DETERMINATION OF REACTION KINETICS USING ONLINE X-RAY DIFFRACTION

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ABSTRACT

X-ray diffraction (XRD) is a powerful technique for the study of polymorphism and polymorphic phase transformations. Monitoring of phase transformation directly has been very limited to-date. The XRD system used in this study was used to determine the rate of transformation of pure glutamic acid α form to β form in a solution mediated phase. On every run starting from the pure α form, the transformation process was monitored continuously at fixed temperature, and separate experiments were performed as a function of temperature. The operating temperature was varied from 36 to 57 ^{o}C with 10% w/w solid concentration. Data were taken every 200 seconds until the transformation was completed. This paper is concerned with a study of the transformation of the alpha (α) form of L-glutamic acid (L-GA) to the beta (β) form in order to determine the kinetic reaction. The rate constant (k), activation energy (Ea) and pre-exponential factor (A) were obtained. Sensitivity tests were also carried out to examine minimum detection limit when both α and β present in the mixture. In addition, effect of particle size on XRD patterns was also determined. The results show that XRD gives useful information to observe polymorphism for pharmaceutical industry.

Keywords: *XRD, polymorphism, glutamic acid, reaction kinetics*

INTRODUCTION

High value-added products in the chemical industry are becoming increasingly complicated in structure. Pharmaceutical compounds almost always exhibit multiple polymorphs and typically the desired polymorph may not be obtained reliably because of unmeasured disturbances during processing. Consequently, the development of a method that permits the in-situ, real-time assay of polymorphs undergoing a phase transformation is extremely advantageous [1].

Polymorphism is the ability of a substance to crystallize as two or more distinct crystal structures. This means that each modification or polymorphic form has the same chemical structure but differs in the packing of atoms, ions or molecules within the crystal lattice [2]. Different polymorphs can exhibit variations in properties such as colour for pigments/dyes, solid-state reactivity for explosive compounds and bioavailability for pharmaceutical compounds. The Pharmaceutical Industry frequently encounters multiple polymorphs for the same chemical entity. Since different polymorphs have different (3-D) crystal structures which provide distinctive X-ray diffraction (XRD) patterns, XRD is the primary tool for the study of polymorphic transformations. Process-induced polymorphic transformations have been observed and documented by many investigators [3-6]. Unfortunately, off-line analysis cannot provide dynamic information about phase transformation processes. Consequently, real-time, in-situ sampling and analysis has become a 'golden dream' of today's analytical chemistry [7].

Powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), solid-state NMR and infrared spectroscopy, are techniques that can be used to measure the distribution of polymorphic forms in a crystalline powder. In this study the long established technique of PXRD, as applied ubiquitously to study dry, static, powdered samples, has been extended through its application to analyse, in real time, flowing slurries of the material glutamic acid. In principle, in-situ PXRD can be employed as a basis for on-line process-control measures to optimise crystallisation processes and hence improve product quality. The on-line PXRD technique offers a number of advantages for process monitoring and enables an improved understanding of crystallisation of pharmaceutical materials. The technique can, potentially, be used in a variety of applications including phase identification and quantification, particle size analysis, and, in particular, in situ studies of the kinetics of crystal growth.

The flow-through cell combined with PXRD can be used to examine crystallisation processes and ascertain information about the inter-relationship between growth conditions and the specific phases that are formed. In principle process parameters such as cooling rates, and crystallisation temperature can then be adjusted in a directed rather than empirical manner to obtain products that are pure in respect of polymorphic form. The PXRD analytical approach described here can be integrated as part of a 2-L batch crystallization system incorporating other advanced in-

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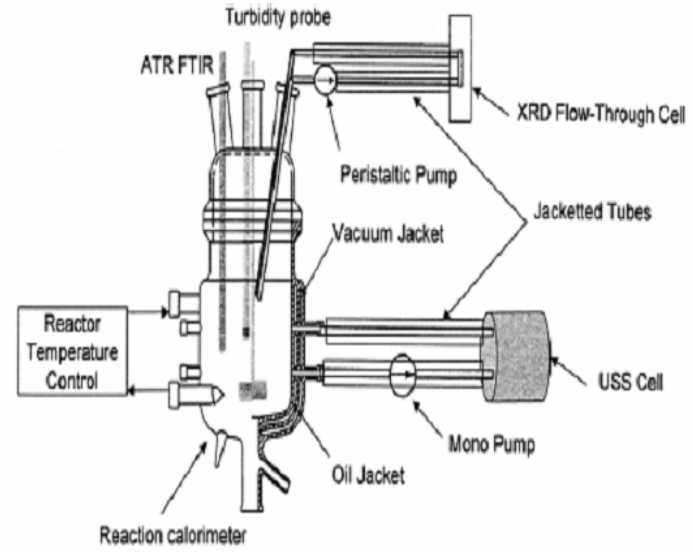

Fig 1. Schematic of the 2-litre batch crystallizer integrating the in-situ process analytical techniques of turbidity and ATR FTIR immersion probes, ultrasonic spectroscopy, and X-ray diffraction flow-through cells.

