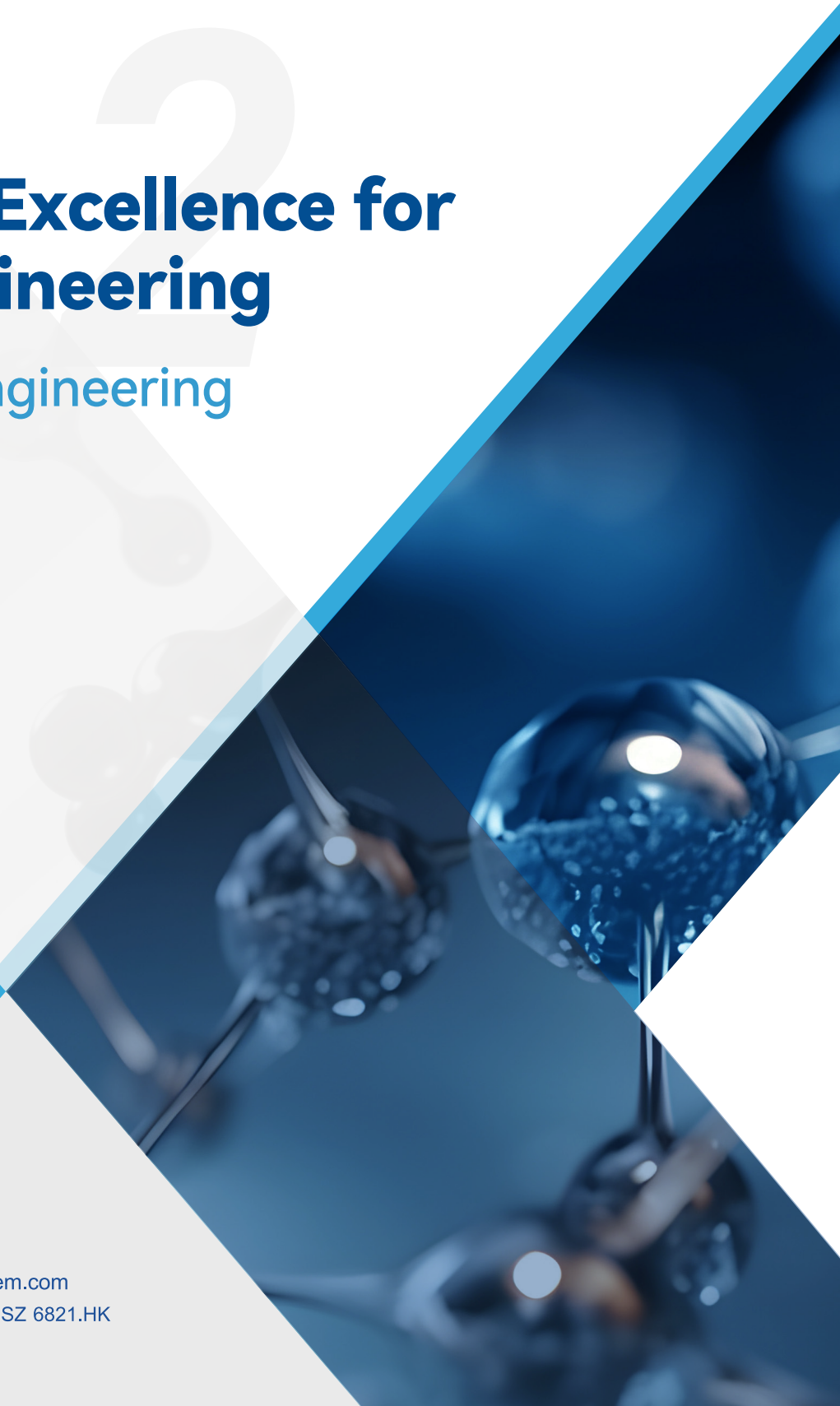
ASYMCHEM

