Use of in-Situ Instrumentation to Characterise Anti-Solvent Addition Crystallization

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Methods for the characterisation of drowning out crystallisation using *in situ* instrumentation are presented. The crystallisation of benzoic acid from ethanol-water mixtures, with water acting as the anti-solvent, is the system studied. *In situ* Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) is used to monitor the liquid phase composition, specifically the concentration of benzoic acid in solution and the mass ratio of ethanol and water in the system. Lasentec Focused Beam Reflectance Measurement (FBRM) and Lasentec Particle Vision and Measurement (PVM) are used to monitor key properties relating to the size and shape of the crystals as they nucleate and grow. A novel approach to defining the solubility of the system is presented. The effects of agitation and the rate of anti-solvent addition on the metastable zone width are investigated. The effect of a slow and fast addition rate on the supersaturation and particle size distribution are investigated.

1. Introduction

Anti-solvent addition is an important crystallization technique that can be used as an alternative to cooling or evaporation. However, as anti-solvent is added to the system the dilution effect combined with the reduced solubility makes conventional expression of important crystallization characteristics, specifically the solubility and metastable zone width, difficult.

This problem can be avoided by defining the concentration of the solute and anti-solvent on an anti-solvent free basis. Supersaturation is expressed in the usual way as a concentration difference or ratio. The metastable zone width is defined as the mass of anti-solvent added to the system at the point of nucleation in excess of the saturated value.

2. Experimental Methods

Benzoic acid in ethanol-water mixtures at 25°C is used as the test system in this work. At this temperature, the solubility of benzoic acid in ethanol is 58 g/100 g ethanol, and in water is 0.34 g/100 g water [1]. ATR-FTIR spectroscopy (ReactIR 4000, Mettler-Toledo) was used to measure solute concentration and solvent composition for all experiments. A PLS model was used to calibrate the system. FBRM (model S400, Lasentec) was used to monitor all solid-phase changes.

Solubility Measurements – Gravimetric Analysis

An excess of benzoic acid was added to a 200 ml ethanol-water mixture, held at 25˚C and agitated at 300 rpm in a 500 ml glass reactor for three hours. After this period, the samples were filtered, weighed and dried and the difference between the initial mass of benzoic acid added and the final mass after drying was defined as the solubility. This was repeated for various water/ethanol mixtures.

Solubility Measurements – ATR-FTIR

An excess of benzoic acid was added to a 200 ml ethanol-water mixture, held at 25˚C and agitated at 300 rpm. The ATR-FTIR probe measured the water and benzoic acid concentrations every 30 seconds. After a hold period of about 30 minutes the concentrations remained constant indicating complete dissolution. In this way the solubility of the benzoic acid in a specific ethanol-water mixture was measured. To gather more data ethanol was added at the end of each hold period, the process was repeated and a new point on the solubility curve was measured.

Solubility Measurements - FBRM

A small amount of benzoic acid was added to an ethanol-water mixture. The solubility of this mass of benzoic acid in this solvent mixture was measured using FBRM. More benzoic acid was then added and the process repeated. The solubility of benzoic acid in the solvent mixture at 25˚C can then be interpolated. This process was repeated for a number of solvent mixtures allowing a number of solubility points at 25˚C to be measured [2].

Metastable Zone Width Determination

A solution containing 75 g of ethanol, 75 g of water and 21 g of benzoic acid was made up and held at 25˚C until all of the benzoic acid dissolved. Water was then added until nucleation was observed using FBRM. Each experiment was repeated four times and the average value was taken. The experiment was repeated at addition rates ranging from 0.05 g/s to 0.48 g/s and agitation values ranging from 250 rpm to 400 rpm.

3. Results and Discussion

Solubility

For this study the solubility of benzoic acid in ethanol-water mixtures, as a function of water concentration, is expressed on a water-free basis. The measured solubility curve for the system at 25˚C is shown in Figure 1.

