Modeling of Mixing-Sensitive Pharmaceutical Drug Substance Processes in Batch Reactors

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Introduction:

Manufacturing of pharmaceutical drug substances involves chemical unit operations that are dependent on effective mixing, particularly crystallizations[1-3].

	Potential Consequences in Crystallization
Slow mixing can cause uneven distribution of chemical species	• Agglomeration in crystallization • Impurity entrapment in crystallization
Fast mixing can generate high shear rate and energy dissipation	• Fast uncontrolled nucleation • Particle attrition • De-agglomeration

In laboratory experiments, we observed faster nucleation kinetics and smaller particle size during crystallization of a drug substance at higher agitation rate. On the other hand, at low agitation rate crystals formed agglomerates, impacting the final drug substance qualities. To analyze the role of mixing attributes in the observed crystallization behavior we employed COMSOL Multiphysics®.

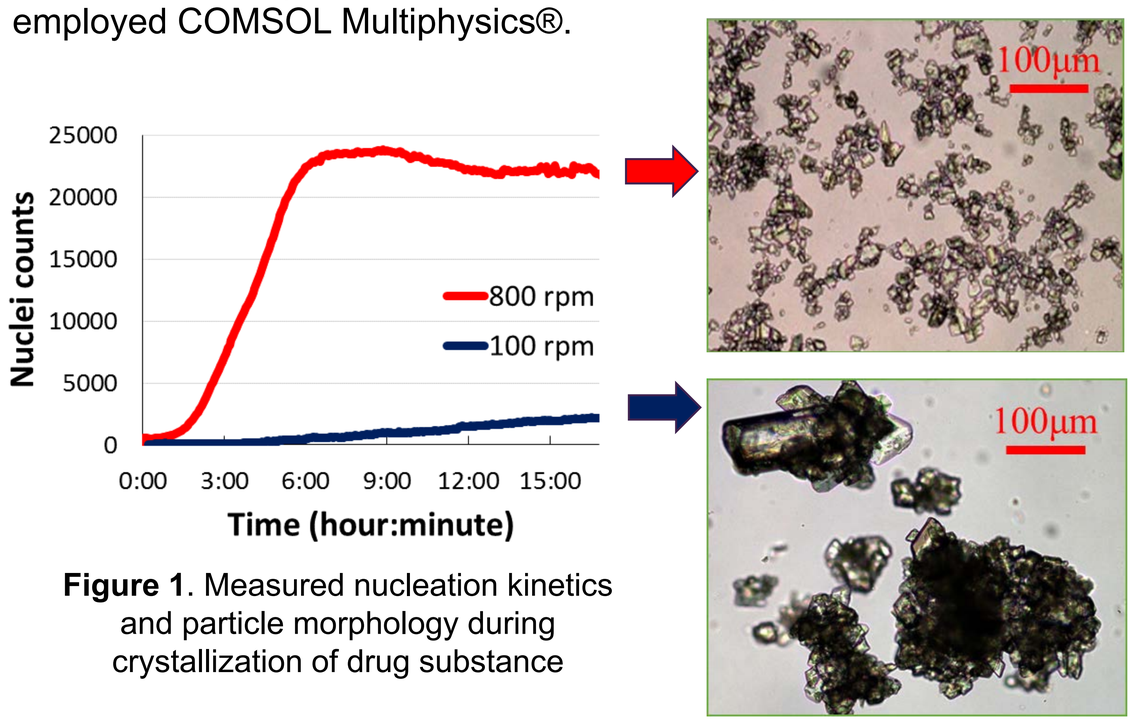

Figure 1. Measured nucleation kinetics and particle morphology during crystallization of drug substance

Computational Methods:

In the present work, flow patterns, chemical species transport and mixing attributes in fed-batch reactors are examined to **identify mixing attributes that can impact the crystallization behavior** and ultimately, final drug substance qualities. A 3D geometry of 1L laboratory reactors at BMS was built using COMSOL (tank diameter of 10.5 cm, tank height of 15 cm, half-moon impeller at a diameter of 75 mm). In the model, water was assumes as bulk solvent. The agitation by impeller was simulated to estimate the mixing attributes during mixing using **Rotating Machinery, Turbulent Flow, k-ω model, Frozen Rotor study**. Agitation rate was simulated between 100 and 800 rpm. Velocity, shear rate, energy dissipation rate profiles were evaluated and linked to observed crystallization behavior.