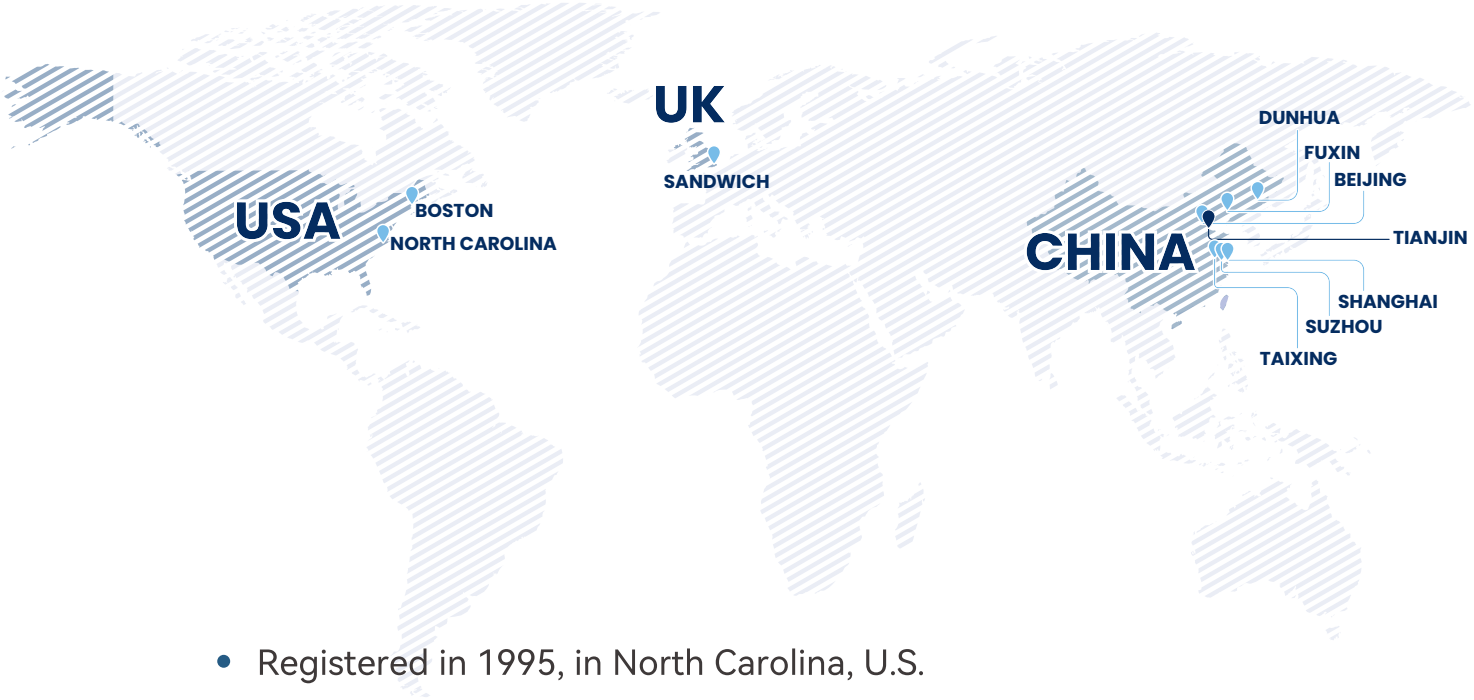
Institute of Excellence for Process Engineering