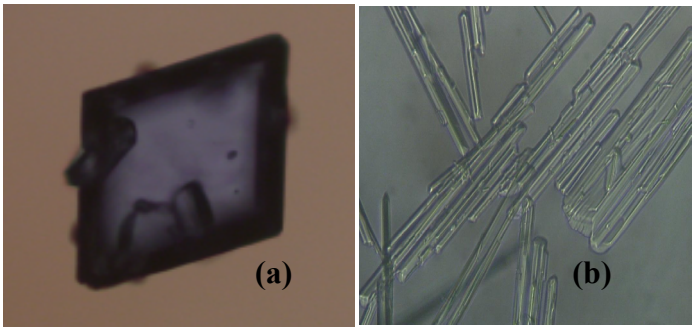

Fig 2. L-Glutamic acid morphology: (a) prismatic α- form and (b) needle-like β-form crystals

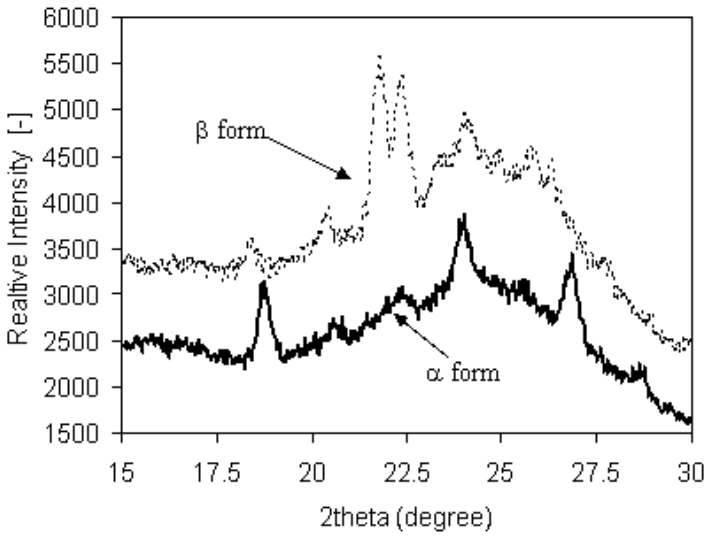

Fig 3. X-ray diffraction profiles of L-GA (a) α form; (b) β form with 10% solid concentration in a solution.

process analytical techniques (optical turbidimetry, ATR FTIR spectroscopy, ultrasonic spectroscopy. The arrangement is illustrated in Fig 1.

L-glutamic acid (L-GA) is known to have two polymorphic forms α and β. Generally the meta-stable α form is preferred as its prismatic crystal habit is more advantageous for handling in industrial processes compared to the needle-like stable β form [8-9]. Thermodynamically, α and β has the same chemical potential at certain temperature and pressure in which equilibrium is reached and then transformation will take place. The crystal morphology of the two polymorphs is shown in Fig 2. The polymorphic behaviour of L-GA in crystallization has been investigated in previous studies [2,6,8-9]. Rapid cooling of aqueous solutions of L-GA yields crystallization of α form, and transformation of α- to β-form GA will take place when α-form crystals are placed in a saturated solution held at an intermediate temperature (>40 °C). Pure samples of the two forms show distinctive XRD patterns. Distinctive peaks in the respective diffraction patterns of the polymorphs were identified readily. Fig 3 illustrates the corresponding PXRD patterns, measured experimentally in the range from 15 to 30 degrees two-theta for the polymorphs in the form of slurries. In this region, α and β forms have different and characteristic peak positions and peak widths. The polymorphs have distinctive peaks at two-theta values of 18.7, 24.1, 25.2 degrees and 21.8, 22.7 and 24.0 degrees, for α and β forms, respectively.

The work reported here was concerned with the determination, in-situ, of parameters associated with the kinetics of transformation of L-GA from α- to β-form using a flow-through PXRD apparatus. The main aim was to investigate the rate of transformation of L-GA from α- to β- form and to determine the kinetics of the process as characterised by a rate constant and activation energy. The performance of the technique for monitoring changes in the relative amount of each polymorphic form for a flowing suspension of crystals was evaluated monitoring a series of batches at a range of different temperatures.

