Modeling Of Mixing-sensitive Pharmaceutical Drug Substance Production Processes In Batch Reactors

Fulya Akpinar, Benjamin Cohen, Jose Tabora,
Andrew Glace, Kathleen Lauser,
Federico Lora Gonzalez, Jacob Albrecht

Chemical Synthetics Development, Bristol-Myers Squibb

COMSOL CONFERENCE
2016 BOSTON

Bristol-Myers Squibb

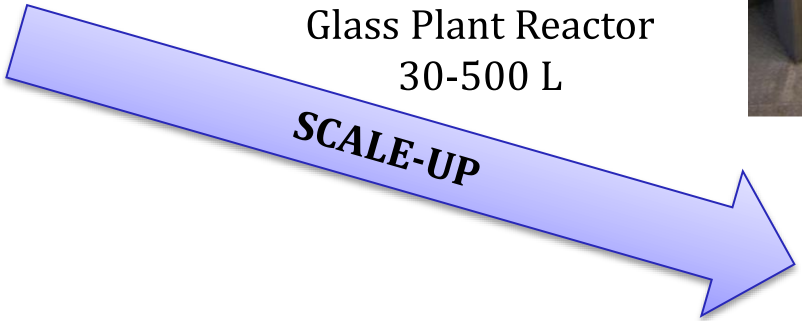
Impact of Mixing on Chemical Unit Operations in Pharmaceutical Industry

- Many chemical unit operations in drug substance production are performed in stirred tank reactors and are transport dependent. Therefore, they can be mixing sensitive.
  - Biphasic reactions
  - Extraction
  - Crystallizations
- Multiple mixing parameters must be considered during scale-up.
  - Reactor and impeller geometry
  - Shear rate
  - Specific energy dissipation rate
  - Power input per volume

