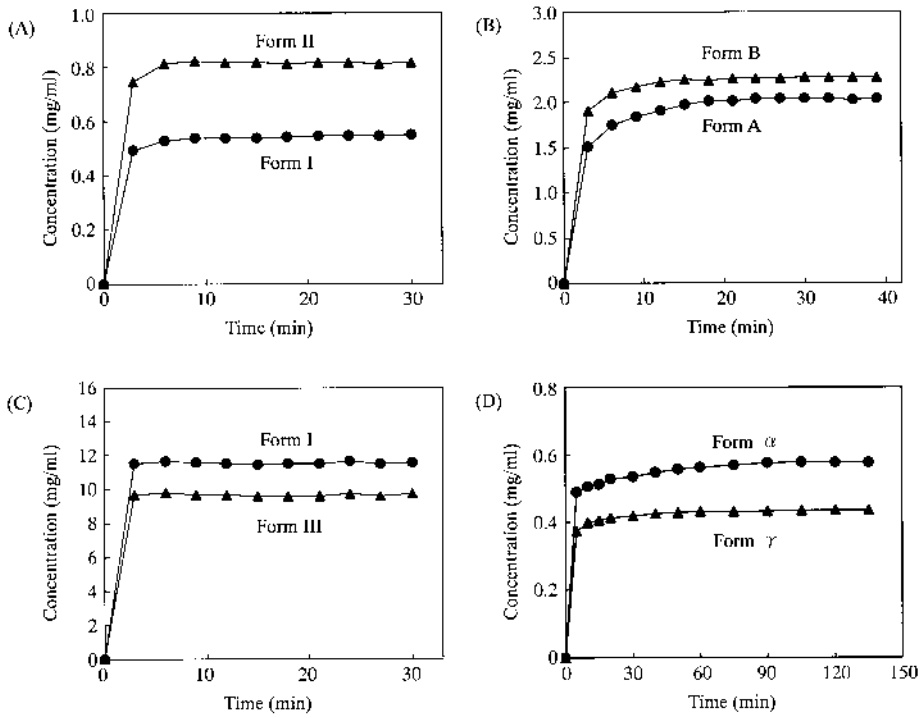

Fig. 3. Dissolution Profiles of Polymorphic Forms of Various Drug Substances at 25 °C

(A) Seratrodast in phosphate buffer solution (pH 8.0, 0.05 mol/l), (B) acetazolamide in phosphate buffer solution (pH 7.0, 0.1 mol/l), (C) carbamazepine in 2-propanol, and (D) indomethacin in 2nd Fluid (JP XIV).

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

Compound	Crystal form	ΔH_{trans} (kJ/mol)	Solubility at 25 °C (mg/ml)	T_{trans} (°C)	
				Calculated value	Literature value
Seratrodast	Form I	6.05	0.543	84.9	83.4
	Form II		0.817		
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		
Indomethacin	Form α	−1.13	0.576	534.3	None[a)]
	Form γ		0.432		

a) "None" means that the polymorphic pair is monotropic.

respectively, which are in good agreement with those reported previously (83.4, 78.4, 73 °C, respectively).[9—11)] Differences between these values could be due to such factors as equipment, chemical purity, polymorphic purity and degree of crystallinity. It is noteworthy that the seratrodast polymorphic pair could be correctly determined to be enantiotropic with a transition temperature at 84.9 °C, even though the DSC curves showed a typical monotropic pattern (exothermal solid-solid transition was observed). Furthermore, the calculated transition temperatures for the indomethacin polymorphic pair fell above the melting point (Form α: 157 °C and Form γ: 163 °C), an unrealistic temperature range. Since this pair has no transition temperature in a realistic temperature range, these polymorphs should be considered to be monotropically related, which is consistent with previously reported results.[12)]

Conclusions

A thermodynamic formula for determining whether a polymorphic pair is monotropic or enantiotropic and estimating the transition temperature for an enantiotropic polymorphic pair has been derived using heat of solution and solubility. Transition temperatures for the polymorphic pairs of seratrodast, acetazolamide and carbamazepine calculated by the formula were in good agreement with the results of previous studies. In particular, the polymorphic pair of seratrodast could be correctly determined to be enantiotropic, even though the DSC curves showed a typical monotropic pattern. Furthermore, the polymorphic pair of indomethacin was determined to be monotropic, which is also consistent with the results of previous studies. This formula requires solubility data at only one arbitrary temperature other than heat of solution data for each polymorph; therefore, the proposed method is much faster than the conventional method requiring solubility data at five or more different temperatures for the preparation of van't Hoff plots. These results demonstrate that the proposed method would be very useful for polymorphic studies on drug substances.

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References

1) Haleblian J., McCrone W., *J. Pharm. Sci.*, **58**, 911—929 (1969).
2) Borka L., *Pharm. Acta Helv.*, **66**, 16—22 (1991).
3) Higuchi W. I., Lau P. K., Higuchi T., Shell J. W., *J. Pharm. Sci.*, **52**, 150—153 (1963).
4) Khalil S. A., Moustafa M. A., Ebian A. R., Motawi M. M., *J. Pharm. Sci.*, **61**, 1615—1617 (1972).
5) Grunenberg A., Henck J.-O., Siesler H. W., *Int. J. Pharmaceut.*, **129**, 147—158 (1996).
6) Burger A., Ramberger R., *Mikrochim. Acta II*, (Vienna), 259—271 (1979).
7) Burger A., Ramberger R., *Mikrochim. Acta II*, (Vienna), 273—316 (1979).
8) Burger A., *Pharm. Int.*, **3**, 158—163 (1982).
9) Ikeda Y., Nishijima K., Tokai N., Nishi K., *Yakugaku Zasshi*, **115**, 937—943 (1995).
10) Umeda T., Ohnishi N., Yokoyama T., Kuroda T., Kita Y., Kuroda K., Tatsumi E., Matsuda Y., *Chem. Pharm. Bull.*, **33**, 3422—3428 (1985).
11) Behme R. J., Brooke D., *J. Pharm. Sci.*, **80**, 986—990 (1991).
12) Kaneniwa N., Otsuka M., Ichikawa J., Hayashi T., Hayashi K., Umezawa O., *Yakugaku Zasshi*, **107**, 308—314 (1987).
13) Carlton R. A., Difeo T. J., Powner T. H., Santos I., Thompson M. D., *J. Pharm. Sci.*, **85**, 461—467 (1996).
14) Wenslow R. M., Baum M. W., Ball R. G., Mccauley J. A., Varsolona R. J., *J. Pharm. Sci.*, **89**, 1271—1281 (2000).
15) Tong H. H. Y., Shekunov B. Y., York P., Chow A. H. L., *Pharm. Res.*, **18**, 852—858 (2001).
16) Kaneniwa N., Otsuka M., Hayashi T., *Chem. Pharm. Bull.*, **33**, 3447—3455 (1985).
17) Umeda T., Ohnishi N., Yokoyama T., Kuroda K., Kuroda T., Tatsumi E., Matsuda Y., *Yakugaku Zasshi*, **104**, 786—792 (1984).