Antisolvent Crystallization of Carbamazepine Dihydrate using a Fluidic Oscillator

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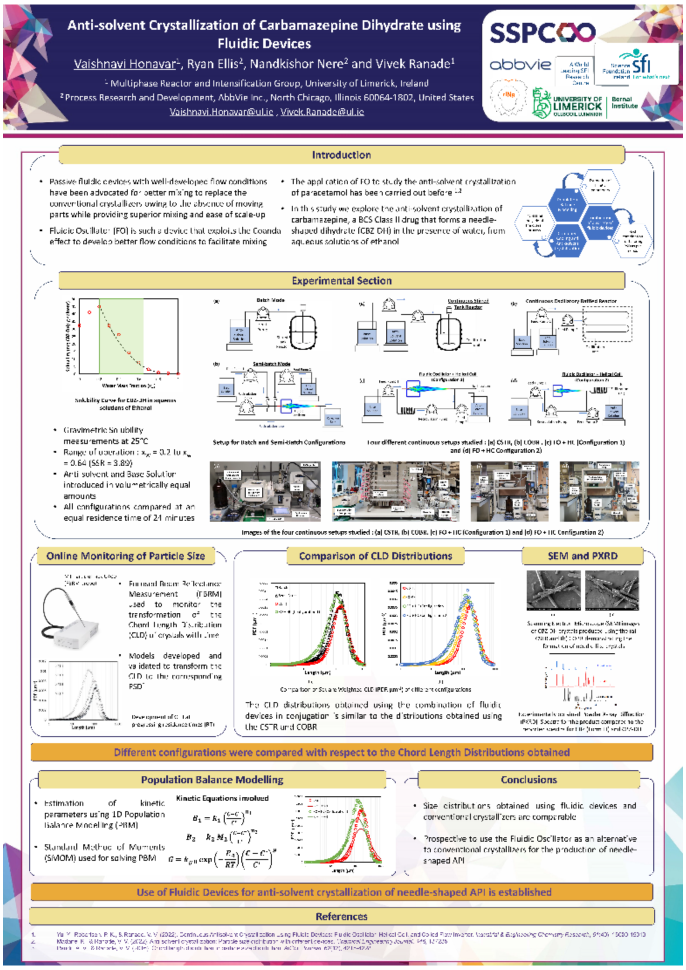

The pharmaceutical industry is rapidly evolving the prevailing crystallization systems to achieve better control over the critical quality attributes of the Active Pharmaceutical Ingredient (API) produced. Fluidic devices provide superior mixing and scale-up possibilities compared to conventional crystallizers, while also facilitating control of the particle size distribution (PSD). The advantages of implementing fluidic devices such as a fluidic oscillator, helical coil, and coiled flow inverter, for the crystallization of paracetamol from methanol solutions using anti-solvent crystallization, have been demonstrated by Yu et al., and, Madane and Ranade (Yu et al., 2022) (Madane & Ranade, 2022). In this study, we investigated the effect of using the fluidic oscillator as a crystallizer for the crystallization of carbamazepine dihydrate (CBZ-DH) from aqueous solutions of ethanol using water as an antisolvent. A loop setup was introduced for the continuous mode of operation of the fluidic device as a crystallizer. Its performance was compared with the performance of batch mode and continuous mode (using a Continuous Stirred Tank Reactor (CSTR)) at the same supersaturation ratio and residence time. The effect of varying the process parameters of the fluidic oscillator such as inlet velocity and recirculation time was also investigated. The acicular dihydrate crystals were monitored online using the Focused

Beam Reflectance Measurements (FBRM), and offline PSD characterization was performed using a laser diffractometer. Population Balance Modelling (PBM) was used to simulate continuous crystallisation and the kinetic parameters were estimated by fitting the simulated PSD to the experimental data. This study will help understand the applicability of the fluidic oscillator for the production APIs with needle-like particles.

Madane, K., & Ranade, V. V. (2022). Anti-solvent crystallization: Particle size distribution with different devices. Chemical Engineering Journal, 446. https://doi.org/10.1016/j.cej.2022.137235 https://doi.org/10.1016/j.cej.2022.137235%20

Yu, Y., Robertson, P. K. J., & Ranade, V. V. (2022). Continuous Antisolvent Crystallization Using Fluidic Devices: Fluidic Oscillator, Helical Coil, and Coiled Flow Inverter. Industrial & Engineering Chemistry Research, 61(40), 15000-15013. https://doi.org/10.1021/acs.iecr.2c02504