Project 11: ***Continuous Processing for Production of Solid-State Pharmaceuticals***
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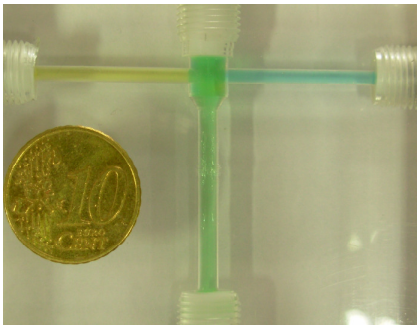
Title: Application of PAT to the Design and Optimization of Plug Flow Crystallizations for API manufacture

Principal Focus: This study applies in situ and at line PAT (FBRM, FT-IR and PVM) to investigate the suitability of plug flow crystallization systems to pharmaceutical production and furthermore to develop a rapid design and optimization methodology.



Experimental Method: The plug flow crystallizer configuration employed consists of a Roughton vortex mixer (**Figure 1**) combined with tubular reactor. Supersaturation is generated via the rapid mixing of a product stream (benzoic acid in ethanol water solution) and anti-solvent (water) in the Roughton mixer with the crystallization reaching equilibrium in the following tubular section. The crystallization is controlled by changing the initial supersaturation by altering the flowrate ratios of product and anti-solvent streams. The crystal population is then characterized in-situ via the application of novel flow cell designs allowing for the in-situ observation of the crystallization using FBRM, PVM and FT-IR.

Figure 1: Passive tracer analysis of mixing within the Roughton Mixer

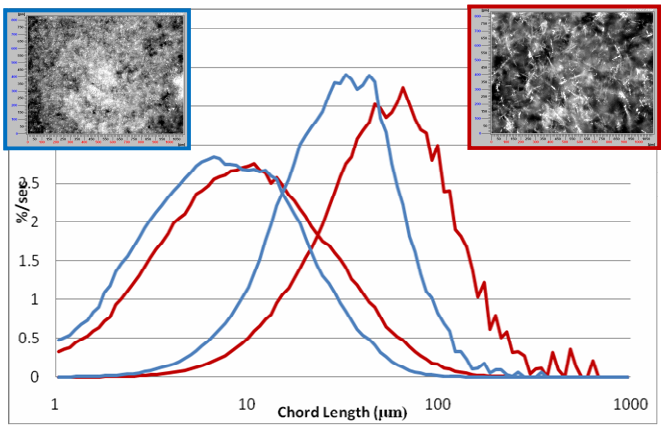


Figure 2: FBRM CLDs and PVM images for high (1:2) and low (9:5) feed : anti-solvent flow rate ratios

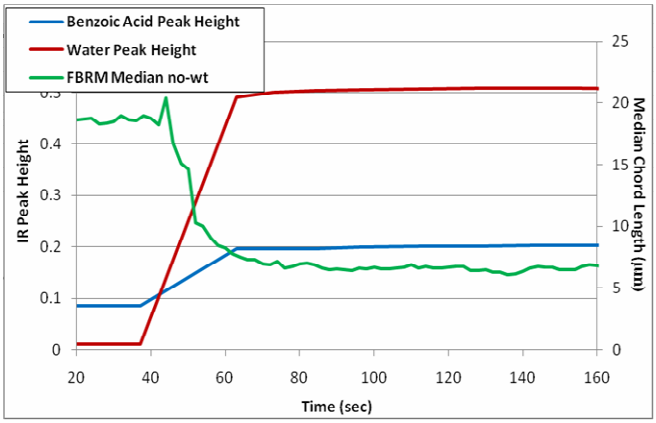


Figure 3: Tracking attainment of steady state using IR supersaturation peak heights[1] and FBRM no-wt mean

Results and Discussion: The results of this work indicate that Plug Flow Crystallizers provide a robust and impressively productive crystallization methodology. Supersaturation was found to be depleted extremely rapidly within the reactor volume, meaning that despite the small size of the crystallizer (~40ml) it was capable of producing approximately 40 kg of product per day. Unlike conventional confined impinging jet mixers, the Roughton mixer design allows for the maintenance of mixing efficiency without the requirement of balancing inlet flowrates[2], allowing for the generation of higher supersaturations and smaller particles which could negate the need for milling operations. This also facilitates the "dialling up" of a wide range of crystal sizes with a given feed concentration as illustrated in **Figure 2** where high and low feed to anti-solvent flow ratios were used to produce loose agglomerates of tiny square plates (1-10 µm) at high supersaturations with lower supersaturations yielding individual needles approximately (10 X 30 µm) respectively. Steady state operation was also obtained in as little as 30 seconds from start up (**Figure 3**). This is potentially a huge advantage of plug flow crystallizers compared to more common tank based continuous crystallizers which require much longer to reach steady state, generating far more material upon start up that may need to be reworked.

Future Work: By applying the analytical methods developed and the knowledge gained from this work it is hoped that a rapid screening and optimization methodology can be developed for any compound via anti-solvent, combined cooling/anti-solvent and reactive crystallization.

1. Barrett, M., McNamara, M., Hao, H., Barrett, P., Glennon, B., Supersaturation tracking for the development, optimization and control of crystallization processes, Chem. Eng Res & Des 2010, 88, 8, 1108-1119
2. Lindenberg, C., Schöll, J., Vicum, L., Mazzotti, M., Brozio, J., Experimental characterization and multi-scale modelling of mixing in static mixers, *Chem. Eng. Sci.* 2008, *63*, 4135-4148.