Order of reaction is assumed as first order which will be tested using experimental data. Theoretically, when the first-order rate equation is true for a reaction rate, as follow:

$$\mathbf{A} \longrightarrow \text{Product}$$

Rate of reaction is written:

$$-r_A = -\frac{dC_A}{dt} = kC_A \qquad (1)$$

Where $-r_A$ is rate of reduction of A, k is rate constant, C_A is concentration of A at time t. Separating and integrating Equation (1), we obtain:

$$-\int_{C_{Ao}}^{C_A} \frac{dC_A}{dC_A} = k\int_0^t dt \quad (2)$$

$$-\ln\frac{C_A}{C_{Ao}} = kt \quad (3)$$

If plot of ln C_A/C_{Ao} vs t gives a straight line through the origin for Eq. (3), it suggests that reaction rate is first order [10]. Rate of transformation of α- to β-form of glutamic acid is believed to follow Eq. (1).

EXPERIMENTAL METHODS

Experiments were carried out using a purpose-designed in-process powder X-ray diffraction system recently enhanced via the provision of a Microsource® (Bede Scientific Instruments Ltd) high brightness X-ray generator [2]. More detailed information on the system setup, its validation and sensitivity testing has been given in some papers. L-Glutamic Acid was investigated using this system. A sensitivity study of the PXRD system using Smoothed Principal Component Analysis (SPCA) has been described previously [11]. Using this system of analysis the lower limit of detection, in terms of the solids concentration in suspension, for both α- and β- forms were enhanced significantly to 0.4 w/w% and 0.2 w/w%, respectively. This approach has improved the reliability of the analysis of the PXRD patterns.

To investigate the transformation of L-GA from α- to β- form and to determine kinetic parameters, it was essential to control and monitor temperature of the system accurately. Using adaptors at the inlet and outlet of flow-cell, two K-type thermocouples were fitted into the pipes through which the crystalline slurries were circulated. This set up enabled the temperature in the flow-cell to be monitored accurately. The slurry pumping lines were water jacketed to minimize any temperature difference between the slurry in the reactor and in the flow-cell (which was a maximum of 0.1 °C).

Preparation of α Form Crystals

The procedure for recrystallisation of L-GA has been well documented in the literature [8,9,12]. L-GA (Sigma Chemicals with chemical purity > 99%) was recrystallised from an aqueous solution using a 20 L reactor. To obtain the pure α-form, a solution of 268 g of L-GA in 10 L of distilled water was prepared at 80 °C using a stirrer speed of 80 rpm. The solution was then cooled to 15 °C at a cooling rate of 0.5 °C/min. The α-form crystals were filtered and rinsed using methanol, and dried immediately at room temperature. The purity of the α-form samples was confirmed by microscope imaging (Fig 2) and PXRD.

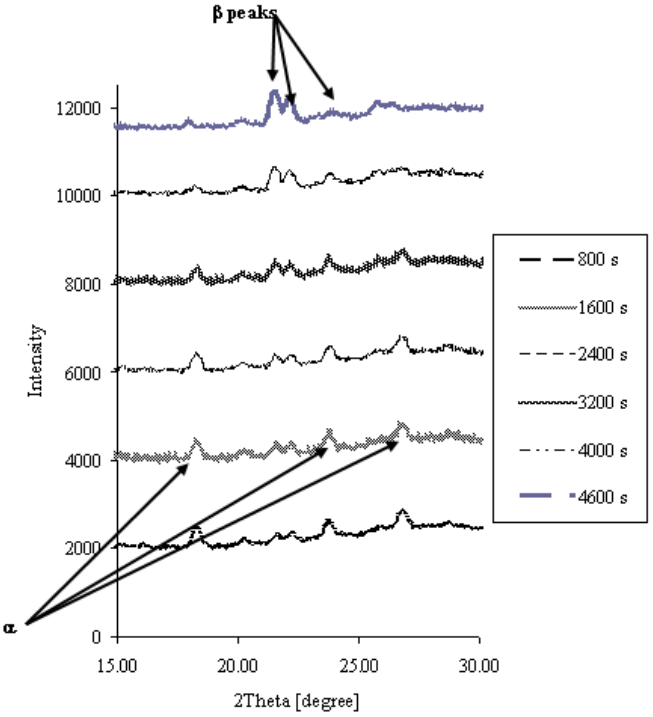

Fig 4. typical PXRD profiles for transformation of α- into β-form L-GA at 54°C. (Note that the profiles are offset along the ordinate for clarity).

