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A kinetic and thermodynamic study of seratrodast polymorphic transition by isothermal microcalorimetry

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Abstract

The development of isothermal microcalorimetry to a study of the kinetic and thermodynamics of polymorphic transitions in seratrodast ((±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid) Form II is reported. Sieved samples of Form II were allowed to convert to Form I, in a reaction vessel of an isothermal microcalorimeter, under 13, 31, 63 and 93% relative humidity (RH) between 48 and 65 °C. The power (Φ, in Watts) versus time curves from the microcalorimeter were integrated into the heat output (q, in Joules) versus time curves to yield fractional extent of Form I converted versus time curves. The change in enthalpy ($-5.70\,\mathrm{kJ\,mol^{-1}}$) agreed very closely with that obtained by differential scanning calorimetry and solution calorimetry, which indicated that the power measured by the microcalorimeter was due only to the Form II-to-Form I transition. Application of the theoretical kinetic method [J. Am. Ceram. Soc. 55 (1972) 74] revealed that the transition took place via a two-dimensional growth of nuclei mechanism at all the studied relative humidities and temperatures. The rate constant increased with increasing RH and temperature, and with decreasing the particle size of sample. The activation energies obtained from Arrhenius plots were 292, 290, 280 and 284 kJ mol^{-1}, and the extrapolated rate constants at 25 °C were also 3.01×10^{-10}, 3.11×10^{-10}, 9.65×10^{-10} and $3.84 \times 10^{-9}\,\mathrm{s^{-1}}$ for 13, 31, 63 and 93% RH, respectively.
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1. Introduction

Investigating the characterization of polymorphic behaviour in pharmaceutical drugs is an essential aspect for the development of pharmaceuticals. Because of the differences in molecular packing, polymorphic forms of solid pharmaceutical drugs with poor water solubility influence not only their dissolution behaviour, i.e. bioavailability but also their solid-state stability (Haleblian and McCrone, 1969; Shibata et al., 1983). In general, the solubility and dissolution rate of metastable polymorphic forms are higher than those of the stable form, therefore, the metastable form should possess several therapeutic advantages over the stable form. It is well known that only one polymorphic form is thermodynamically stable and all other metastable forms convert, eventually, to the more stable form. If, however, the metastable form or the pharmaceutical product containing it is ensured to be sufficiently stable, i.e. has an acceptable shelf-life, it could be used in a formulation. For these reasons, investigation of the kinetics of polymorphic transitions of pharmaceutical drugs under various controlled storage conditions is of importance.

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In order to investigate polymorphic transitions of pharmaceutical drugs, several samples of a crystalline material are usually stored in a thermostat for a varying period of time, followed by some means (often powder X-ray diffractometry (PXRD) or differential scanning calorimetry (DSC)) of quantitative determination of the amount of crystalline form converted into another form. Following this general procedure, polymorphic transitions of some pharmaceutical drugs, e.g. phenylbutazone (Matsuda et al., 1984), acetazolamide (Umeda et al., 1985), phenobarbital (Otsuka et al., 1993) and seratrodast (Ikeda et al., 1995), were successfully determined and kinetically analysed. However, this conventional method is very troublesome because data are required at many time points, as fractions of conversion over the period of the reaction. Moreover, establishing quantitative determination methods as well as preparing calibration curves with mixtures of crystal forms at various mixing ratios are essential.

Isothermal microcalorimetry, the continuous measurement of the heat flow evolved by chemical or physical processes at a constant temperature, is an important experimental tool in the study of mechanisms for reacting system. It allows the determination of not only kinetic parameters but also thermodynamic parameters (n, the order of the reaction; k, the rate constant; and ΔH, the reaction enthalpy change) from power–time curves (Willson et al., 1995; Gaisford et al., 1999; Beezer et al., 2001a,b). In this paper, we present a fast and convenient method for the kinetic and thermodynamic study of polymorphic transitions of pharmaceutical drugs by isothermal microcalorimetry. As a contribution to this study, seratrodast ((±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid; Fig. 1), a thromboxane A_2 antagonist used as an anti-asthmatic, was chosen as a model compound. It has been already reported (Ikeda et al., 1995) that seratrodast has two crystal forms: Form I (stable form) and Form II (metastable form). Form II is easily converted to Form I by heating. In the context of the work reported here, "fast" means that a significant fractional extent of reaction, α (0.15–0.50), will be achieved over the experimental observation time (hours). A subsequent paper (Beezer et al., in press) will explore microcalorimetric studies of solid-state reactions where $\alpha \leqq 0.001$.