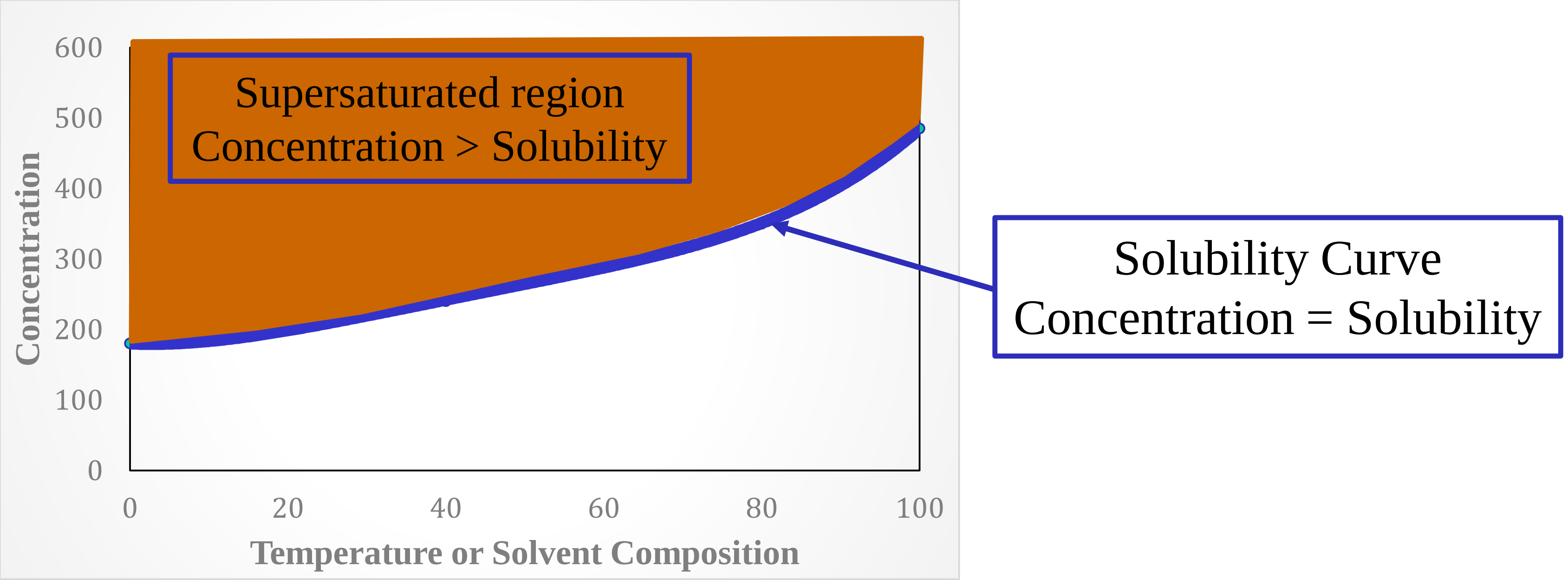
Lab Reactor
0.1-40 L

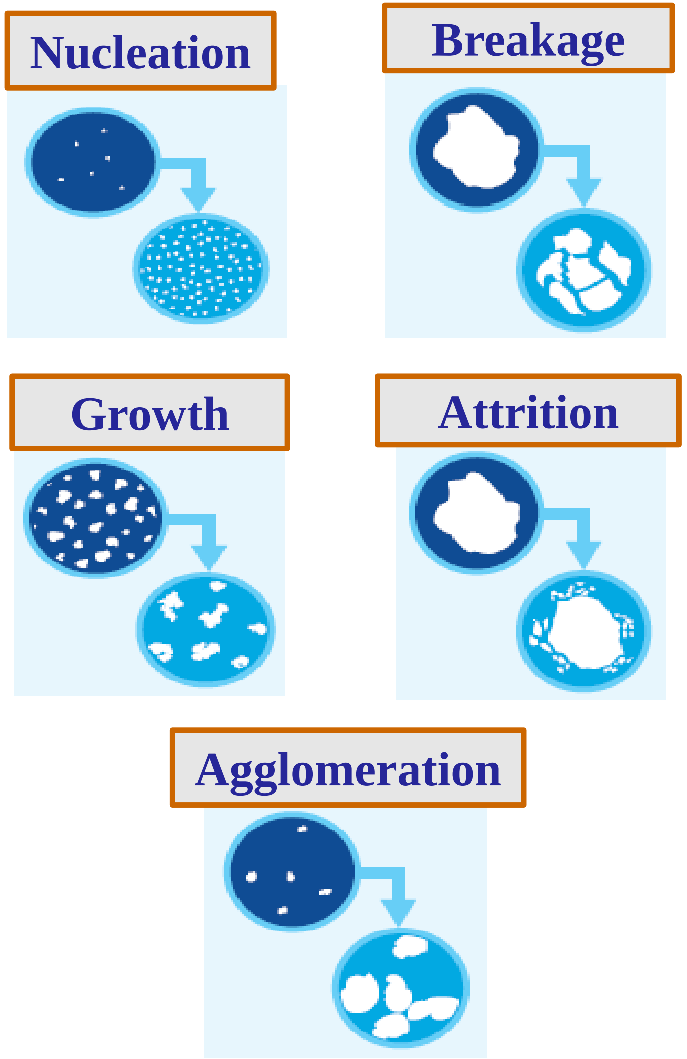
Glass Plant Reactor
30-500 L

Plant Reactor
1000- 40000 L



Case Study: Crystallization – Drug Substance Purification Process



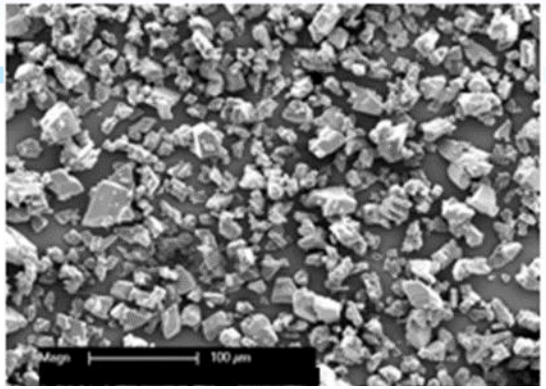


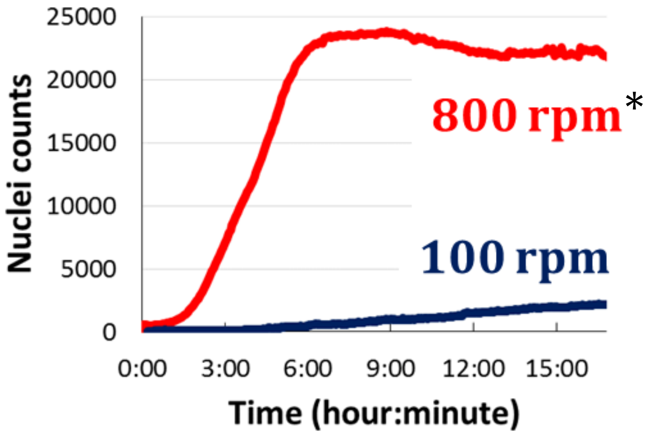
- Typical crystallization process operations:
  - Antisolvent* addition to achieve supersaturation
  - Heating to increase nucleation and growth kinetics
  - Cooling and aging for the completion of crystallization

