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Supporting Information for Deposition

Kinetics of the aqueous-ethanol solution mediated transformation between the beta and alpha polymorphs of para-aminobenzoic acid

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Abstract

Supporting information to the main paper is provided comprising the following;

S1 Presentation of a new X-ray transmission flow through cell for use during in-situ XRD experiments to study crystallisation processes

S2 Commissioning of the new in-situ flow through cell to determine the count rate on the detector utilising a laboratory X-ray source together with the cell. Calculation of the limit of detection for a given solid phase in a slurry when using a laboratory X-ray source and the new flow through cell

S3 Solubility measurements of alpha PABA in 70:30 DI Water:Ethanol solvent mix using gravimetric analysis

S4 Discussion of high temperature seeded experiments at 32 and 34°C

S5 Unseeded Runs of Beta to Alpha Phase Transformation at High Temperature

S6 Assessment of the experimental reproducibility for calculation of dissolution and growth rate constants during the beta to alpha phase transformation

S1 Construction of an in-situ X-Ray Transmission Cell

The In-situ studies of the SMPT of the two PABA polymorphs required an instrument to flow the crystal slurry to the X-ray source for analysis; this resulted in the design and construction of a new flow cell for in-situ X-ray diffraction (XRD) work.

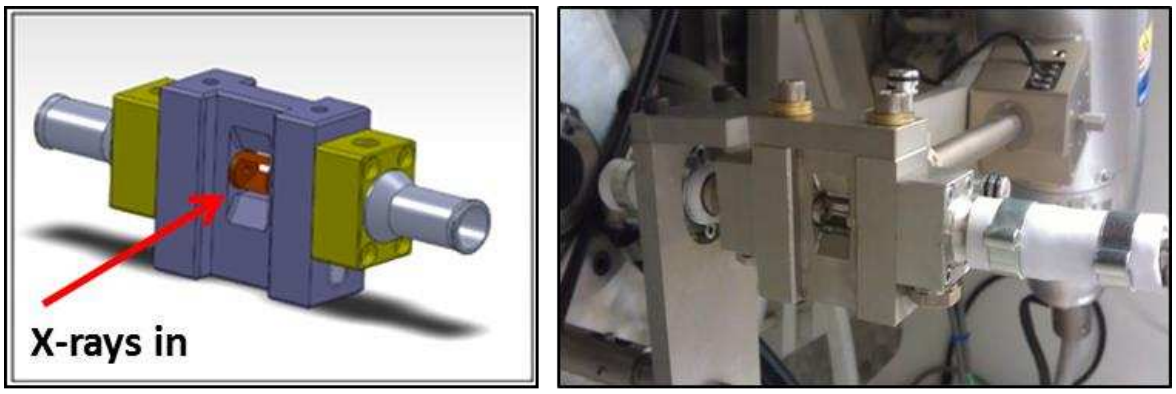

Figure 1 Drawing of the new transmission cell and also the cell housed within the X-ray cabinet with the X-ray generator

The capillary transmission cell Figure 1 has a biaxial hose connection where the inner connection contains a hose for the slurry line and allows the flow of slurry to reach the sample cartridge for X-ray analysis. The outer hose connection allows cooling/heating liquid from the re-circulation bath to flow around the steel body of the cell, this allows complete temperature control of the slurry throughout the system for cooling or heating; the cartridge where the sample slurry flows is unjacketed doe 1mm which prevents large temperature losses.

The recirculation fluid had to be sent around the capillary cartridge where the main cell contains a bypass tube which flows the jacket liquid around the cell and rejoins before exiting the opposite biaxial hose connection. The capillary cartridge is a steel tubular construct which houses a borosilicate glass capillary tube with a 10μm wall thickness which is adhered to either end of the tube with solvent resitant glue, this design allows X-rays to impinge upon the sample for analysis. The design allows quick removal and replacement of blocked or broken capillary tubes during experimental work and replacement with a new cartridge.