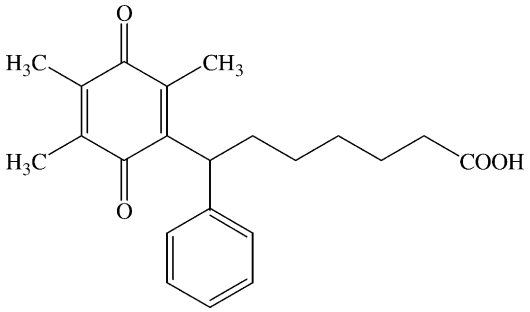

Fig. 1. Chemical structure of seratrodast.

2. Materials and methods

2.1. Materials

Seratrodast (Form I) was prepared in-house by Takeda Chemical Industries, Ltd. (Osaka, Japan). Powder talc (>10 μm) was obtained from Aldrich Chemicals, Ltd. and dried prior to use.

2.2. Preparation of seratrodast polymorphs

Form II was prepared by melting Form I at 130 °C and cooling it slowly to room temperature. After grinding slightly with a mortar and pestle, the crystalline powder of Form II was sieved to obtain 53–75, 75–100 and 100–150 μm sieved fractions.

2.3. Identification of polymorphic forms

Each polymorphic form was identified by PXRD and DSC, and chemical purity was determined by high performance liquid chromatography (HPLC). The PXRD patterns were measured at room temperature with an 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 $6^\circ\,\mathrm{min}^{-1}$ over a 2θ range between 3 and 40°. The DSC curves were measured using a 220CD Differential Scanning Calorimeter (Seiko Instruments Inc., Tokyo, Japan), with samples of approximately 5 mg weighed into non-hermetically sealed aluminum pans, under nitrogen gas flow at a heating rate of $5\,^\circ\mathrm{C\,min}^{-1}$. The HPLC system used was a Waters 2690 with an ultraviolet detector (detection wavelength: 269 nm)

and a 4.6-mm i.d. × 75-mm column containing 5-μm octadecylsilanized silica gel (YMC-Pack Pro C18 AS-307, YMC Co., Ltd.). 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}.

2.4. Kinetic and thermodynamic analysis of polymorphic transition by isothermal microcalorimetry

The isothermal microcalorimeter used in this study was a MicroDSC III (Setaram, Caluire, France) operated in the isothermal mode. The microcalorimeter was housed in a temperature-controlled environment ($21 \pm 1.0 \times 10^{-1}$ °C). About 0.2 g of samples, accurately weighed, were placed in 1 ml Hastalloy batch vessels. The head-space air in the vessels was replaced by air adjusted to 13, 31, 63 and 93% relative humidity (RH; various saturated salt conditions) in a desiccator at 25 °C. It was confirmed by PXRD and DSC, in advance, that polymorphic transition did not occur during these operations. The vessels were sealed with Hastalloy caps with stoppers provided with O-rings as quickly as possible after the vessels were removed from the desiccator. The samples were placed into the microcalorimeter, vessels with 0.2 g of talc were used as the reference. These were allowed to equilibrate for 15 min inside the calorimeter before data collection commenced. The experiments were performed at temperatures of 50, 52, 55, 58, 60, 62 and 65 ($\pm 1.0 \times 10^{-3}$) °C, and the measurements for each storage condition were repeated three times. The power (Φ, in Watts) from the samples was recorded using the dedicated SETSOFT software package operating under WINDOWS™. Data analysis was performed using a graphics fitting program, ORIGIN (Microcal Software Inc., MA).

3. Results

3.1. Kinetic and thermodynamic analysis of transition behaviour

Fig. 2 shows the typical power–time curves obtained from seratrodast Form II in various sieved fractions (53–75, 75–100 and 100–150 μm) under 63% RH at 58 °C. These curves were also integrated into heat output (q, in Joules) versus time curves to yield fractional extent of Form I converted (α) versus time curves. The fractional extent of conversion increased sigmoidally with time, and the change in enthalpy, i.e. enthalpy of transition (ΔH_{trans}) was −5.72, −5.70 and −5.74 kJ mol^{-1} for 53–75, 75–100 and 100–150 μm fraction (Table 1). After finishing the measurements, the samples were quickly removed