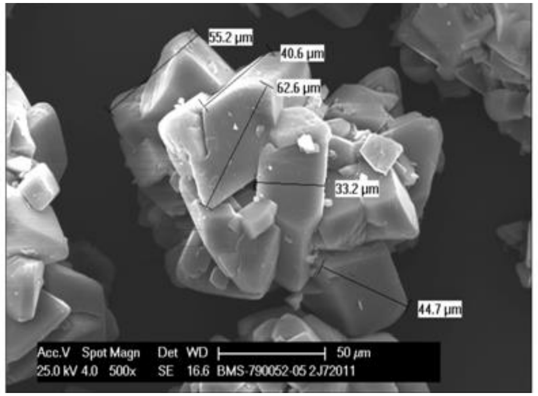
*antisolvent – solvent with low product solubility

Mixing Sensitivity in Crystallization

	Potential Consequences
Fast mixing	• Fast uncontrolled nucleation • Particle attrition • De-agglomeration







*rpm – rotations per minute

Bristol-Myers Squibb

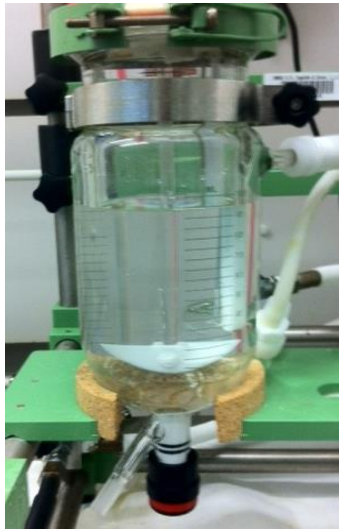
COMSOL Model to Assess Mixing Sensitivity in Drug Substance Crystallization

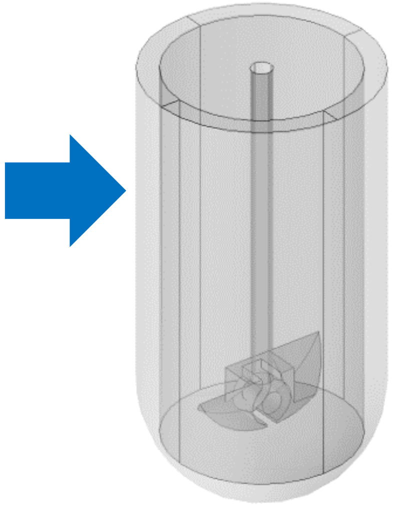
- Solve Navier-Stokes equation on the 3D reactor geometry
  - Rotating Machinery, Turbulent Flow k-ω model
    - Frozen rotor study – Reynolds-averaged NS
    - Time dependent study
- Account for specific reactor geometry and configurations
- Provide solution of the flow field to determine velocity, shear and energy dissipation rate profiles throughout the reactor
- Provide fast estimation of mixing attributes at scale
- Couple multiple physics
  - Flow
  - Reactions/transport of species
  - Heat transfer

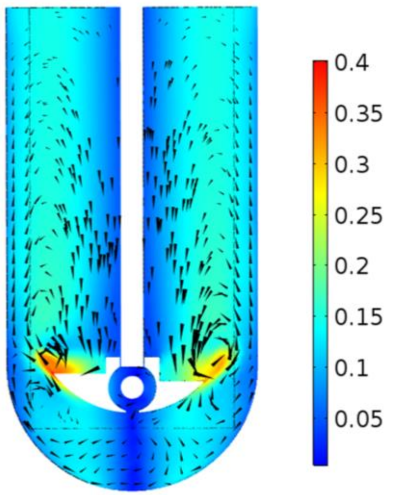
$$\frac{\partial \rho}{\partial t} + \nabla\cdot(\rho \mathbf{u}) = 0, \quad \text{----- Continuity Equation} \quad (1)$$

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u}\cdot\nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \mathbf{F} + \frac{\mu}{\rho}\nabla^2\mathbf{u}, \quad \text{----- Equations of Motion} \quad (2)$$