Monitoring Phase Transformation of L-GA from α- to β- Form in Aqueous Suspension

Isothermal experiments were carried out at 39, 42, 45, 48, 51and 54 °C with an initial 10 w/w% α form concentration. In-line PXRD measurements were carried out at every temperature in separate experiments to determine the rate of transformation from α- to β- form. For each temperature, an almost saturated solution of α-glutamic acid was prepared in a 0.5 L jacketed holding vessel and pumped through temperature stabilized co-axial pipes to the in-process X-ray cell using a peristaltic pump. The almost saturated solution was prepared based on published solubility data for α-form L-GA [9,13]

Once a constant temperature had been achieved in the flowing solution, α-form crystals were added to the solution in an amount that was sufficient to produce a 10 w/w% suspension. This addition point was taken as time zero for the transformation process. The data acquisition conditions were optimised so that PXRD patterns were captured with accumulation over 200 seconds. PXRD patterns were collected continuously until no further significant changes in the relative intensities of the diffraction peaks was observed as shown in Fig 4. For clarity only several data are shown in the figure. As mentioned earlier, the polymorphs have distinctive peaks at two-theta values of 18.7, 24.1,

25.2 degrees and 21.8, 22.7 and 24.0 degrees, for α and β forms, respectively.

Quantitative Analysis of Polymorphic Content

The analysis of the experimental data was carried out using Bede Polycrystal Software to determine the fractional intensities of peaks from α- and β- forms during polymorphic transformation. The Bede Polycrystal Software (Bede Scientific Instruments Ltd.) is a Windows-based programme for the analysis of X-ray diffraction data from polycrystalline materials. Given the influence of the presence of a solution on the PXRD patterns, a diffraction patterns for the corresponding pure solution was subtracted from the diffraction patterns of the slurries measured in-situ. The background-subtracted in-situ patterns were then used to determine the polymorph fraction. Using the software, smoothing, background subtraction, peak searching, and peak fitting, of the PXRD patterns were performed. Analysis of the PXRD profiles enabled the relative proportions of the two polymorphs, by mass, to be determined as a function of elapsed time.

RESULT AND DISCUSSION

The area under selected peaks, characteristic of the individual polymorphs, was determined as a function of elapsed time to determine the rate of transformation at a given temperature. Since SPCA shows a linear relationship between peak area and concentration of polymorphs [10], determination of the rate of transformation is based on the peak areas. In this work, peaks for α and β-forms are represented by two-theta values of approximately 18 and 21 degrees, respectively. Typical results of data analysis are shown in Fig 5 and 6 at 39 and 54 °C, respectively. These figures show that the phase transformation from α to β-form took 191 minutes at 39 °C and 73 minutes at 54 °C, where at these time α completely transform into β-form . The temperature dependence of the transformation rate was clearly observed. As the temperature increases, the transformation rate becomes faster.

Data analysis shows that hypothesis of first-order reaction is true. From the slope between initiation and completion of transformation from α- to β-form the rate constant was determined for each transformation temperature as shown in Table 1. An Arrhenius plot for transformation rate constant against temperature is shown in Fig 7. The activation energy (E_a) obtained from this analysis is 54.79 kJ/mol and pre-exponential factor, A, is 2.07×10^7 with $R^2 = 0.9$.

Through this work it has been demonstrated that in-situ PXRD measurements are sufficiently accurate to monitor the polymorphic change of L-GA. The in-situ monitoring is an essential method to enable process control and process optimisation. The kinetic parameters represent essential information in the construction of a kinetic model for prediction of polymorphic behaviour under varying conditions of process operation.

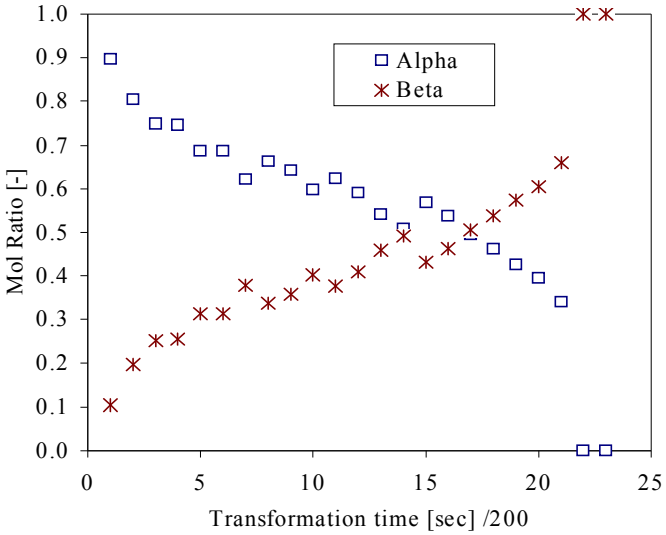

Fig 5. Concentration profiles of α- and β-forms of L-GA at a transformation temperature of 54 °C