Crystallization Engineering



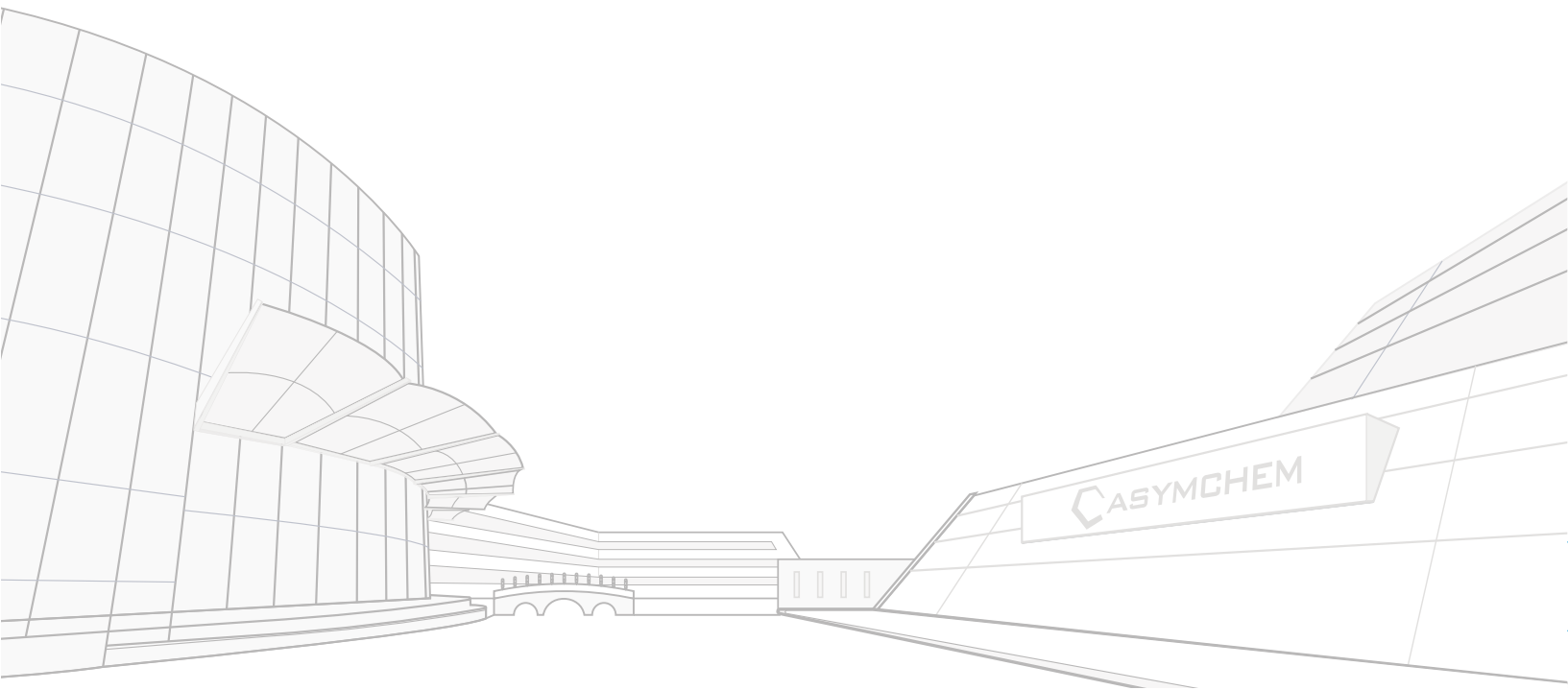
www.asymchem.com

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- Registered in 1995, in North Carolina, U.S.
- First China site established in 1999
- A+H: Shenzhen Stock Exchange listed company (SZ.002821)

  Hong Kong Stock Exchange listed company (HK.006821)
- China's largest commercialized stage chemical drug CDMO



Introduction of Crystallization Engineering

Crystallization Engineering team has more than 30 members and 90% of the team have the Master's/Doctor's degree. We have rich R&D experience of crystallization process development and optimization in small molecules and chemical macromolecules. We complete 500+ R&D projects/steps from domestic and international clients every year, providing professional R&D services for process optimization and eliminating scale-up risks (such as form & PSD control, filtration & drying efficiency, wall sticking, product solvent residue and purity). The team is committed to providing fast and high-quality technical solutions and scale-up technology transfer.