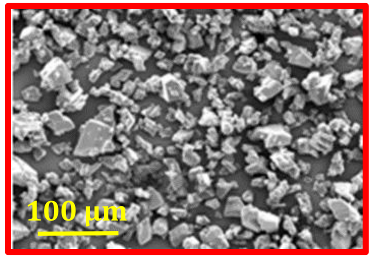
$$\rho\left(\frac{\partial\varepsilon}{\partial t} + \mathbf{u}\cdot\nabla\varepsilon\right) - \nabla\cdot(K_H\nabla T) + p\nabla\cdot\mathbf{u} = 0. \quad \text{----- Conservation of Energy} \quad (3)$$



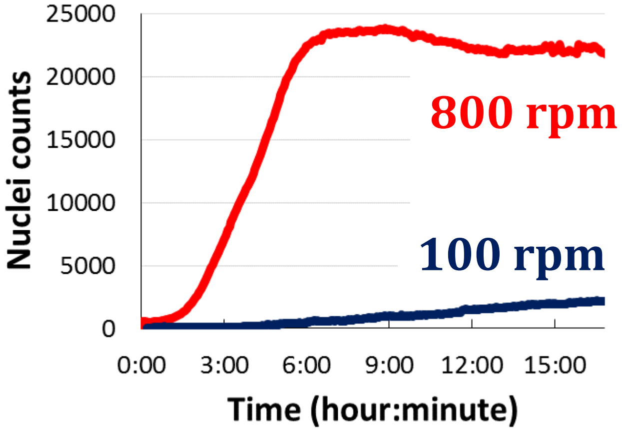


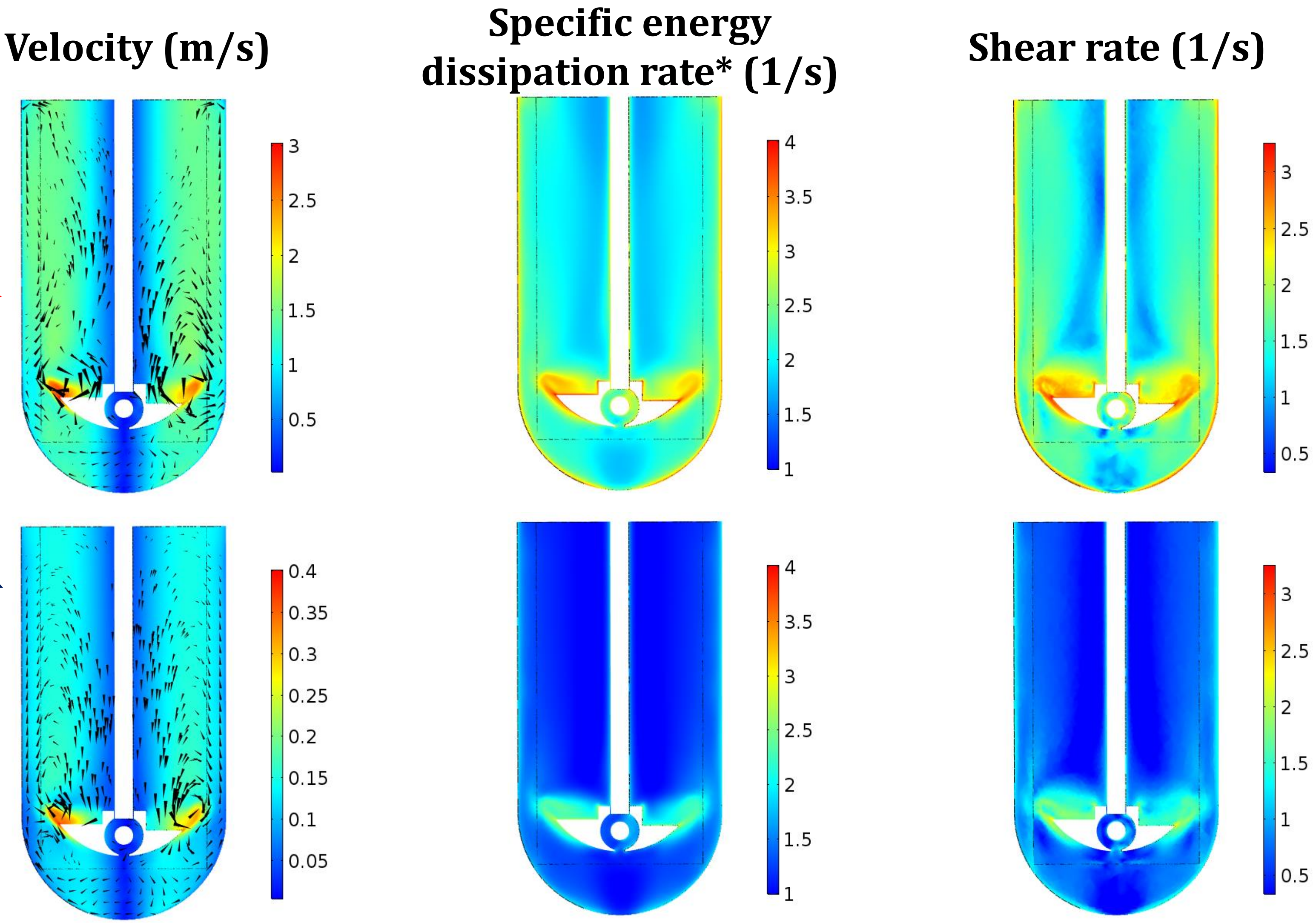


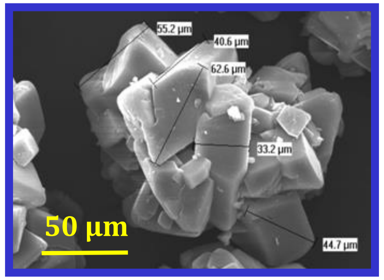
