

# Antisolvent Crystallization of Carbamazepine Dihydrate using a Fluidic Oscillator

Vaishnavi Honavar, Vivek V. Ranade

**Anti-solvent Crystallization of Carbamazepine Dihydrate using Fluidic Devices**  
 Vaishnavi Honavar<sup>1</sup>, Ryan Ellis<sup>2</sup>, Nandkishor Nere<sup>2</sup> and Vivek Ranade<sup>1</sup>  
<sup>1</sup> Multiphase Reactor and Intensification Group, University of Limerick, Ireland  
<sup>2</sup> Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064-1802, United States  
 Vaishnavi.Honavar@ul.ie, Vivek.Ranade@ul.ie

**SSPCOO**  
 abbvie | A Chair in Process Innovation | SFI  
 UNIVERSITY OF LIMERICK | School of Chemical Engineering

**Introduction**

- Passive fluidic devices with well-developed flow conditions have been advocated for better mixing to replace the conventional crystallizers owing to the absence of moving parts while providing superior mixing and ease of scale-up
- Fluidic Oscillator (FO) is such a device that exploits the Coanda effect to develop better flow conditions to facilitate mixing
- The application of FO to study the anti-solvent crystallization of paracetamol has been carried out before [2]
- In this study we explore the anti-solvent crystallization of carbamazepine, a BCS Class II drug that forms a needle-shaped dihydrate (CBZ-DH) in the presence of water, from aqueous solutions of ethanol

**Experimental Section**

• Cylindrical in-line fluidic oscillators at 25°C  
 Range of operation:  $u_{in} = 0.2$  to  $u_{in} = 0.84$  (SR = 3.09)  
 Anti-solvent and Base Solution introduced in volumetrically equal amounts  
 All configurations compared at an equal residence time of 21 minutes

**Online Monitoring of Particle Size**

• Focused Beam Reflectance Measurement (FBRM) used to monitor the transformation of the Chord Length Distribution (CLD) of crystals with time  
 Models developed and validated to transform the CLD to the corresponding PSD

**Comparison of CLD Distributions**

• The CLD distributions obtained using the combination of fluidic devices in configuration 1 is similar to the distributions obtained using the CSTR and COBR

**SEM and PXRD**

• Scanning electron microscope (SEM) and Powder X-ray diffraction (PXRD) used to monitor the morphology and phase of the crystals

**Different configurations were compared with respect to the Chord Length Distributions obtained**

**Population Balance Modelling**

• Estimation of kinetic parameters using 1D Population Balance Modelling (PBM)  
 Standard Method of Moments (SMM) used for solving PBM

**Kinetic Equations Involved**

$$\frac{dN_i}{dt} = \sum_{j=1}^{i-1} R_{j,i} N_j - \sum_{j=i+1}^{\infty} R_{i,j} N_i$$

$$R_{i,j} = k_{i,j} \left( \frac{C_i}{C_j} \right)^n$$

**Conclusions**

- Size distributions obtained using fluidic devices and conventional crystallizers are comparable
- Prospective to use the Fluidic Oscillator as an alternative to conventional crystallizers for the production of needle-shaped API

**Use of Fluidic Devices for anti-solvent crystallization of needle-shaped API is established**

**References**

1. Yu, Y., Ranade, V. V., & Ranade, V. V. (2022). Continuous Flow Anti-Solvent Crystallization of Paracetamol: Role of Coiled Flow Inverter and Coiled Flow Inverter. *Journal of Applied Pharmaceutical Science*, 14(1), 1000-1010.  
 2. Yu, Y., Ranade, V. V., & Ranade, V. V. (2022). Continuous Flow Anti-Solvent Crystallization of Paracetamol: Role of Coiled Flow Inverter and Coiled Flow Inverter. *Journal of Applied Pharmaceutical Science*, 14(1), 1000-1010.

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>