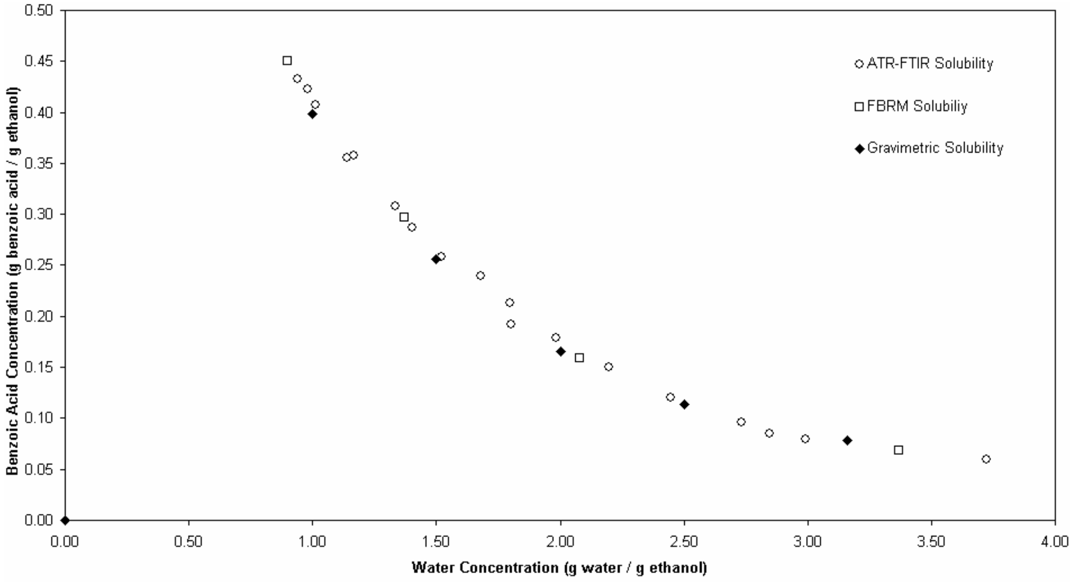


Figure 1: Solubility of Benzoic Acid in Ethanol Water at 25˚C

Metastable Zone Width

Since the metastable zone width is heavily dependent on the rate of supersaturation generation, experiments were performed for a number of anti-solvent addition rates. The results are plotted in Figure 2.