Crystallization Technical Service and Solutions

Small Molecule

Specification	Form, PSD, chiral, purity, solvent residual
Manufacture	Oiling, wall sticking, filtration and drying
Cost	Yield improvement, solvent substitution, process simplification, engineering enhancement

Macromolecule

Peptide	Instead of lyophilization
Oligo	Instead of chromatography
Polymer	Filtration improvement
Linker	

Bulk Chemical Products

Recovery of Valuable Materials	Form, PSD, chiral, purity, solvent residual
Chemicals Agrochemicals Additives	Cost reduction and process optimization Product specification: particle size, dissolution rate, stability

Powder Properties

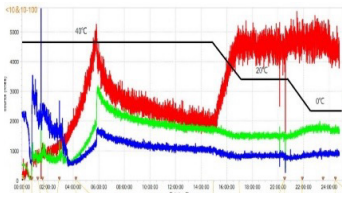
- Formulation morphology and flowability improvement
- API + excipients co-precipitation process development

Registration Required Study

- Complete solutions and R&D services for API registration

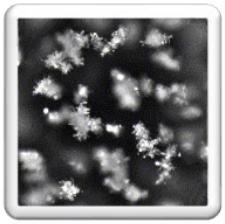
Crystallization Capability and Technology Platform

PAT-based Process Assessment & Optimization

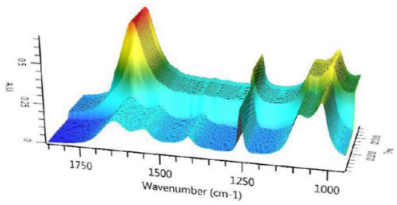


FBRM technology for in-situ particle size monitoring



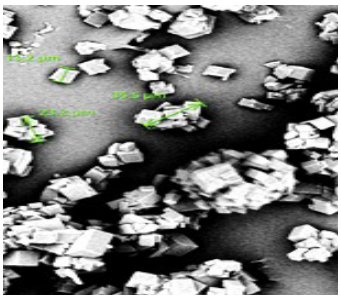


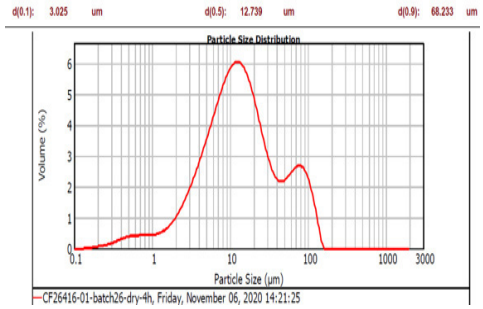
Easy-viewer for morphology monitoring

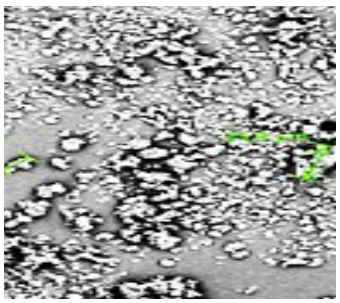


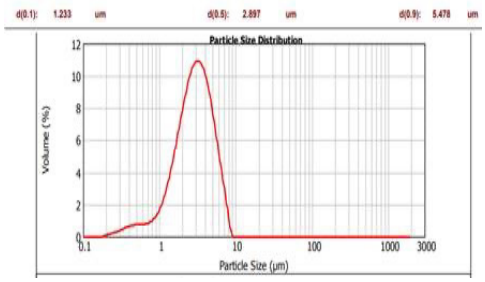
PAT-React IR

Particle Size / Flowability Improvement



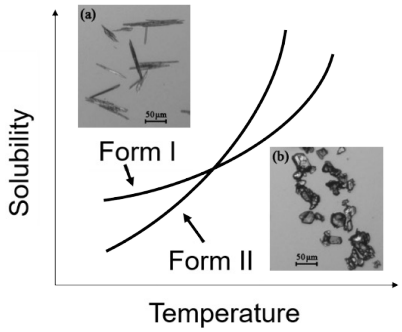




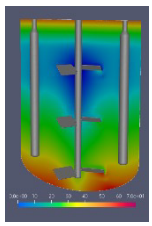


Crystallization + Milling for PSD control and flowability improvement

Polymorph Control Study

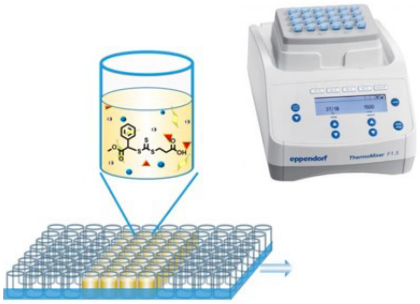


Technology Transfer & Scale-up





High-throughput Screening for Solvent Selection and Polymorph Screening



- High-throughput screening for solubility measurement and process assessment
- Reduce process development time by about 1/3
- Material and solvent requirements are reduced by 50%-70%