Mixing Attributes for Fast and Slow Mixing in Lab Reactor



- Fast nucleation
- Small particle size







- Slow nucleation
- Agglomeration
- Large particle size

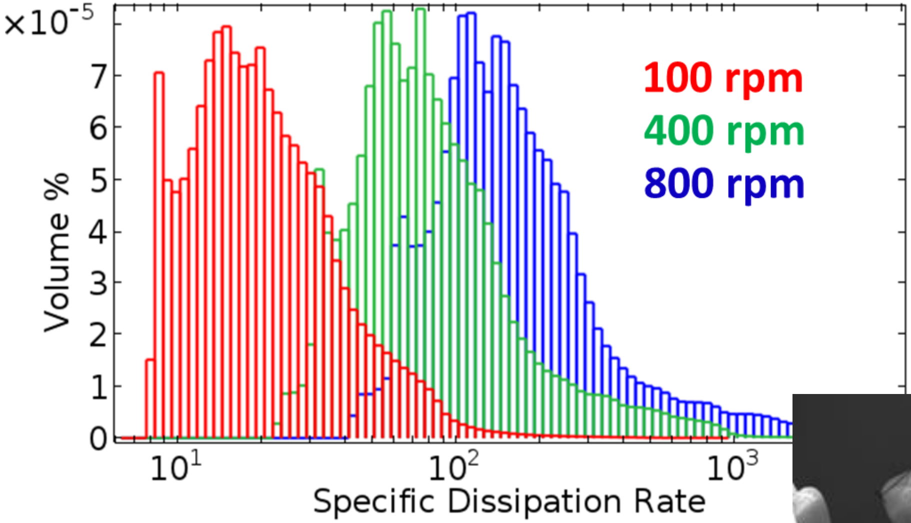
Bristol-Myers Squibb

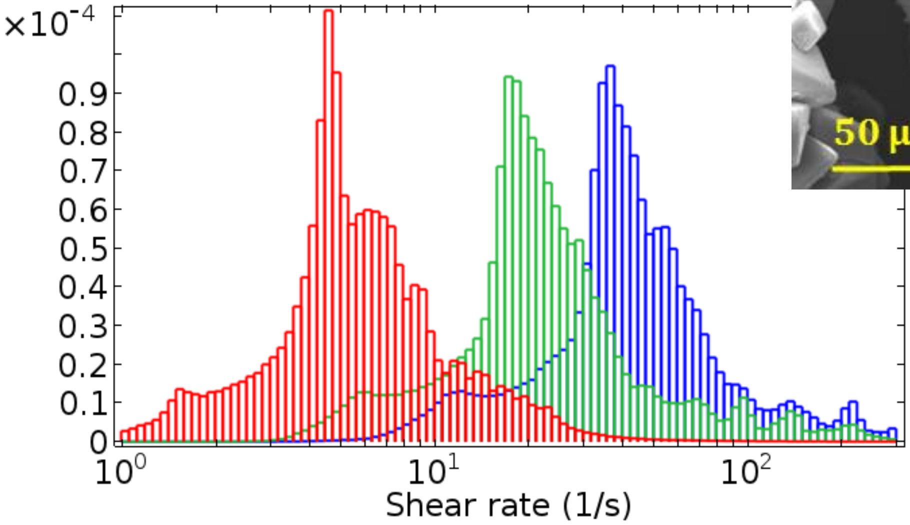
* Rate at which turbulent energy converts to thermal internal energy