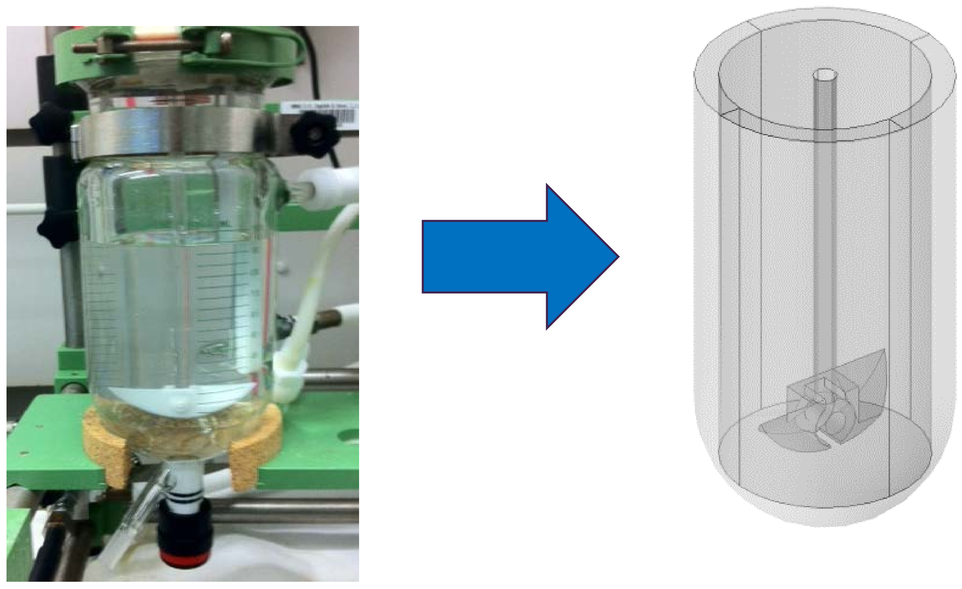

Figure 2. 3D geometry of laboratory reactor

Results:

Velocity, shear rate and specific dissipation rate increase with increasing agitation rate (Figure 3). This increase is observed also in the mean of specific dissipation rate; however, the coefficient of variance (standard deviation normalized by mean) does not change significantly (Figure 4), suggesting a uniform increase in energy dissipation rate across the reactor with higher agitation rate. It is also important to note that specific dissipation rate (and shear rate) is high particularly around the impeller blade. Possibly, such high rate of conversion of turbulence energy to thermal energy triggers nucleation, increasing the nucleation rate. Additionally, the high shear generated at fast agitation conditions may induce breakage of formed crystals and agglomerates, leading to smaller particle size.

