In-situ monitoring of crystallisation processes in MSMPR reactors using non-invasive Raman spectrometry

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1. Introduction

- Conventional crystallisation is carried out in batch reactors with the use of off-line analytical techniques commonly resulting in problems with product quality and consistency
- MSMPR reactors can be employed for continuous crystallisation and are commonly used to study the kinetics of different polymorphs in crystallisation processes
- The aims of the project were to operate at a point supersaturated with respect to either alpha or beta L-glutamic acid to obtain the pure forms. This can be achieved by changing the temperature, concentration or residence time.
- In this work *in-situ* Raman spectrometry has been employed to provide information on how changes in reactor temperature or residence time and the addition of seeds affect the formation and growth of particles in real time. The measurements were able to show differences in the nucleation temperature, polymorphic composition and growth profiles of the crystals

2. Experimental

- Aqueous solutions of L-glutamic acid prepared (40 g/L)
- Heated to 80˚C and added at a constant flow rate to a vessel at a fixed temperature of either 25°C or 45°C. The residence time was determined by the flow rate and 10% of the reactor contents was removed at fixed time intervals.
- Operating conditions determined the initial polymorph obtained and the transformation time to the stable form.
- Experiments were repeated by seeding with either 5, 10 or 100% alpha or beta form.
- Raman spectra recorded using Kaiser Raman PhAT probe (6 mm spot size) through wall of vessel every 70 s.

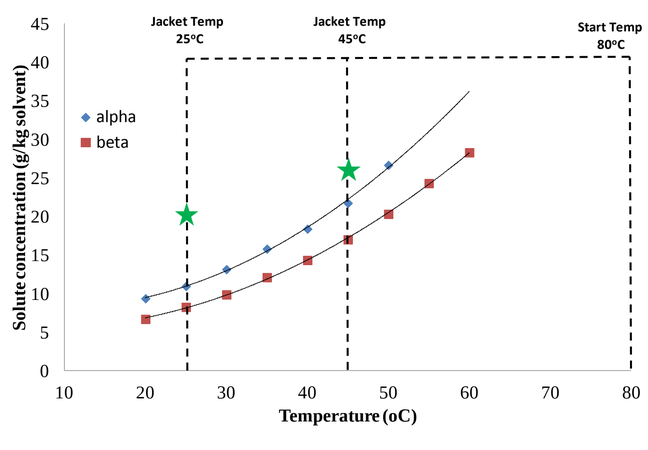

Figure 1 a): Set up of MSMPR b) Phase diagram of alpha and beta LGA showing the liquid phase concentrations at 25°C and 45°C using a 30 min RT