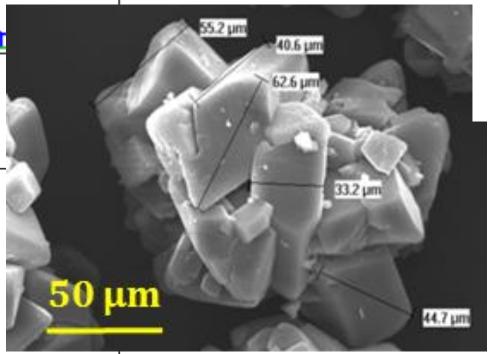
Shear Rate Correlates with Particle Size and Agglomeration Index

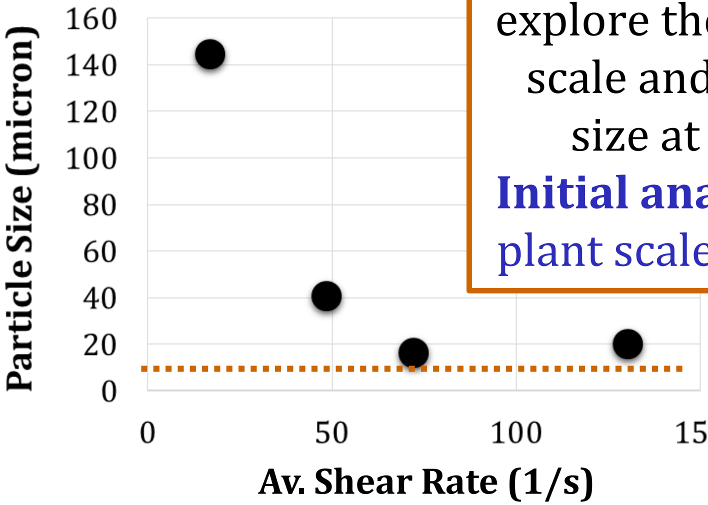
Next Step: Extension of COMSOL modeling to the plant reactors to explore the studied correlations at scale and to predict the particle size at manufacturing scale

