Crystallization

Antisolvent crystallization

In-process characterization

- **Ensure fast and efficient scale-up by optimizing crystallization early in development**
- **Target particle size specifications to speed up downstream processing**
- **In-process tools improve productivity and safety by eliminating the need for sampling and offline measurement**

Abstract

In-process tools can provide a deeper understanding and allow for faster characterization and development of crystallization processes. Effective implantation of in-process tools allows crystallization processes to be monitored in real-time with no need for sampling. Sampling can be time consuming and non-representative especially for crystallization systems where samples can change due to nucleation, growth, agglomeration and/or breakage once removed from the crystallization vessel. In-process tools may also be implemented at a range of scales making it possible to compare crystallization experiments performed in the laboratory with batches run in the pilot-plant or at the full productions scale. This is especially important for anti-solvent systems where changes in mixing conditions between scales can make effective scale-up, and subsequent optimization of manufacturing processes, difficult.

In this study, the impact of antisolvent addition rate on crystal size and morphology is assessed through experiments based on the unseeded crystallization of benzoic acid from ethanol-water mixtures using water as the antisolvent. The results of two experiments are presented in a summarized form, one at 'fast' antisolvent addition rate – 0.2 gs^{-1} – and one at 'slow' antisolvent addition rate – 0.1 gs^{-1}. Supersaturation, monitored using ReactIR™, was approximately twice as high for the fast addition rate compared to the slow addition rate. Lasentec® FBRM® distributions indicate that a fast addition rate produces significantly smaller crystals compared to the slow addition rate. Lasentec® PVM® images confirm these findings and show that the crystals tend to be finer needle-shaped crystals with significant agglomeration at the faster addition rate.

Figure 1
Lasentec® FBRM® and PVM® technologies are directly installed in a RC1e® automated lab reactor for in-process measurement of the crystal product.

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Introduction

Undersaturated solutions of benzoic acid in aqueous ethanol solutions were prepared and held at a constant temperature of 25ºC. Benzoic acid is an organic compound, poorly soluble in water but soluble in ethanol with no known polymorphs cited in the literature. Water was added at a fixed rate of 0.1 gs^{-1} and 0.2 gs^{-1} respectively and the resulting crystallization was monitored using in-situ process analytical tools. Lasentec® FBRM® and PVM® were used to track the crystalline solid phase and ReactIR™ (ATR-FTIR spectroscopy) was used to monitor the liquid phase i.e. the supersaturation. The experiments were performed in a LabMax® vessel allowing the temperature and anti-solvent addition rate to be programmed and controlled automatically.

Results and discussion

Figure 2 (a) shows concentration profiles for both addition rates as well as the solubility curve for benzoic acid in ethanol-water. The concentration profile shows that the solution begins in the undersaturated region and as water is added becomes supersaturated. The Metastable Zone Width (MSZW) in each case is narrow with a slightly wider MSZW observed at the fast addition rate. The concentration decreases upon crystal nucleation, stays close to the solubility curve, and at the end of antisolvent addition period drops to the solubility curve. The prevailing level of supersaturation is clearly seen in Figure 2(b) where anti-solvent concentration vs. supersaturation is displayed. Evidently, the faster addition rate supersaturation is higher. This is important information as supersaturation is the driving force for crystallization and influences the nucleation and growth rates. Differing levels of supersaturation typically lead to different final product size and in this case with Lasentec® FBRM® and PVM® it is possible to quantify the difference in the product distribution.

Figure 3 shows Lasentec® FBRM® distributions at the end of the experiment for the fast and slow addition rates. Clearly, the fast addition rate has produced significantly more fine material and the slow addition rate has produced larger crystals. The difference can be quantified by examining the mean of the FBRM® distributions. Operating at the slow addition rate results in a mean value of 39µm compared to 30µm for the fast addition rate, an increase of almost 30%. As expected, the slower addition rate and resultant low level of supersaturation has resulted in growth being favored over nucleation and a larger final crystal size. The fast addition rate and subsequent high levels of supersaturation favors nucleation