S2 Commissioning of the in-situ Transmission Flow Cell

In-situ diffraction methods pose a number of technical issues when collecting and analysing the data, one of these is the limit of detection (LOD) of the system. This is the lowest amount of solids in a slurry which the instrument can detect. During in-situ diffraction the main component which effects this is the solvent background which effectively reduces the signal to noise ratio of the fingerprint peaks for the phase in question. Further to this the count rate at which a visible fingerprint peak can be observed in the diffraction pattern is also required to determine the response time of the detector.

To improve the LOD for this system a mathematical method was applied to the data this is called smoothed principal component analysis (SPCA) this specific version of SPCA was developed and applied to this system in previous work[1]. In this next section, an overview of the experiments carried out to determine the unprocessed data quality of the transmission cell followed by application of SPCA methods to improve data quality is presented.

S2.1 XRD Count Rate Experiments

To determine the recorded count rate, i.e. the number of counts at the detector from a known sample, a 10% wt/wt slurry of alpha PABA in 70:30 water:ethanol mixes was prepared and analysed under normal operating conditions of the X-ray unit this could provide data around the time resolution for future in-situ experiments. Diffraction patterns were recorded every 10 seconds for 2 minutes; these are highlighted in Figure 2.

Every diffraction pattern in Figure 2 is the summation of diffracted intensity collected over 10 seconds and summed to previous intensity, providing count rate data over 2 minutes in 12 separate scans. The data indicates that generally the diffraction of the periodic solid phase contributes to the recorded intensity more so than the background and solution scattering, the (1 0 3) finger print peak at ~15.5 2θ is visible quickly after 10s.