Initial analysis: Low shear rate at plant scale – risk of agglomeration

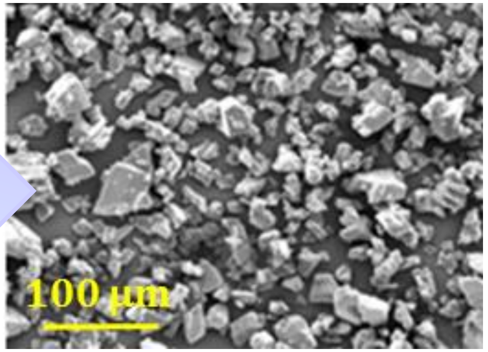


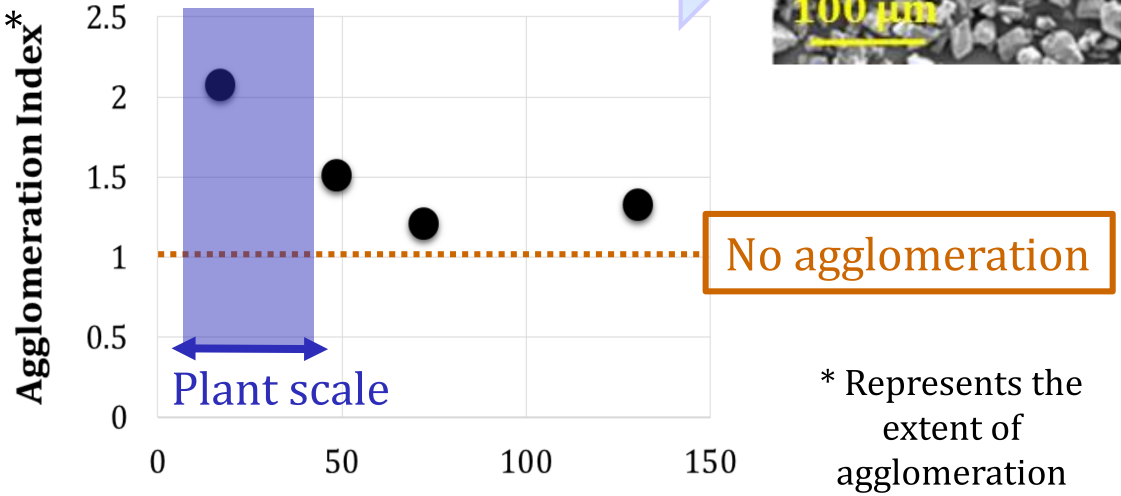






Particle attrition, breakage and de-agglomeration





* Represents the extent of agglomeration

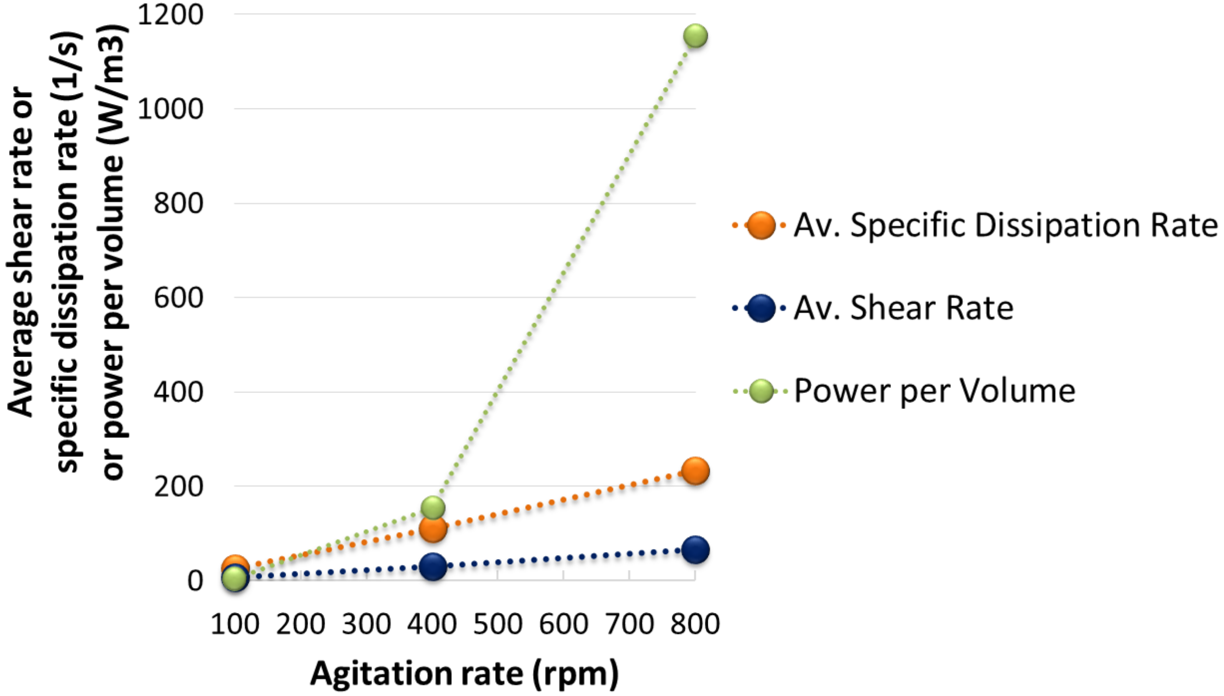
Bristol-Myers Squibb

Summary

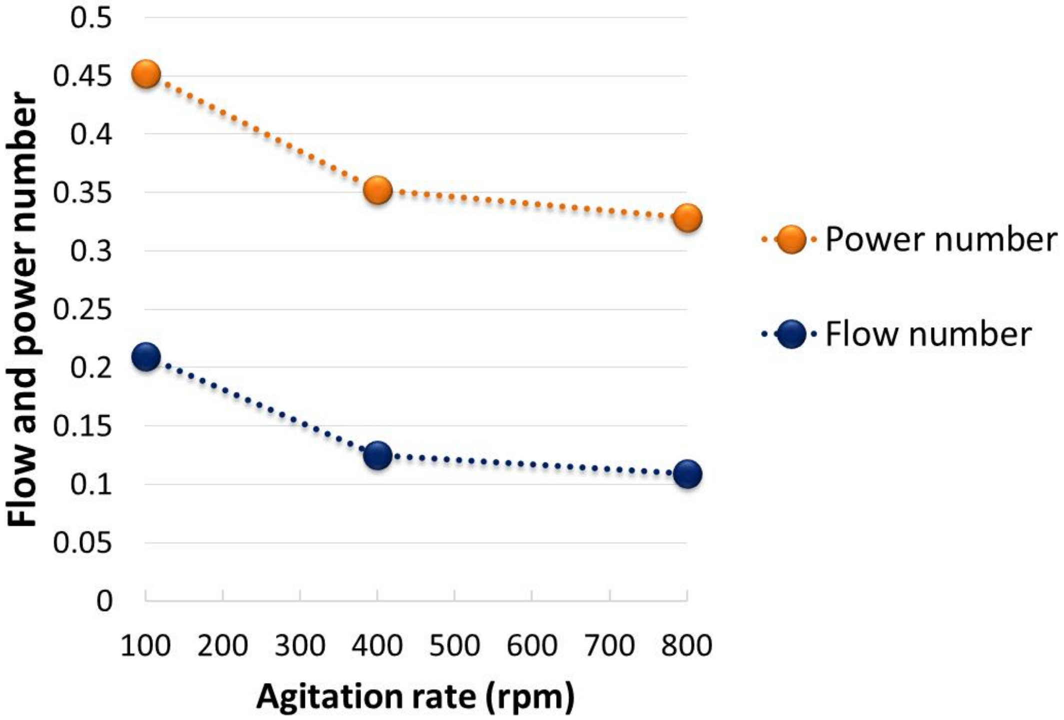
- High shear rate enhances de-agglomeration and particle breakage, reducing particle size and agglomeration index.
- COMSOL is helpful in estimating the mixing attributes that can be used to predict the crystallization process behavior and final drug substance particle properties.

