

PAT for Drug Substance Particle Size Monitoring - A Process Development Case Study

BMS PAT Team

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PAT Applications at BMS in API Process Development

		NIR	Raman	FTIR	FBRM
Reaction Monitoring	End Point Determination	√	√	√	
	Kinetics & Mechanism	√	√	√	
	Control of Selectivity	√	√	√	
Crystallization	Onset of Nucleation		√		√
	Crystal Size				√
	Crystal Polymorph	√	√		
Filtration	Particle Size				√
	Particle Polymorphism	√	√		
Drying	End Point Determination	√			
	Particle Size				√
	Particle Polymorphism	√	√		
Milling	Particle Size			√	√
	Particle Polymorphism	√	√		

- **Issues**
- **Use of PAT in**
 - Monitoring PSD during crystallization
 - Monitoring PSD during downstream processing
i.e. filtration, drying
 - Scale up assessment

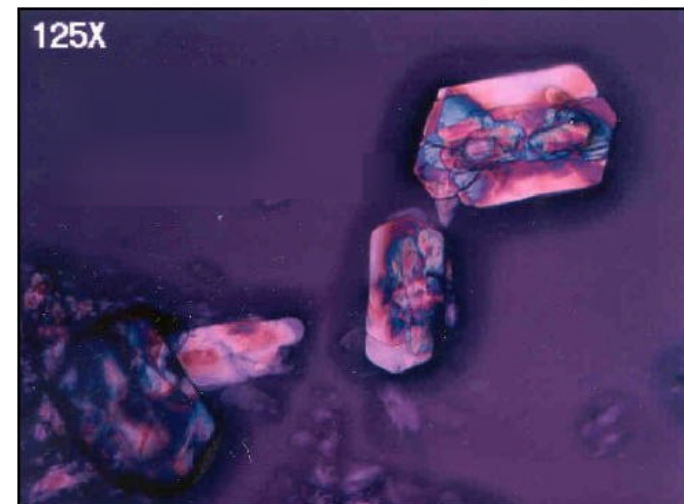
Issues for Product A

During Formulation

- **Dusting**
- **Equipment dependence**
- **Variability of binder amount**

Post API Synthesis

- **Dryer-dependent performance of API**
- **No analytical method to judge performance except final dissolution testing**



Blame Game

Is it the API ?

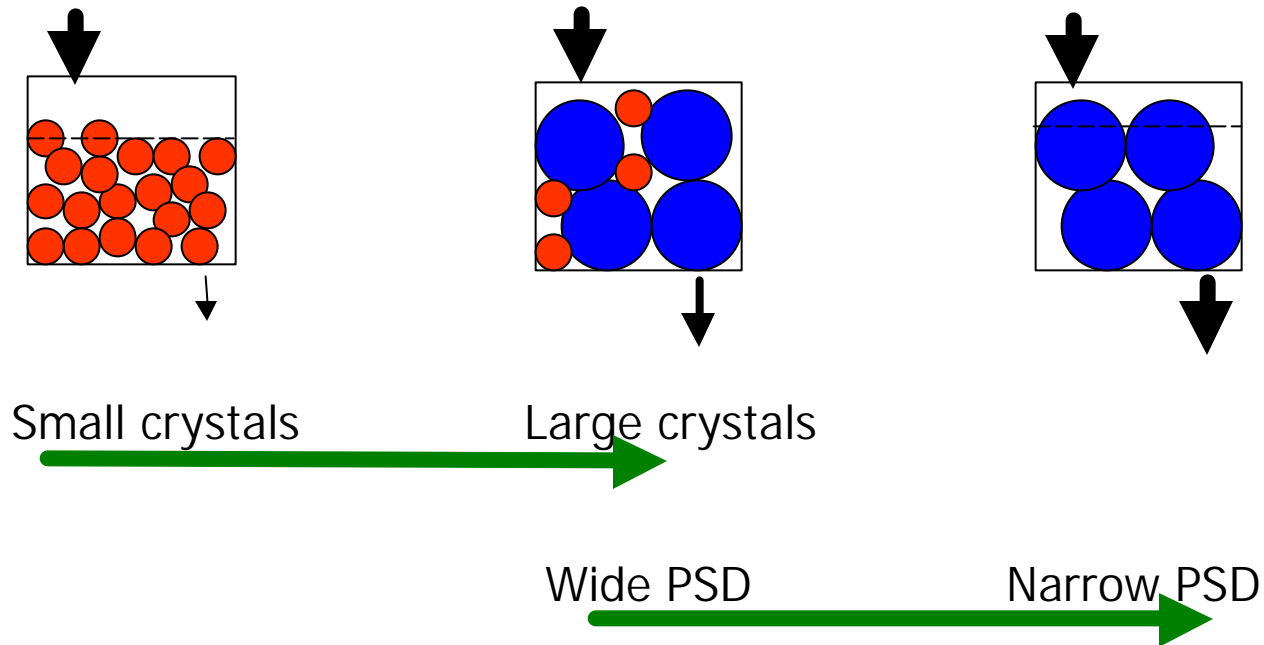
- Process chemistry changes (impurities?)
- Solvent system changes
- Crystallization protocol changes
- Different isolation equipment

Is it the formulation ?

