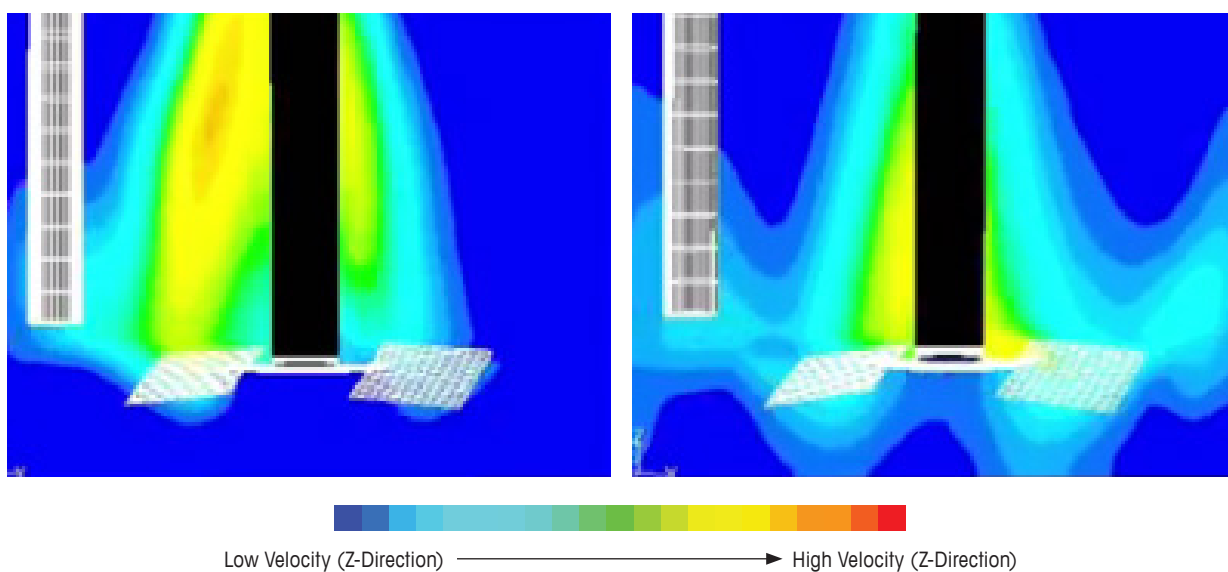


# Crystallization Process Development

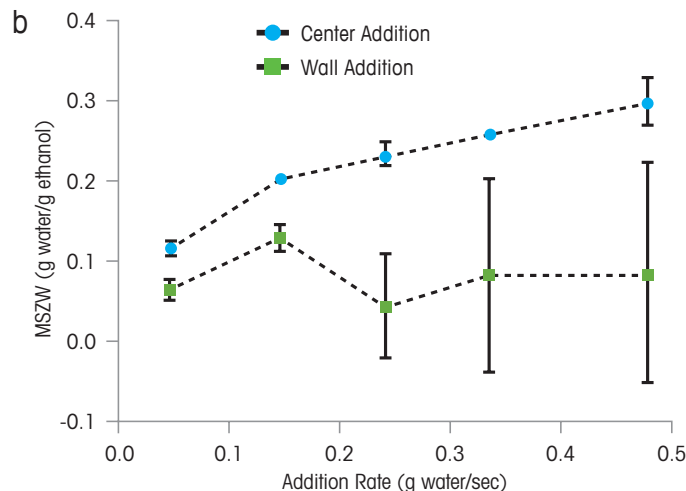
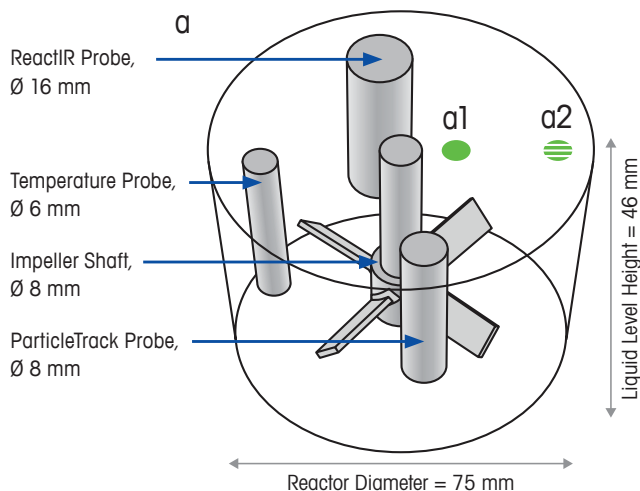
## The Role of Mixing

Changing the scale or mixing conditions in a crystallizer can directly impact the kinetics of the crystallization process and the final crystal size. Heat and mass transfer effects are important to consider for cooling and anti-solvent systems respectively, where temperature or concentration gradients can produce inhomogeneity in the prevailing level of supersaturation. This often results in pockets of very high supersaturation close to the walls of the vessel for a cooling crystallization, or at the addition location for anti-solvent (and also reactive) crystallizations.

Computational fluid dynamics can help scientists understand how different mixing configurations influence supersaturation gradients in a crystallizer (Figure 1). When anti-solvent is added above the surface and close to the wall, it is difficult to effectively incorporate the liquid into the bulk solution. When anti-solvent is added closer to the impeller, incorporation of the anti-solvent occurs immediately. For this crystallization system, the difference in anti-solvent incorporation and the associated difference in the homogeneity of supersaturation through the vessel causes significant differences in the nucleation and consistency of the crystallization process.



**Figure 1.** Anti-solvent incorporation from two insertion points, close to the vessel wall (left); close to the center (right), at the same time point after addition starts



**Figure 2.** (a) Reactor schematic; (a1) Center addition point; (a2) Wall addition point; (b) Antisolvent required to induce nucleation as a function of addition rate. Nucleation point detected by ParticleTrack™.

The effect of local supersaturation build-up on crystallization is shown in Figure 2, where the repeatability of the nucleation point for an unseeded crystallization is shown for an anti-solvent crystallization system. For this process when anti-solvent is added above the liquid surface and near the wall of the reactor, especially at higher addition rates, the nucleation point is extremely inconsistent, with wide error bars shown for these experiments that were conducted in triplicate (D. O’Grady, M. Barrett, E. Casey, and B. Glennon. (2007) The Effect of Mixing on the Metastable Zone Width and Nucleation Kinetics in the Anti-solvent Crystallization of Benzoic Acid. Chemical Engineering Research and Design, 85, 945 – 952).

Additionally, when adding anti-solvent above surface and at the wall of the crystallizer, nucleation consistently occurs sooner, and at lower anti-solvent concentrations than when anti-solvent is added in the center near the impeller. The reason for these two concerning results is that when anti-solvent is added close to the wall, the mixing conditions in the crystallizer make it difficult for the anti-solvent to be incorporated easily, and supersaturation builds up at the feed location. This result demonstrates that for this crystallization process, mixing is a critical variable that must be characterized and controlled across scales in order to ensure consistency.



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