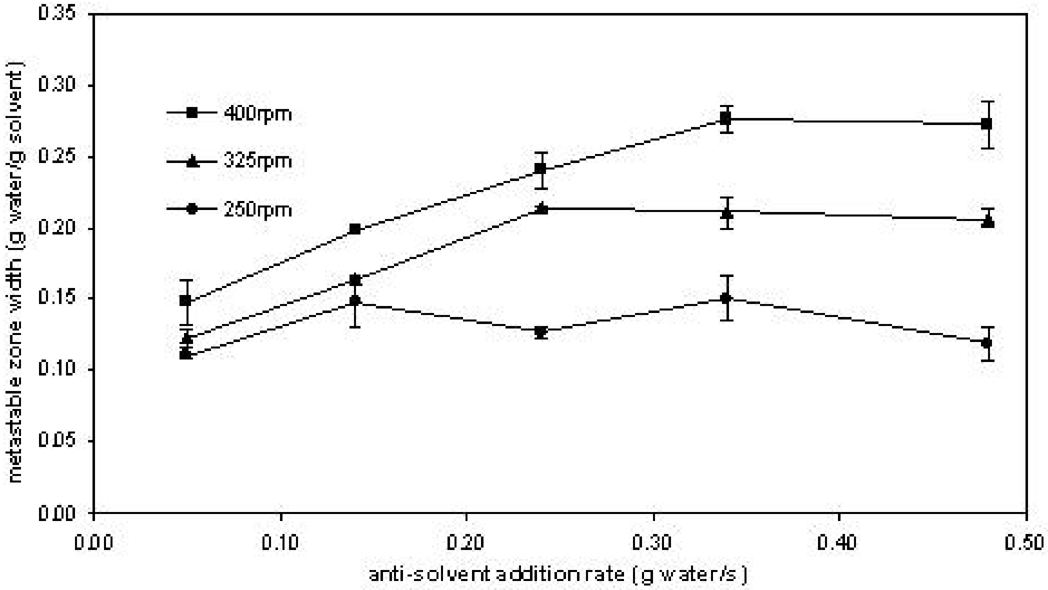


Figure 2: Anti-solvent addition rate vs. metastable zone width

It is clear that as the addition rate increases the metastable zone width increases. However, at the highest addition rate (0.48g/s) the metastable zone width does not increase. This can be explained by considering mixing in the vessel. At high addition rates it is more difficult to disperse the anti-solvent fully and achieve a homogenous mixture. Locally high regions of supersaturation ensue, close to the addition point, and nucleation is premature. This results in a narrower metastable zone width. The metastable zone width is further reduced at lower agitation speeds, due to the inability to rapidly disperse the anti-solvent (see Figure 2). At the lowest agitation rate used the metastable zone width is essentially constant for all addition rates used.

Comparison of a Fast and Slow Addition Rate

To highlight the use of *in situ* tools for the characterisation of anti-solvent addition crystallization two modes of operation were considered. The first with an addition rate of 0.34 g water/s and the second with an addition rate of 0.05 g water/s. In each case, the same mass of water was added to a saturated solution and subsequently held for 30 minutes. The slurry was filtered and dried and the crystals were examined microscopically. Both crystallizations were monitored with FBRM and ATR-FTIR.

Figure 4 shows the solution concentration profiles over the course of each run. As may be expected, at the slower addition rate, less water is required to induce nucleation, and the level of supersaturation remains lower throughout. The crystals produced are larger, as indicated by both off-line microscopy (Figure 5 a,b) and *in situ* FBRM measurement (Figure 6). The fast addition rate product is characterised by the presence of substantially more fine material (Figure 7).

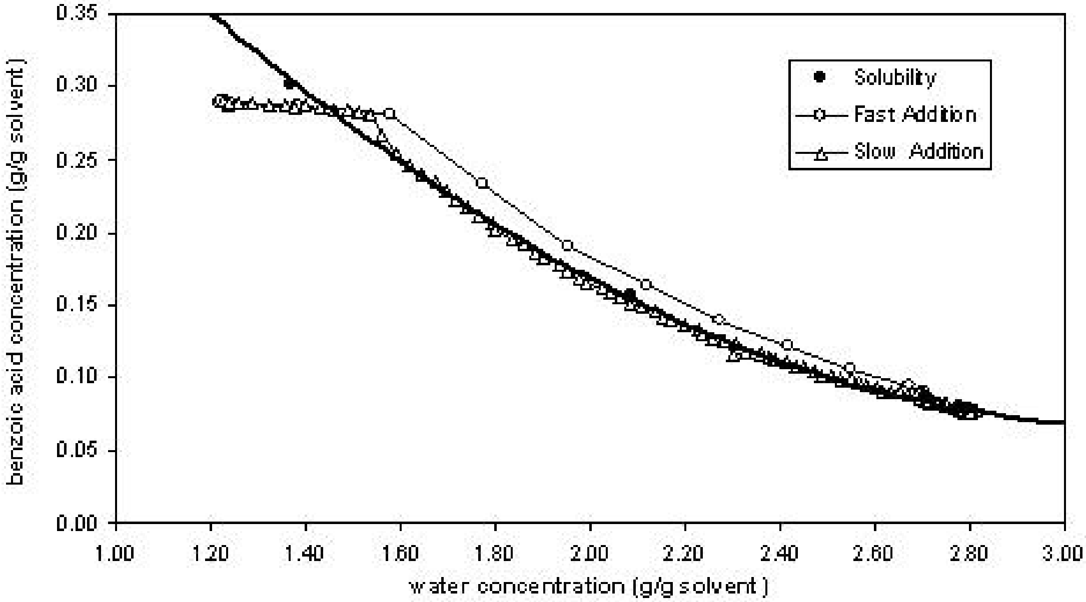
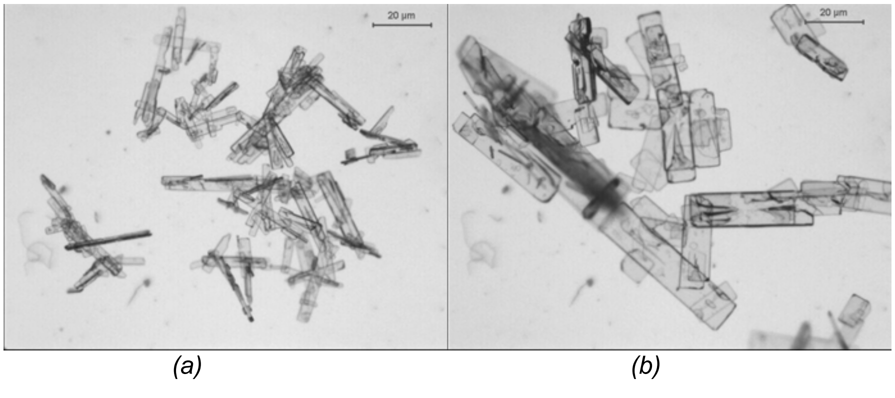