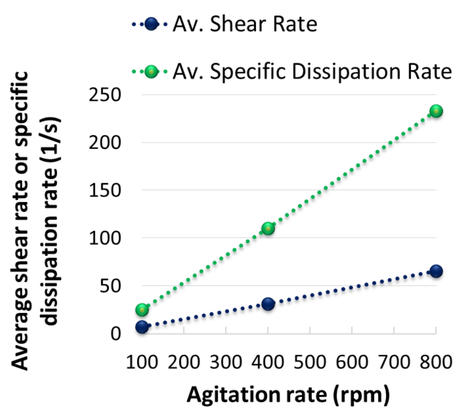

Figure 3. Trends in mixing attributes

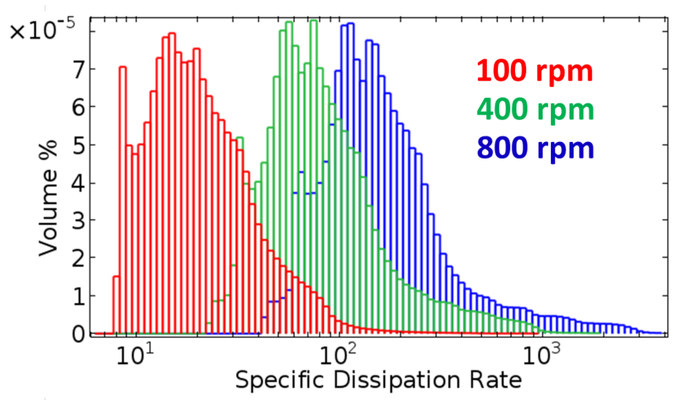

Figure 4. Specific Dissipation Rate Distributions

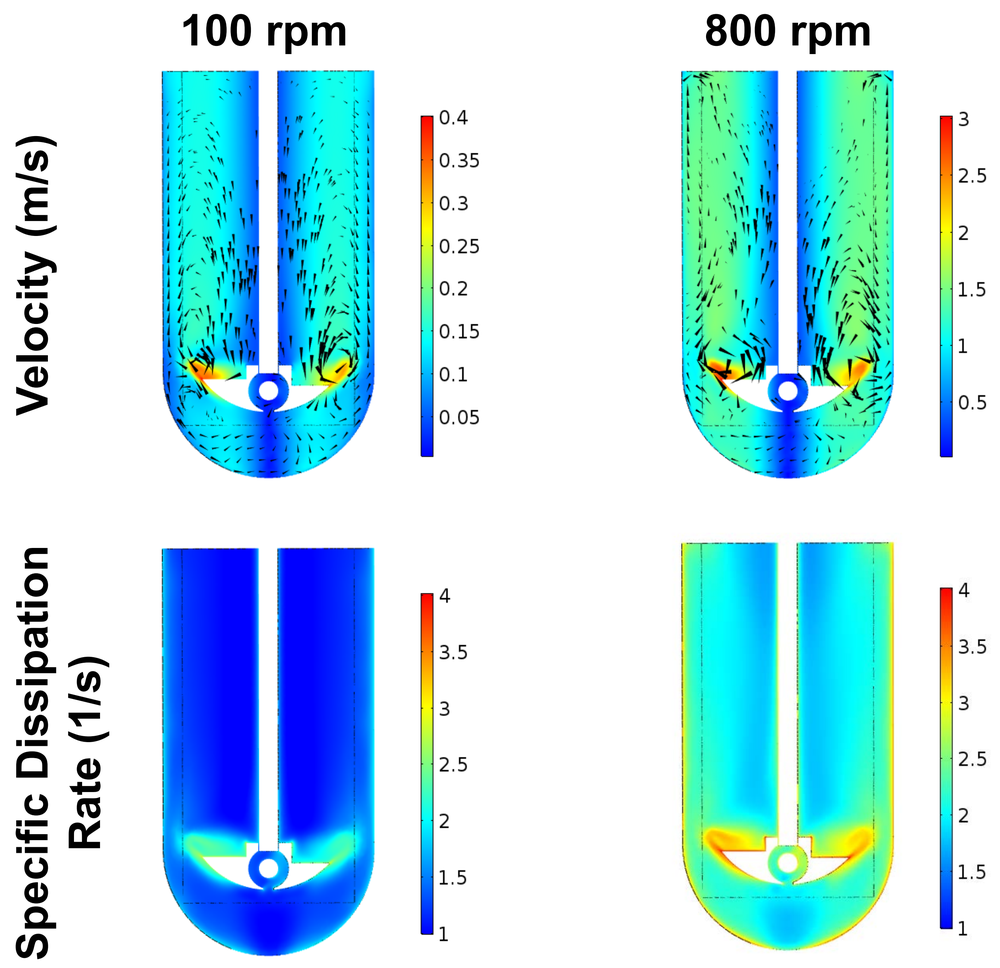

Figure 5. Velocity and specific dissipation rate profile across the reactor

Conclusion:

The issues related to mixing sensitivity in crystallization can be minimized by the optimization of process parameters, reactor configuration and mixing conditions, such as agitation rate, reactant feed rate and reactor configurations in batch reactors. COMSOL Multiphysics® provides a platform to study the effect of mixing in these processes and to optimize the mixing conditions for better control of the final drug substance quality.

References:

1. Bourne, John R. 2003. “Mixing and the Selectivity of Chemical Reactions.” *Organic Process Research & Development* 7(4): 471–508.
2. O’Grady, D.,. 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(7): 945–52.
3. Yu, Z.Q., 2005. “Effects of Operating Conditions on Agglomeration and Habit of Paracetamol Crystals in Anti-Solvent Crystallization.” *Journal of Crystal Growth* 279(3): 477–88.

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