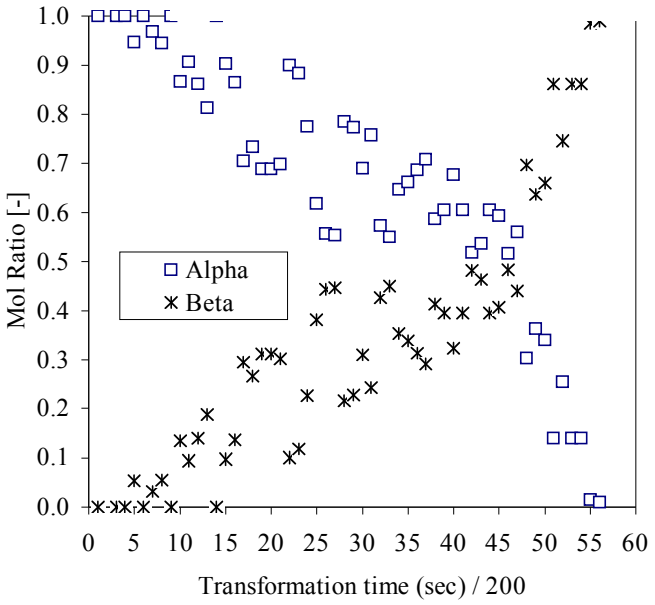

Fig 6. Concentration profiles of α- and β-forms L-GA at transformation temperature of 39 °C

The analysis technique employed up to now is based on a single representative peak for each polymorph. Further analysis is being carried out based on the full PXRD profiles using chemo-metric analysis. This more sophisticated approach will enhance reliability of data analysis for obtaining kinetic parameters.

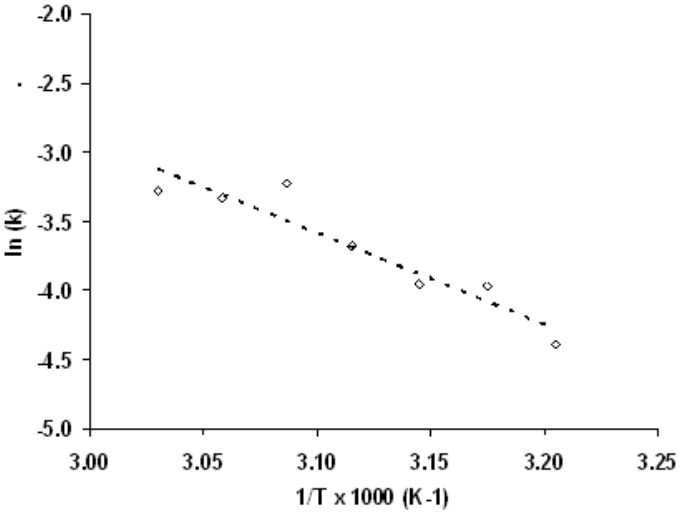

Fig 7. Arrhenius plot for transformation rate of α- to β-form L-GA as a function of temperature.

Table 1. Rate constant of α- to β-form L-GA transformation as a function of temperature

T (°C)	k (s^{-1})	ln (k)
39	0.0124	-4.390
42	0.0188	-3.974
45	0.0191	-3.958
48	0.0253	-3.677
51	0.0397	-3.226
54	0.0357	-3.333

CONCLUSION

In-process PXRD was used to measure the isothermal polymorphic transformation from α- to β-form L-GA at different temperatures in a solution-mediated process. The respective PXRD profiles contain distinctive peaks for α- and β-forms thus enabling the monitoring of the transformation between the different solid forms. The rate of transformation increases with increasing temperature. Reaction of transformation is first-order which follows Eq. (1) dan (3) above. with rate constant (*k*) varies with temperature. The activation energy (E_a) of polymorphic transformation of α- to β-form L-GA determined experimentally is 54.8 kJ/mol and pre-exponential factor, *A*, is 2.07×10^7 s^{-1}. Further data analysis based on full PXRD profiles will be carried out using more advanced chemo-metric techniques to improve the accuracy of the determination of the kinetic parameters describing the rate of polymorphic transformation.

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