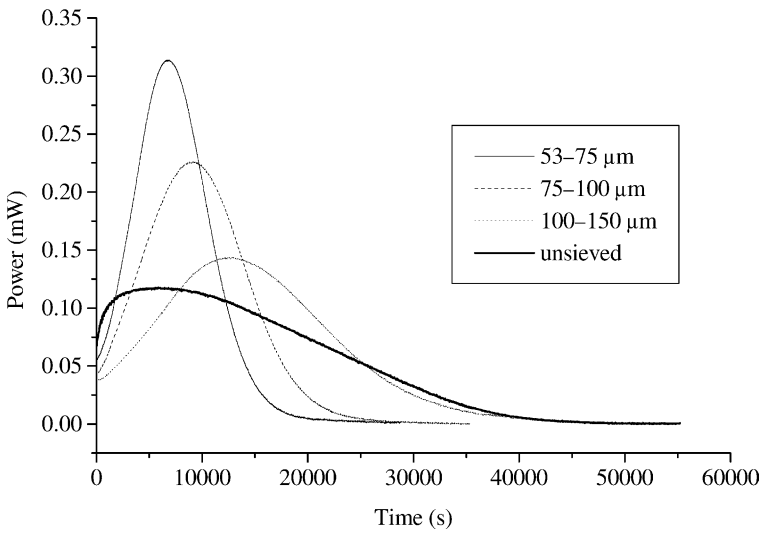

Fig. 2. Power–time curves for the transformation of seratrodast Form II under 63% RH at 58 °C.

Table 1
Kinetic and thermodynamic parameters for the transformation of seratrodast Form II in various sieved fractions under 63% RH at 58 °C

Sieve fraction (μm)	Change in enthalpy (kJ mol^{-1})	m	Rate constant (s^{-1})
53–75	−5.72 (−5.60 to −5.80)	2.09 (2.03 to 2.20)	1.22×10^{-4} (1.13×10^{-4} to 1.29×10^{-4})
75–100	−5.70 (−5.63 to −5.77)	2.10 (1.90 to 2.25)	8.08×10^{-5} (7.71×10^{-5} to 8.62×10^{-5})
100–150	−5.74 (−5.65 to −5.84)	1.99 (1.88 to 2.18)	5.57×10^{-5} (5.22×10^{-5} to 5.81×10^{-5})

Triplicate experiments performed at each sieve fraction mean and range values for the determined quantities are shown.

from the microcalorimeter to be analysed by PXRD, DSC and HPLC. These results indicated that Form II was completely converted to Form I and did not chemically decompose.

In order to analyze kinetically the calorimetric data for the polymorphic transition, the theoretical kinetic method proposed by Hancock and Sharp (1972) was applied. In this method, when the range of α is limited to values from 0.15 to 0.50, the reaction mechanism is indicated by the value of m, the Hancock–Sharp constant, calculated as the slope of the following equation:

$$\ln[\ln(1-\alpha)] = \ln B + m \ln t \quad (0.15 \leqq \alpha \leqq 0.50)$$

where B is a constant. Table 2 lists the various theoretical equations of solid-state kinetic model corresponding to the various values of m. The Hancock–Sharp plots ($\ln[\ln(1-\alpha)]$ versus $\ln t$ plots) for various sieved fractions gave straight lines ($r > 0.999$), from which m values of 2.09, 2.10 and 1.99 were obtained for each sieved fraction (Table 1). This value indicates that the Form II-to-Form I transition for each sieved fraction proceeds by two-dimensional growth of nuclei mechanism (Avrami–Erofeev equation; Avrami, 1939). Avrami–Erofeev plots ($[-\ln(1-\alpha)]^{1/2}$ versus t plots) gave straight lines ($r > 0.999$) (Fig. 3) and the rate constants, k, obtained from the slopes increased as the particle size decreased (Table 1).

3.2. Effect of RH and temperature on transition behaviour

For the 75–100 μm sieved fraction, samples were measured under various levels of RH (13, 31, 63 and 93%) and temperature (48, 50, 52, 55, 58, 60, 62 and 65 °C), and the data were analysed in a similar manner to that described above (Table 3). The change in enthalpy of the complete reaction was not determined in some study conditions (see Table 3), i.e. those conditions in which reactions were not completed in a reasonable period (>24 h). However, the change in enthalpy for the other study conditions showed almost same value of $-5.70 \pm 1.13 \times 10^{-1}$ kJ mol^{-1} (mean ± S.D., $n = 48$). Therefore, the mean value (-5.70 kJ mol^{-1}) was used to calculate the values of m and rate constant for the study conditions which lack the values of change in enthalpy. As shown in Table 3, a value of m ranging from 1.91 to 2.13 was obtained for all of the study conditions, supporting the two-dimensional growth of nuclei mechanism. The rate constant showed a dependence on RH; it increased