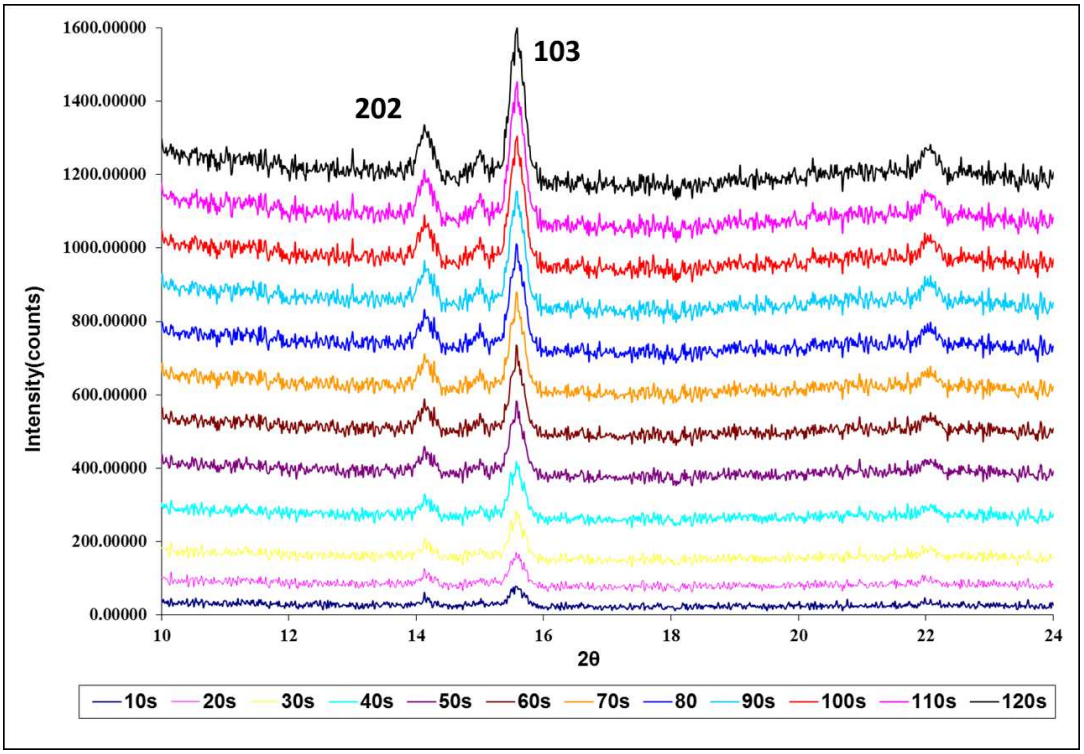

Figure 2 Count rate test for a 10% wt/wt slurry of alpha PABA

S2.2 Application of Smoothed Principal Component Analysis for Limit of Detection

The LOD was determined by inspecting various concentrations of an alpha PABA slurry prepared in 70:30 water:ethanol solvent; the concentration range used was 0.1–0.9 wt/wt% in 0.1 wt/wt% increments. The diffraction patterns were collected for 300 seconds, as this gave a good response at the detector, where the alpha PABA (1 0 3) peak at 15.5 2θ was used to establish the presence of the alpha solids. The collected diffraction data is presented in Figure 3 and highlights an overlay of unprocessed XRD patterns of alpha−PABA slurry's as a function of increasing concentration (offset along the ordinate for clarity). The data here highlights that the LOD for the unprocessed data is ~ 0.9 wt/wt%.

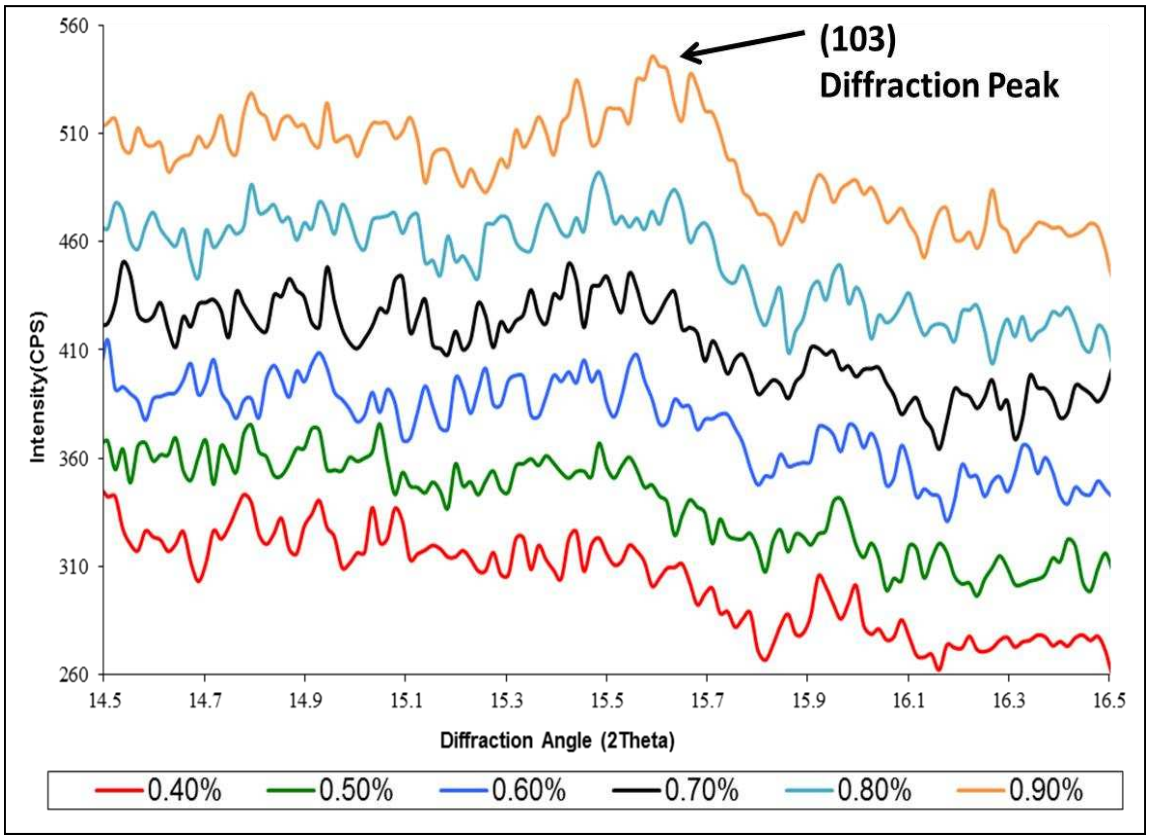

Figure 3 Diffraction patterns recorded for alpha PABA in increasing concentrations of slurry