3. Results and Discussion

a) *In-situ* analysis: unseeded experiments-45ºC

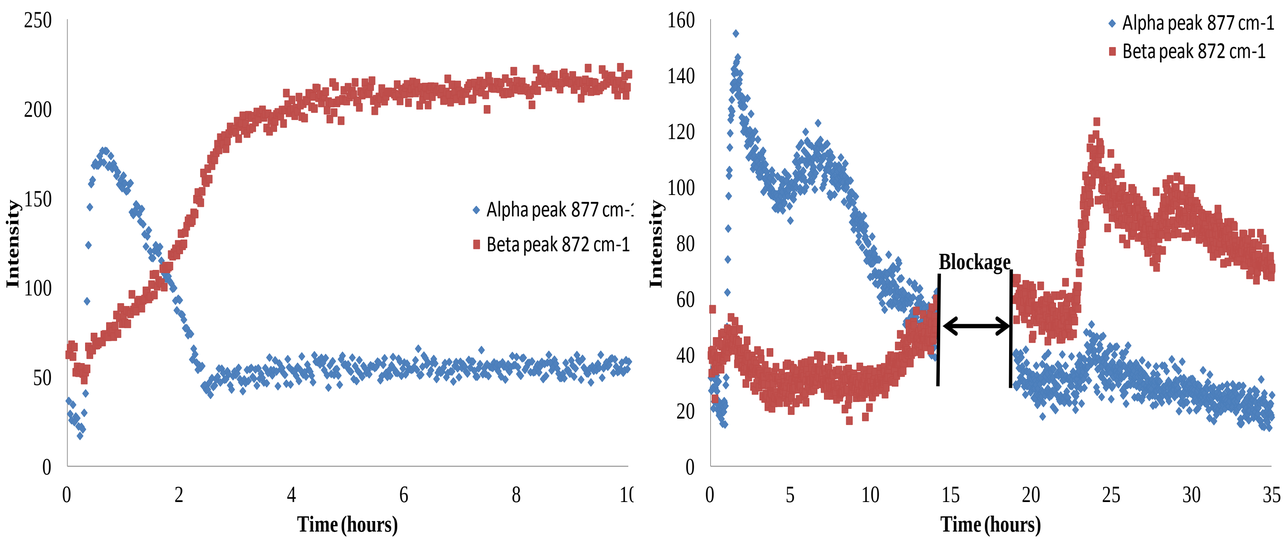

Figure 2 a) Crystallisation profile showing transformation from majority alpha to beta LGA in a batch STR at 45°C b) Crystallisation profile showing transformation from majority alpha to beta in a MSMPR at 45°C and 30 min RT

b) Effect of residence time on polymorphic form and transformation time

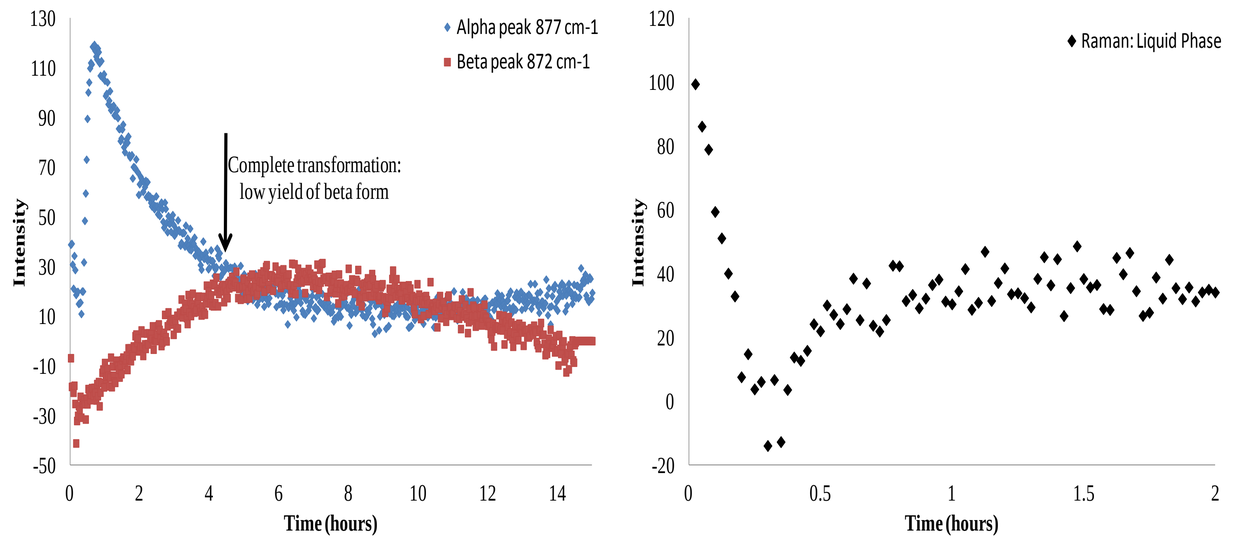

Figure 3 a) Crystallisation profile showing transformation from alpha to beta LGA in an MSMPR using a 60 min RT b) Crystallisation profile of LGA solution obtained in a MSMPR using a 15 min RT

c) Effect of seeding on nucleation and growth (5 and 10% beta)