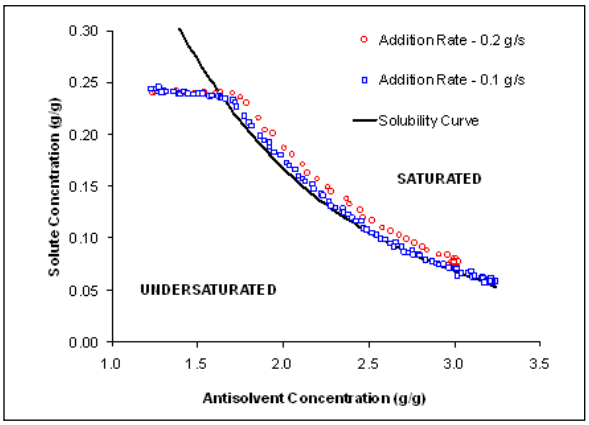

Figure 2a
Concentration Profiles for both addition rates with solubility curve

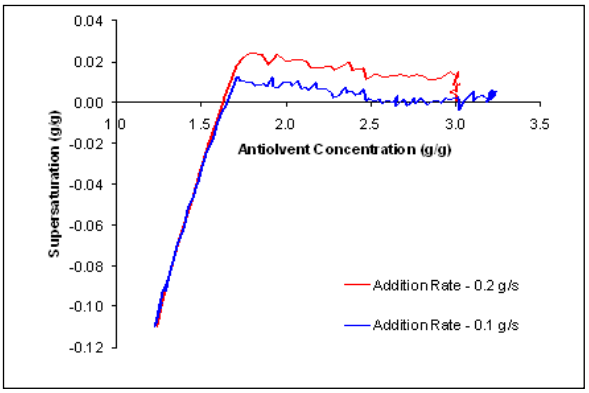

Figure 2b
Supersaturation data for each addition rate

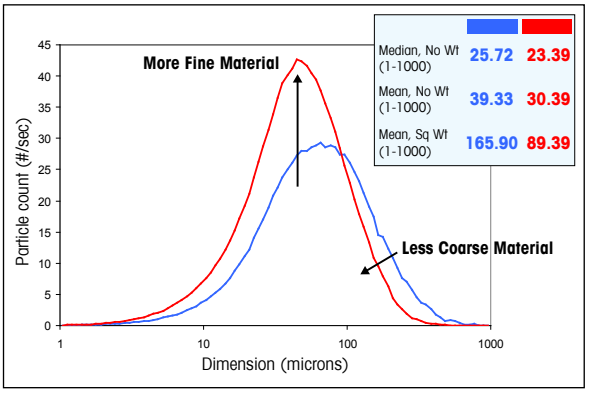

Figure 3
FBRM® distributions at both addition rates (0.1gs^{-1} – blue; 0.2gs^{-1} – red)

over growth, resulting in a smaller average crystal size in this case.

Further information can be gathered from the same experiment by studying the Lasentec® PVM® images. Figure 4 shows PVM® images at both addition rates and it is clear that the fast addition rate results in agglomerated fine material whereas the slow addition rate results in large well formed needle-like crystals. This is valuable information as the size and morphology of the crystals at the end of the crystallization can severely impact product characteristics, such as purity, as well as downstream process performance during filtration and drying. Agglomerates can lead to inclusions of solvent in the crystal structure decreasing purity levels and increasing the potential for polymorphic transitions in the drying steps. Such inclusions can also lead to longer drying times and if agglomerates are prone to breakage filtration times can be significantly extended.

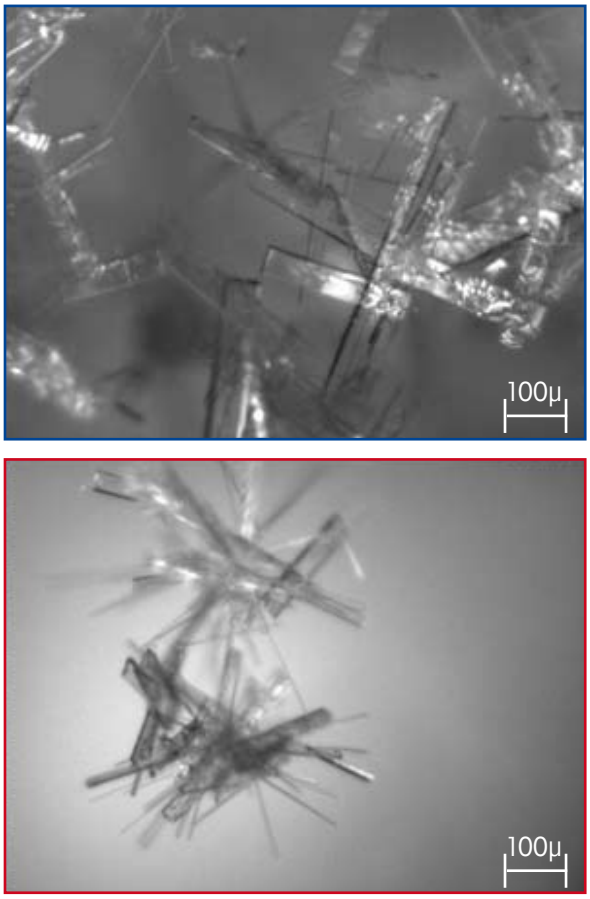

Figure 4
PVM® images at both addition rates ($0.1gs^{-1}$ – blue; $0.2gs^{-1}$ – red)

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Conclusion

This application note highlights the high quality information that may be gathered in real time for the characterization of crystallization systems. In this case, the impact of addition rate on particle size and morphology was studied and the mechanism for the difference was confirmed; elevated supersaturation at higher addition rates. The impact of other process parameters including operating temperature, mixing regime, antisolvent used, addition location, initial solute concentration and seeding protocol may all be studied in a similar fashion for a comprehensive development of a robust crystallization process. By utilizing in-process tools at the small scale, crystallization development is facilitated and scale-up can be expedited.

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