The observed experimental LOD was improved further by applying a techniques of SPCA which was developed by Chen et al[1] and was applied during the data processing stage of the analysis. The recorded signal is effectively smoothed by the SPCA algorithm reducing background noise and improving signal to noise ratio. This greatly benefits not only the qualitative routine of polymorph identification at low concentrations but also improves the ability to quantify small concentrations of the solid phases present in the slurry. The application of the SPCA to raw data produces much smoother data and this presented in Figure 4. This reduction in instrumental noise and solution scattering reduces the LOD from 0.9 wt% to ~0.5 wt% after smoothing; greatly increasing the system's ability to detect small changes in solids concentration.

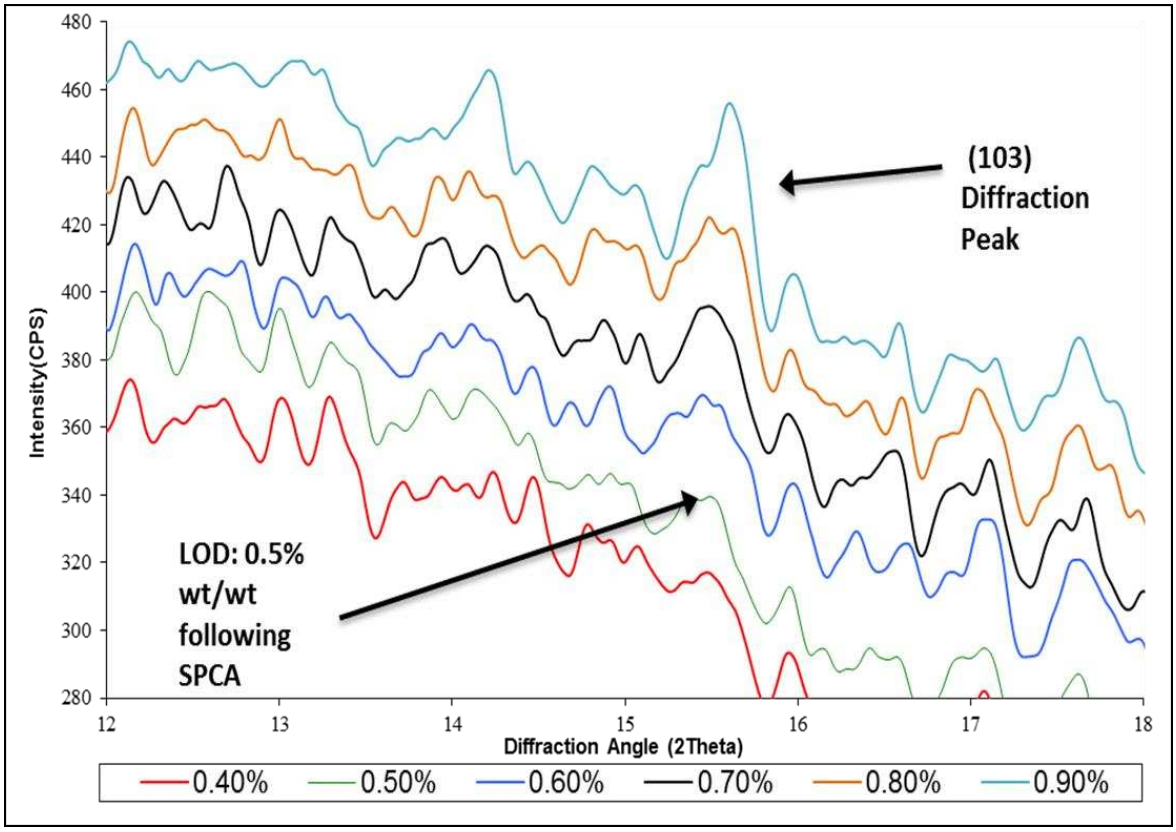

Figure 4 Smoothed PABA alpha XRD pattern for increasing slurry concentration (SPCA applied).