Table 2
Kinetic equations for most common mechanism of solid-state reactions

Equation	m[a]	Mechanism
$\alpha^2 = kt$	0.62	One-dimensional diffusion
$(1-\alpha)\ln(1-\alpha) + \alpha = kt$	0.57	Two-dimensional diffusion
$[1-(1-\alpha)^{1/3}]^2 = kt$	0.54	Three-dimensional diffusion (Jander equation)
$1 - 2\alpha/3 - (1-\alpha)^{2/3} = kt$	0.57	Three-dimensional diffusion (Ginstling–Brounshtein equation)
$-\ln(1-\alpha) = kt$	1.00	Random nucleation, one nucleus on each particle
$1-(1-\alpha)^{1/2} = kt$	1.11	Phase boundary reaction, cylindrical symmetry
$1-(1-\alpha)^{1/3} = kt$	1.07	Phase boundary reaction, spherical symmetry
$\alpha = kt$	1.24	Zero-order mechanism (Polany–Winger equation)
$[-\ln(1-\alpha)]^{1/2} = kt$	2.00	Random nucleation, two-dimensional growth of nuclei (Avrami–Erofeev equation)
$[-\ln(1-\alpha)]^{1/3} = kt$	3.00	Random nucleation, three-dimensional growth of nuclei (Avrami–Erofeev equation)

[a] $\ln[-\ln(1-\alpha)] = \ln B + m \ln t$, $0.15 \leqq \alpha \leqq 0.50$.

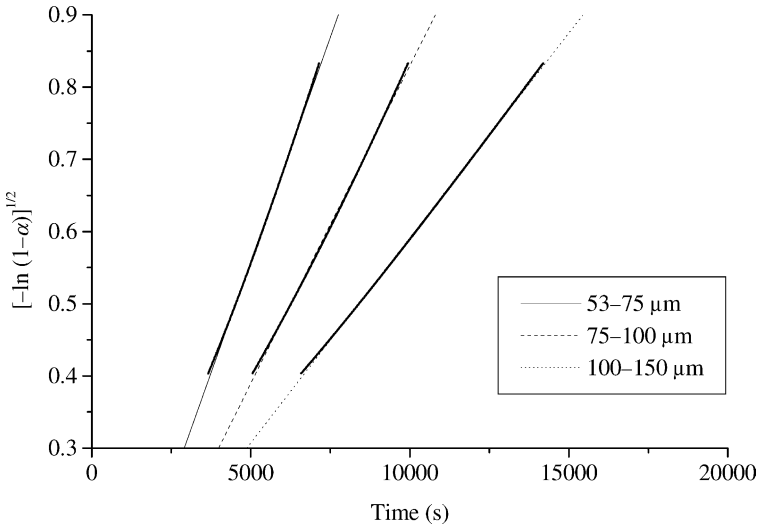

Fig. 3. Avrami–Erofeev plots for the transformation of seratrodast Form II in various sieved fractions under 63% RH at 58 °C.

Table 3
Kinetic and thermodynamic parameters for the transformation of seratrodast Form II in 75–100 μm sieved fraction under various RH and temperature

Relative humidity (%)	Temperature (°C)	Change in enthalpy (kJ mol^{-1})	m	Rate constant (s^{-1})
13	55	–[a]	2.05	1.10×10^{-5}
	58	−5.79	2.09	2.70×10^{-5}
	60	−5.74	2.06	4.90×10^{-5}
	62	−5.74	2.13	1.19×10^{-4}
	65	−5.73	1.95	2.18×10^{-4}
31	55	–[a]	2.02	1.14×10^{-5}
	58	−5.70	2.06	3.34×10^{-5}
	60	−5.71	2.11	5.85×10^{-5}
	62	−5.67	1.98	1.25×10^{-4}
	65	−5.78	2.03	2.47×10^{-4}
63	52	–[a]	2.12	1.06×10^{-5}
	55	−5.66	1.91	2.95×10^{-5}
	58	−5.70	2.10	8.08×10^{-5}
	60	−5.73	2.05	1.44×10^{-4}
	62	−5.67	2.02	2.20×10^{-4}
93	48	–[a]	1.99	1.39×10^{-5}
	50	−5.68	2.11	2.51×10^{-5}
	52	−5.60	2.13	5.54×10^{-5}
	55	−5.67	2.00	1.57×10^{-4}
	58	−5.74	2.05	3.14×10^{-4}

Each value represents the mean for triplicate experiments.
[a] Change in enthalpy was not determined because of long period of reaction.