THANK YOU FOR YOUR ATTENTION!

BACK-UP SLIDES

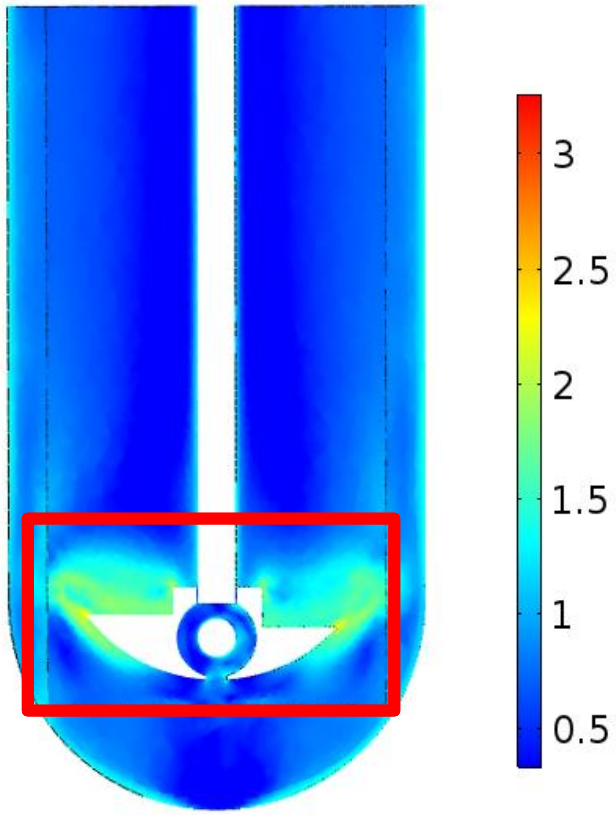


1200
1000
800
600
400
200
0
Average shear rate or specific dissipation rate (1/s) or power per volume (W/m3)
100 200 300 400 500 600 700 800
Agitation rate (rpm)
Av. Specific Dissipation Rate
Av. Shear Rate
Power per Volume



0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Flow and power number
100 200 300 400 500 600 700 800
Agitation rate (rpm)
Power number
Flow number

Correlation at Scale-up



High shear zone-to-Total Volume ratio
4L Lab reactor = 0.18
1L Lab Reactor = 0.11