S3 Solubility Determination of alpha PABA in 70:30 Water:Ethanol Solvent Mix

The solubility of alpha PABA in 70:30 water:ethanol solvent mix was determined through gravimetric analysis using three repetitions to obtain standard deviations of the recorded temperature dependant solubility. Solutions of saturated alpha PABA were prepared in 20ml screw top vials by holding the solutions at the desired temperature in a shaker for 24 hours. The resulting solutions were allowed to settle at the set temperature for 12 hours to allow an aliquot of the saturated solution to be weighed using a four figure balance into a screw top vial. The solvent was then removed in a vaccum oven set at -1bar pressure and 50°C. The resulting dry solid mass was then weighed on a four figure balance to provide a measure of solubility. The recorded solubility data with standard deviations is plotted in Figure 5, whereby the data is fitted using an exponential function $y = 7.584\ e^{0.047x}$.

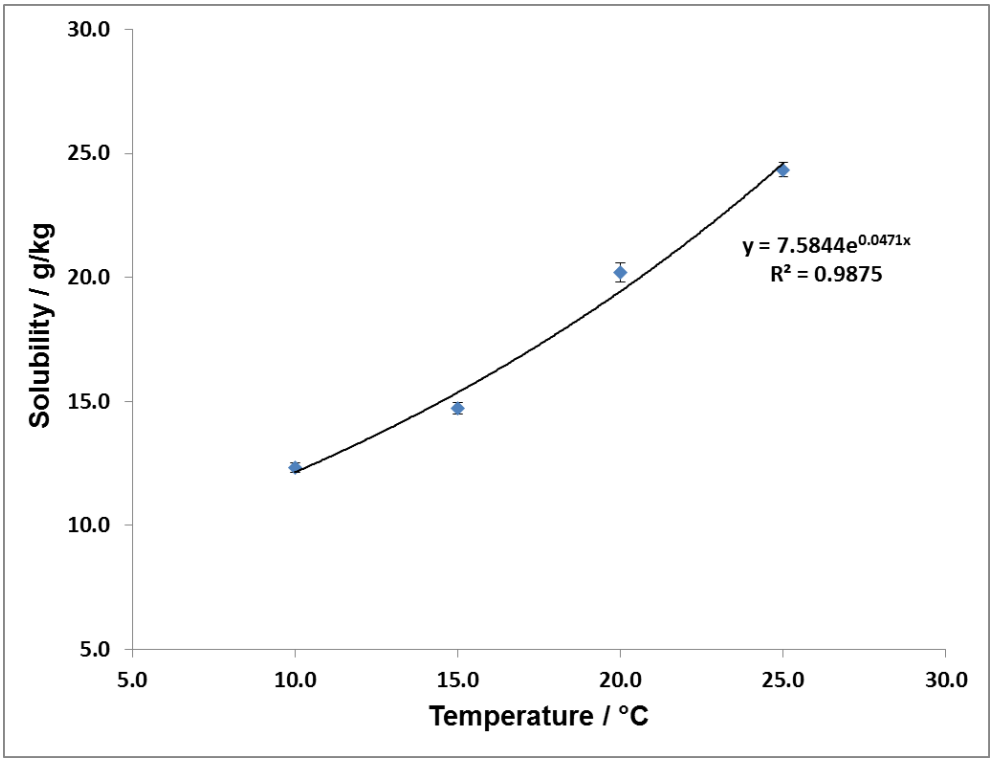

Figure 5 Solubility of alpha PABA in 70:30 Water:Ethanol solvent mix as determined by gravimetric analysis

S4 Seeded Runs of Beta to Alpha Phase Transformation at High Temperature

High temperature experiments were carried out for the seeded beta to alpha phase transformation; however at the elevated temperatures of 32 and 34°C the transformation occurred too rapidly to monitor the solid phase composition with in-situ XRD. Figure 6 shows the mass fraction conversion plots for both the higher temperature experiments performed as can be seen in both cases the majority of the alpha phase growth and beta phase dissolution has already occurred by the first or second measurement time. Hence fitting of kinetic models to only a few data points was not considered due to high errors in calculated kinetic parameter's, as such only the lower temperature seeded experiments were used to assess the phase interconversion kinetics.