Figure 4: Concentration profiles for fast and slow addition rates



(a) (b)

Figure 5: Optical micrographs for (a) fast addition and (b) slow addition

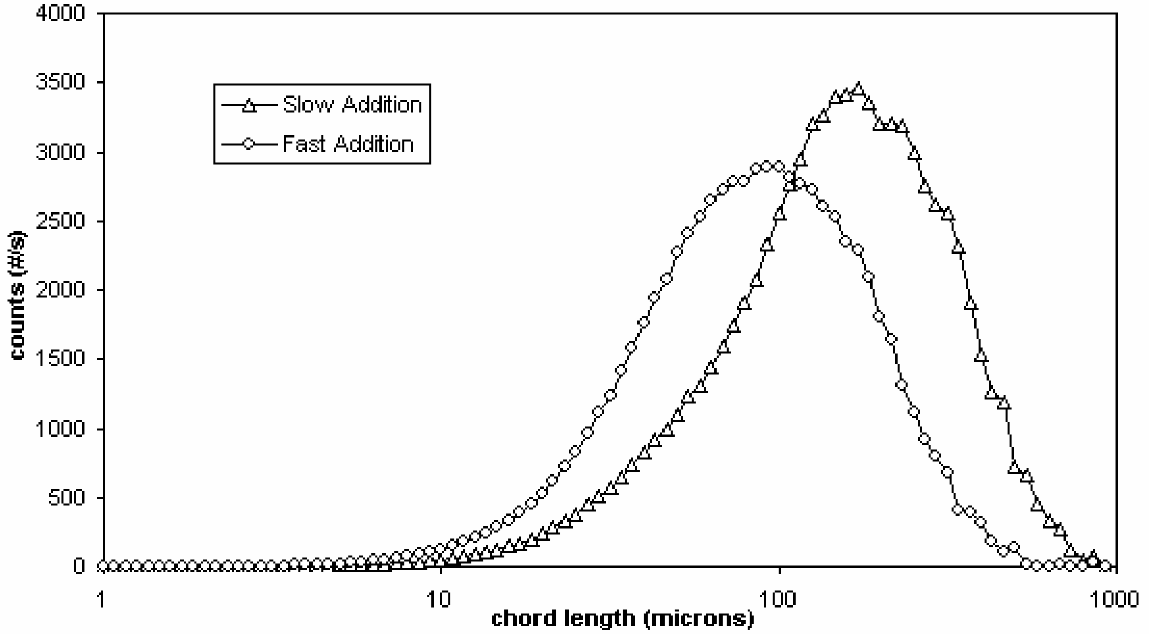


Figure 6: FBRM distribution at the end of the run (square weighted)