Table 4
Extrapolated rate constant and shelf-life (t_{90}) for seratrodast Form II in 75–100 μm sieved fraction

Temperature (°C)	Relative humidity (%)	Rate constant (s^{-1})	t_{90} (day)
25	13	3.01×10^{-10}	12493
	31	3.11×10^{-10}	12070
	63	9.65×10^{-10}	3893
	93	3.84×10^{-9}	977
40	13	7.38×10^{-8}	50.9
	31	7.94×10^{-8}	47.3
	63	2.14×10^{-7}	17.5
	93	9.30×10^{-7}	4.0

significantly as RH increased. Arrhenius plots ($\ln k$ versus $1/T$) yielded activation energies of 292, 290, 280 and 284 kJ mol^{-1} ($r = 0.995$, 0.996, 0.997 and 0.997) for 13, 31, 63 and 93% RH, respectively. Based on the assumption that the degradation mechanism over the study temperature range is the same, the theoretical rate constant and the shelf-life (t_{90}) at 25 and 40 °C were calculated and are listed in Table 4.

4. Discussion

In previous kinetic studies (Matsuda et al., 1984; Umeda et al., 1985; Otsuka et al., 1993; Ikeda et al., 1995) on isothermal transitions of polymorphs, many samples of the starting crystalline material were stored, for each storage condition (temperature and RH), in a thermostat for various time intervals. In the case of extensive studies (Matsuda et al., 1984; Otsuka et al., 1993) including varying storage conditions, a great number of samples were subjected to quantitative analysis based on PXRD or DSC, which makes such studies laborious. The present study, using isothermal microcalorimetry, required only a single portion of a sample from start to finish for each storage condition, and the power evolved from the sample was automatically measured. The only real experimental operations were to weigh the sample into the vessel, to replace the head-space air with air adjusted to desired RH and to load the sealed vessel into the microcalorimeter. Moreover, neither establishing a quantitative determination method nor preparing calibration curves was necessary, although they are indispensable for the previous types of studies.

The enthalpy of transition of Form II to Form I was also determined through solid–solid transition exothermal peak (89 °C) in a DSC curve. The value obtained from the peak area of the transition peak was −5.79 kJ mol^{-1}, which is in agreement with those obtained from all the measurements (see Tables 1 and 3) determined using the microcalorimeter. One of us has further reported (Urakami et al., 2002a,b) the value of −6.04 kJ mol^{-1} as the difference in heat of solution (ΔH_{soln}), determined by solution calorimetry (25 °C), between the two crystal forms. In addition, Form II was completely converted to Form I at the end of the measurement, and did not chemically decompose (see Section 3). The main disadvantage of microcalorimetry is the lack of specificity in defining the reactions that occur in a reaction vessel. However, it is reasonable, for the reasons given above to consider that the power measured by the microcalorimeter was due only to the Form II-to-Form I transition.

Ikeda et al. (1995) have concluded that the Form II-to-Form I transition takes place according to a zero-order mechanism ($m = 1.31$), and this is in conflict with the results of our present study. The differences in experimental conditions between the studies are as follows: in the previous study (Ikeda et al., 1995), Form II crystals were not sieved into fractions and they were allowed to convert to Form I under atmospheric humidity. Limited additional microcalorimetric measurements within the study reported here of the Form II-to-Form I transition for an unsieved sample (63% RH, 58 °C) suggested a zero-order mechanism ($m = 1.28$, $r = 0.999$; Fig. 2). It is possible that an unsieved sample could react with an apparent zero-order mechanism as a consequence of the summation of the individual rates (sieved size fractions plus size fractions not studied in the work reported here, i.e. <53 μm and >150 μm; two-dimensional as noted above).

5. Conclusion

From the results reported here for seratrodast, we believe that the microcalorimeter can, with sensitivity, discriminate between reaction mechanisms and identify those outputs which are the sum of the individual reactions associated with particular size fractions. These results also demonstrate the facility and

simplicity of the calorimetric technique in characterising morphological change. If the strategy described here for such change is general then we also conclude that there is significant saving in the time required for such investigations (i.e. for reactions in which significant values of α are achieved within hours). Clearly a different approach (Beezer et al., in press) will be required for long, slow solid-state reaction studies.

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