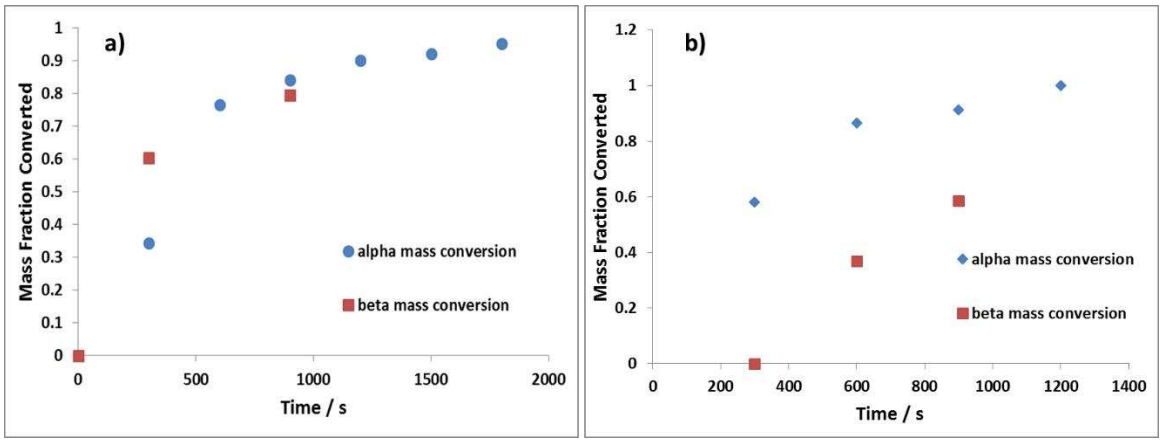

Figure 6 Mass fraction conversion plots for the alpha and beta solid phases during the a) 32°C and b) 34°C transformation experiments

S5 Unseeded Runs of Beta to Alpha Phase Transformation at High Temperature

Unseeded phase transformations were also carried out to determine the phase transformation time as a comparison to the seeded transformations. These were performed at the high temperatures of 35 and 45°C due to the relatively slow conversion rate in the higher temperature seeded experiments. Figure 7 shows the mass conversion plots for the alpha polymorph as a function of time during these unseeded experiments. What is immediately obvious that similarly to the higher temperature seeded experiments in S5, these unseeded experiments also show a very high conversion rate, where dissolution of the beta phase is not recorded in the two experiments, as the dissolution is faster than the data collection time of 5 minutes. Furthermore the growth of the alpha phase is almost completed in both experiments over the data collection time resulting in poor fitting of the data to kinetic models. This further highlights the inability of a laboratory X-ray source to monitor fast phase inter-conversions, again indicating the possible requirement for a synchrotron radiation to monitor these fast processes.