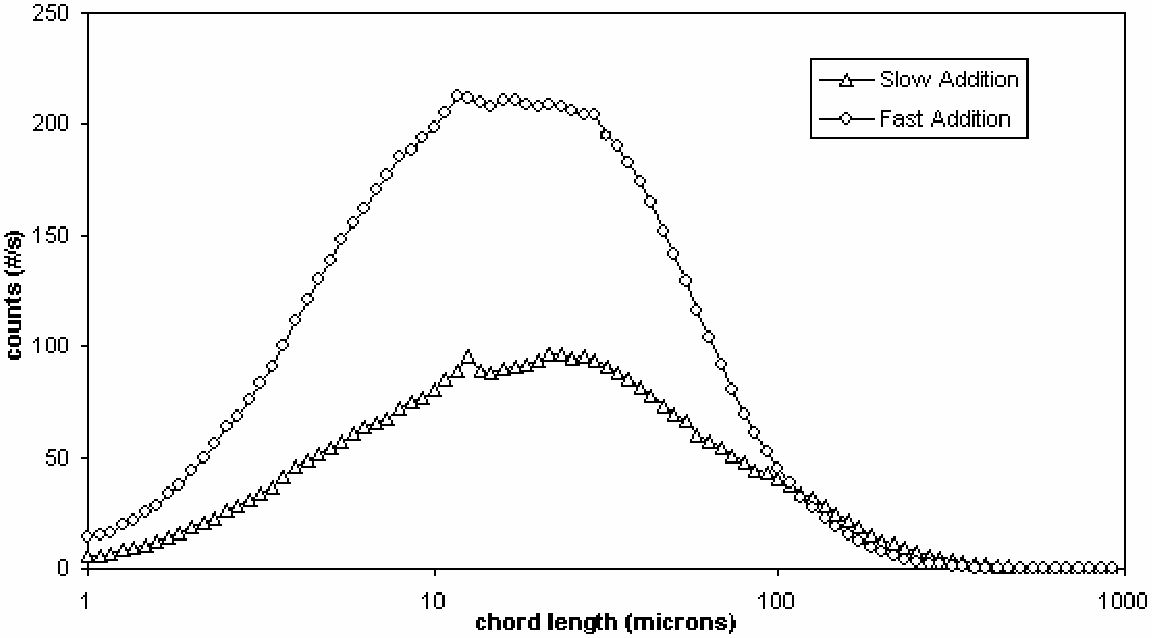


Figure7: FBRM distribution at the end of the run (unweighted)

4. Conclusions

The crystallization of benzoic acid from ethanol-water mixtures, using water as an anti-solvent, has been examined. The difficulty of expressing the solubility of the system, due to the dilution effect, has been eliminated by defining the concentration of the solute on an anti-solvent free basis. Supersaturation and metastability are easily expressed.

The effect of addition rate and agitation on the metastable zone width has been investigated. In general, the metastable zone width is wider at higher addition rates. However, at very high addition rates the metastable zone width does not widen and may even decrease. This is due to poor mixing in the vessel leading to a region of high supersaturation near the addition point and ultimately premature nucleation. The effect is exacerbated at low agitation values.

Growth and nucleation behaviour for two crystallizations, with a fast and slow addition rate, were examined in detail. The slow addition rate crystallization nucleated first and the level of supersaturation was lower throughout the run. This resulted in larger crystals with a smaller number of fine material.

6.References

1. Perry R.H., and co-workers, Perry’s Chemical Engineer’s Handbook, McGraw-Hill, New York, 1984

2. Barrett, P.; Glennon, B. Characterizing the Metastable-Zone Width and Solubility Curve Using Lasentec FBRM and PVM, Chemical Engineering Research and Design, 80, 799-805. 2002