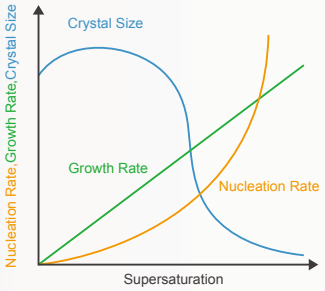


Case Studies

Case 1: Productivity Improvement and Cost Reduction Based on Crystallization Dynamics

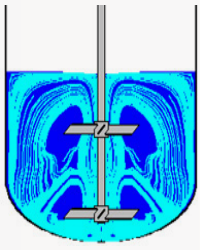
Goal

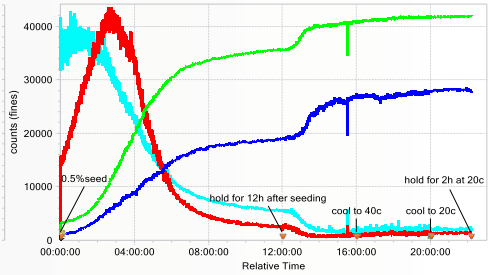
1. Improve productivity and process stability
2. Prepare the target crystal form
3. Solve mixing and filtration problems



Super-saturation determines nucleation and growth rate

- **Multiple 100+kg batches of successful production**
- **Solvent use reduced by 24%**
- **Operation time reduced by 69%**





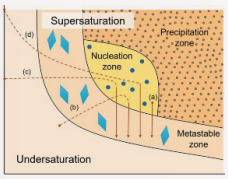
Simulation and Calculation

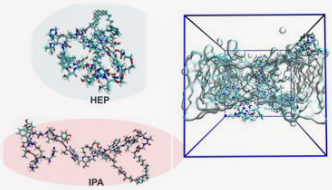
1,000L Production ← **Lab Scale Process Development**

Case 2: Platform of Macromolecule Precipitation / Crystallization Development

◉ Macromolecule Recipitation Platform

- **Precipitation process instead of lyophilization and chromatography, significantly improve productivity and efficiency**
- **Solvent screening and assessment supported by simulation**





High-throughput screening + simulation

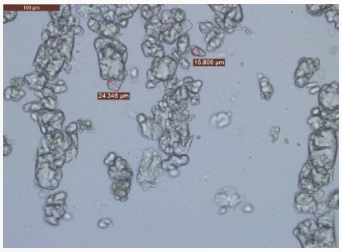


PAT-based process assessment & optimization



Technology transfer

◉ Case of Precipitation Development





Successfully developed precipitation process with large particle solid product with no oil out, no wall sticking, and no need of lyophilization.

◉ Platform Value

- **Promote process sustainability**
- **Reduce R&D time and improve efficiency**
- **Lower energy consumption and production time**

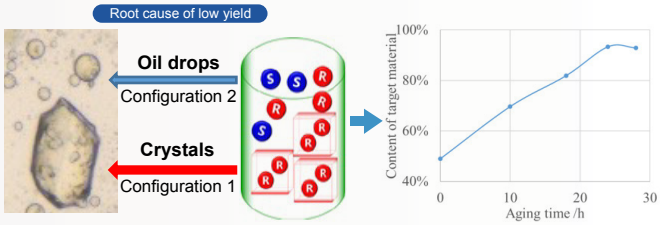
Case 3: Dynamic Chiral Resolution and Crystallization Optimization