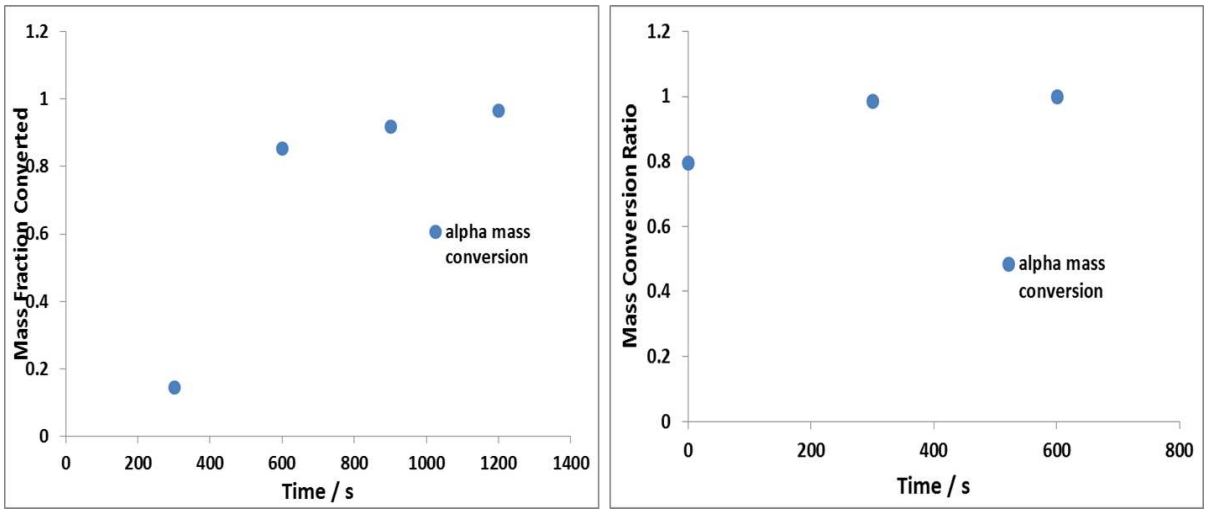

Figure 7 Mass fraction conversion plots for the alpha and beta solid phases during the a) 35°C and b) 45°C unseeded transformation experiments

S6 Reproducibility Testing

The in-situ XRD system was also tested for reproducibility regarding calculation of the kinetic parameters for the SMPT of the beta to alpha conversion. Six repetitions of the analysis at the isothermal temperature of 28°C were carried out and the subsequent growth and dissolution rate constants calculated at each repetition to analyse the deviation of the calculated kinetic parameters due to system noise and human error in the experiments.

Table 1 Calculated values of the growth and dissolution rate constants from the 6 repeat experiments at 28°C highlighting the standard deviation as a percentage relative to the mean value in each case

Repeat	k alpha (wt% s^{-1})	k beta (wt% s^{-1})
1	9.93×10^{-4}	4.98×10^{-4}
2	1.01×10^{-3}	5.81×10^{-4}
3	9.72×10^{-4}	4.05×10^{-4}
4	1.19×10^{-3}	8.13×10^{-4}
5	1.11×10^{-3}	4.35×10^{-4}
6	9.60×10^{-4}	4.74×10^{-4}
S.D.	9.11×10^{-5}	6.75×10^{-5}
S.D. %	8.77	12.62

Table 1 presents the results of the repeat analysis at 28°C providing the calculated growth rate and dissolution rate constants upon fitting the mass fraction vs time data to first order and zero order models respectively. The data show that the calculated standard deviation for the growth rate constant of the alpha phase is 8.77% and the dissolution rate constant of the beta phase is 12.62%.

The observed higher error in the beta dissolution rate constant can be explained by the variation in peak intensity ratios in the diffraction pattern, which is greater than those observed for the alpha phase. This is likely due to the alpha phase possessing a needle like morphology resulting in preferential orientation along the needle axis upon application of a flow to the crystals.

This could be beneficial for the calibration model as the (1 0 3) peak used for concentration calibration is perpendicular to the needle axis and hence will be increased in intensity relative to peaks in the a and c planes. This has the effect of increasing the signal to noise ratio particularly at low concentrations and hence the calibration model and thus the calculated kinetic parameters are less subject to systematic error. The opposite is true for the beta phase which has a more prismatic and isotropic structure which is reflected in its experimental diffraction pattern where the intensity is more evenly distributed between various reflections. This has the opposite effect where larger systematic errors will be seen for lower concentrations relative to the same case in the alpha phase.

[1] Z. P. Chen, J. Morris, E. Martin, R. B. Hammond, X. Lai, C. Y. Ma, E. Purba, K. J. Roberts, R. Bytheway, *Anal. Chem.* 2005, *77*, 20, 6563