

Continuous Crystallization within the ResonantAcoustic® Mixing Platform



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Objectives

- Understand the key challenges in crystallization processes
- Benefits of continuous crystallization processes
- Demonstrate surrogate energetic crystallization in ResonantAcoustic® Mixing Vessel
- Development of ResonantAcoustic® Continuous Crystallizer



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Why Crystallization

- **Crystallization:** Formation of ordered solid from liquid solution
- **Key Industrial Applications:**
 - **Pharmaceuticals:** Purification and Separation of APIs
 - **Chemical Production:** Separation and isolation of products from reaction mixtures
 - **Food and Beverage Industry:** Formation of salt and sugar crystals
 - **Semiconductor Manufacturing:** Growth of high-purity single crystals
 - **Biotechnology:** Protein crystallization for structural analysis
 - **Wastewater Treatment:** Removal of impurities from industrial effluents.



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Types of Crystallization

- Natural Crystals:
 - Formed in nature over long period of time
 - Quartz, Diamond, Rock Salt
- Artificial Crystallization:
 - Controlled process for specific properties
 - Goal is uniform, highly pure, defect free crystals
- Methods:
 - Cooling Crystallization
 - Anti-solvent Crystallization
 - Evaporative Crystallization
 - Reactive Precipitation

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The Crystallization Process

Key Factors Influencing Crystallization:

- Temperature
- Solubility
- Concentration
- Cooling rate
- Impurities

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Crystal Nucleation and Growth

- Crystal Nucleation: Initial Nuclei formed in solution or on surfaces
- Crystal Growth: Layer-by-layer incorporation of new molecules into the crystal lattice

Key factors to control crystal Nucleation and Growth:

- Pressure
- Temperature
- Supersaturation
- Seeding/additives
- Proper Mixing

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Continuous Flow Crystallization

Motivation:

- Improved Product Quality
- Eliminate Batch Variability
- Integration of Process Analytical Technology
- Automation
- Process Intensification
- Scale-up
- Safety

Current Industrial Methods:

- Mixed-Suspension, Mixed Product Removal Crystallizer
- Fluidized Bed/Draft Tube Baffle Crystallizer

Advanced Methods:

- Tubular Flow Crystallizer
- Segmented Flow Crystallizer
- Oscillatory Flow or Oscillatory Baffle Crystallizers



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RAM Continuous Crystallization Goals

- Perform crystallization in a continuous RAM flow setup
 - Better control, repeatability, less waste
- Flexible to Multiple Crystallization Types
- Achieve Crystal Size Control
 - Goal: 20% narrower CSD
- Future Goal: Integrate Process Analytical Technologies (PATs)
 - Ultrasonic TOF, In-line Particle Measurement and Visualization, RAMAN spectroscopy
- Fundamental Questions:
 - Impact of key process variables (Flowrates, T, P)
 - Impact of RAM-specific variables (Acceleration, gas-to-liquid ratio)
 - Morphology differ between batch and continuous modes?



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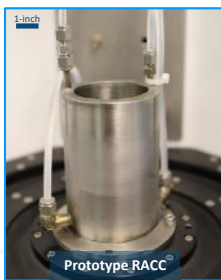
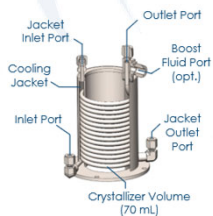
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Continuous Crystallizer Design

Continuous Crystallizer Prototype Design:

- Optimized for Cooling Crystallization
- Saturated solution fed through coil
- Jacket supplied with coolant
- Slurry product filtered



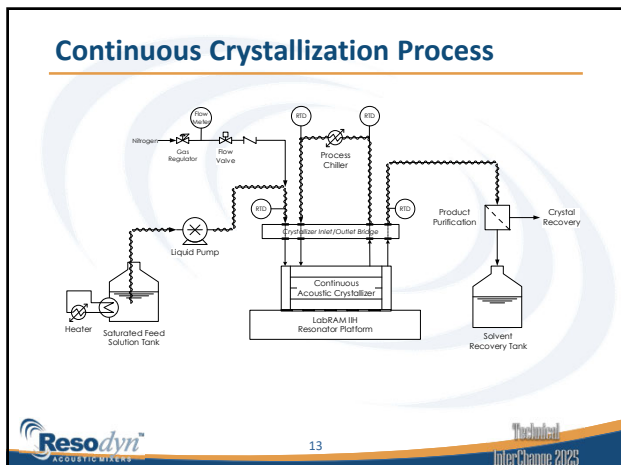
Crystallizer Volume (70 mL)



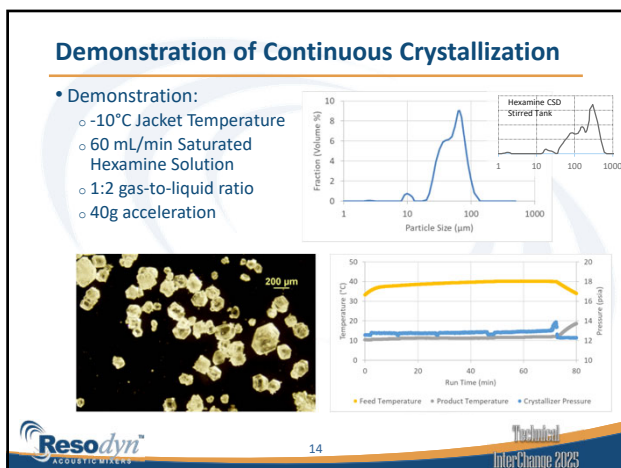
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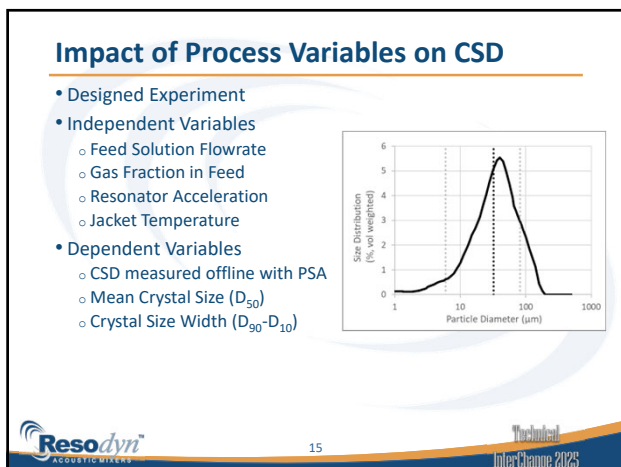
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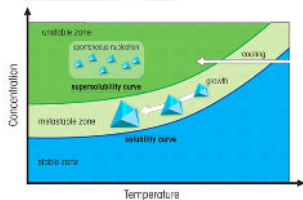


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Crystal Growth Mechanisms Continuous RAM



- Large ΔT :
 - Spontaneous Nucleation, Large number of nucleation sites, Fast Solute Depletion, Small crystals
- Small ΔT :
 - Slow growth within the metastable zone, larger crystals

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Continuous RAM Crystallization Summary

Key Accomplishments:

- Improved the durability with boost fluid addition to outlet of crystallizer
- Successful demonstration continuous crystallization of hexamine
- RAM Crystallization achieves a 75% Reduction in CSD Width
- Ability to control mean crystal size by adjusting jacket temperature

Further Opportunities:

- Further Optimization of Slurry Product Flow Dynamics
- Integration of PATs
- Demonstration of different types of crystallization
- Integrate seeding and polymorph control

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Thank you for your time
and attention.



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