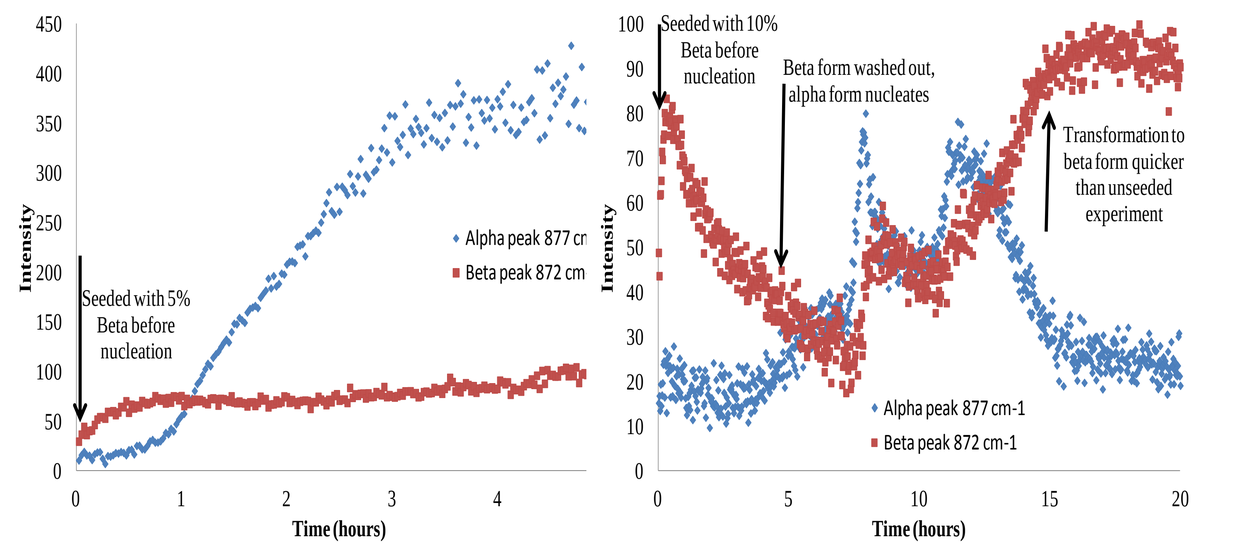

Figure 4 a) Crystallisation profiles of alpha and beta LGA when a MSMPR was seeded with 5% beta using a 30 min RT b) Crystallisation profiles for alpha and beta LGA when a MSMPR was seeded with 10% beta using a 30 min RT

d) Effect of seeding (100% alpha and beta)

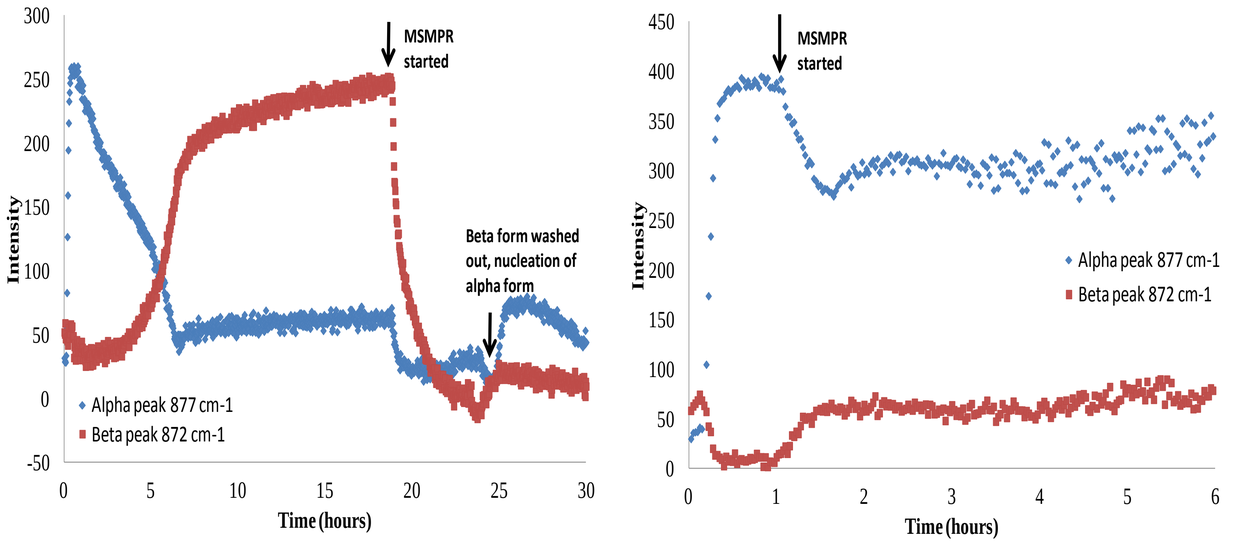

Figure 5 a) Crystallisation profiles of alpha and beta LGA when an MSMPR was seeded with 100% beta b) Crystallisation profiles of alpha and beta LGA when an MSMPR was seeded with 100% alpha

4. Conclusions

- Alpha form was obtained at 25°C and remained after 65 hours, a mixture of forms was obtained at 45ºC which transformed to beta after 23 hours
- Pure beta form obtained using seeding but quickly washed out and a mixture of forms nucleated as in the unseeded experiments

5. Further Work

- Investigate results further using nucleation kinetics and MSMPR model to explain outcome of experiments
- Compare results to those obtained in batch and continuous OBR using L-glutamic acid

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