1. Issues of the Original Procedure

Lower yield and fluctuates between 60% and 80% in manufacturing

2. Mechanism Investigation

1.Two major chiral configurations
2.Different crystallization behavior
✓Configuration 1 → crystals
✓Configuration 2 → oiling out



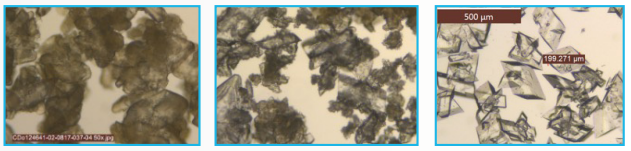
Identified the configuration transformation mechanism from 2 to 1

Investigations of effects of aging time and solvent volume on dynamic configuration transformation

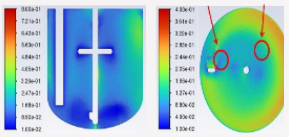
3. Further Optimizations of the Procedure

- **Lower temperature promotes solidification**

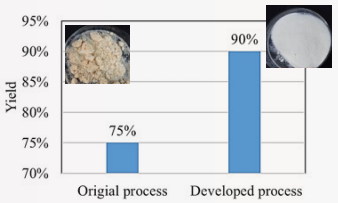
30°C, Lots of oil ➡20°C, More crystals ➡ 5°C, No oiling



- **Lower addition rate and improved meso-mixing design enabled complete de-supersaturation**



CFD simulation and meso-mixing analysis

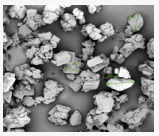


- Yield of manufacturing increased by 15% (from 75% to 90%) with good process robustness.
- Product with desired morphology was achieved

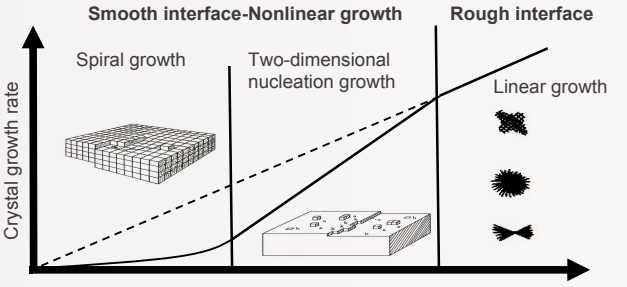
Case 4: Crystal Flowability Improvement by Mediated Crystal Growth

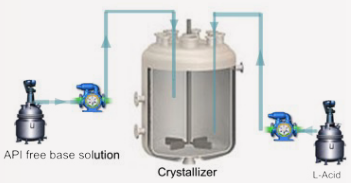
1. Issues of the Original Procedure

1. Issues of agglomeration
2. Flowability and non-agglomeration morphology required by downstream formulation

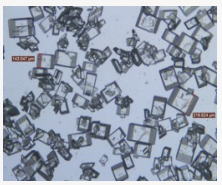


2. Seeding and Supersaturation Optimization



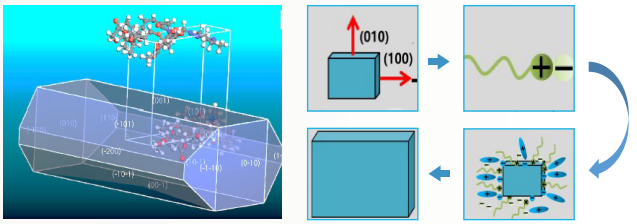


Dual stream addition generate low supersaturation



Much less agglomeration but not enough

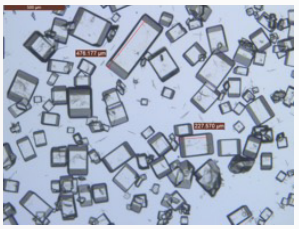
3. Additive Affects the Secondary Nucleation



Additive on crystal surface occupied the nucleation station which inhibited the secondary nucleation and affected growth rate, therefore inhibited the agglomeration.

Further Improvement

4.Project Outcomes



1. Well-developed morphology and flowability without agglomeration on scale-up
2. Bulk density increased from 0.38 to 0.56g/ml



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