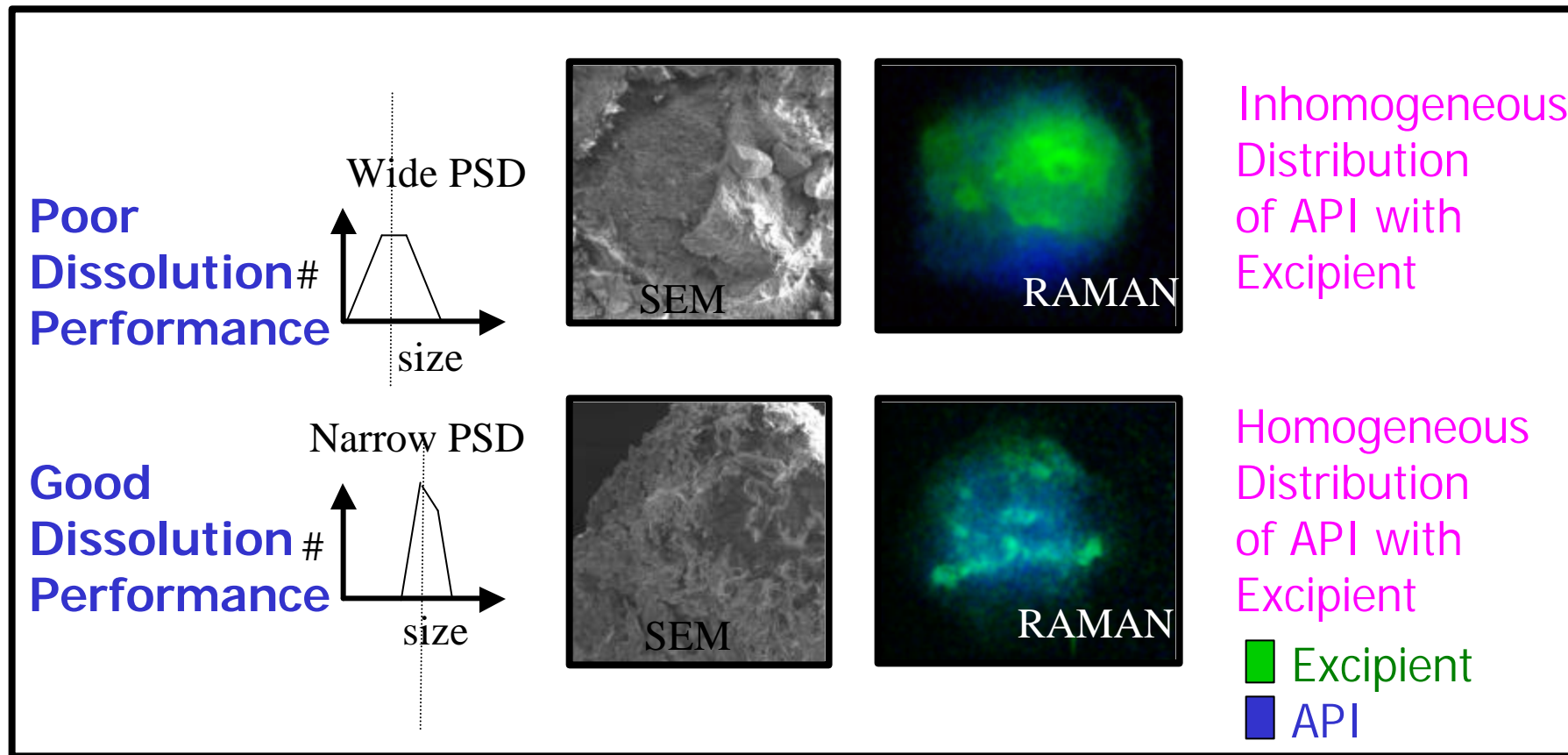
- Robust process for slight variation in API
- Formulation process issues

Impact of Crystal Properties On Isolation/Washing

Improvement in isolation performance



Impact of Crystal Properties on Formulation

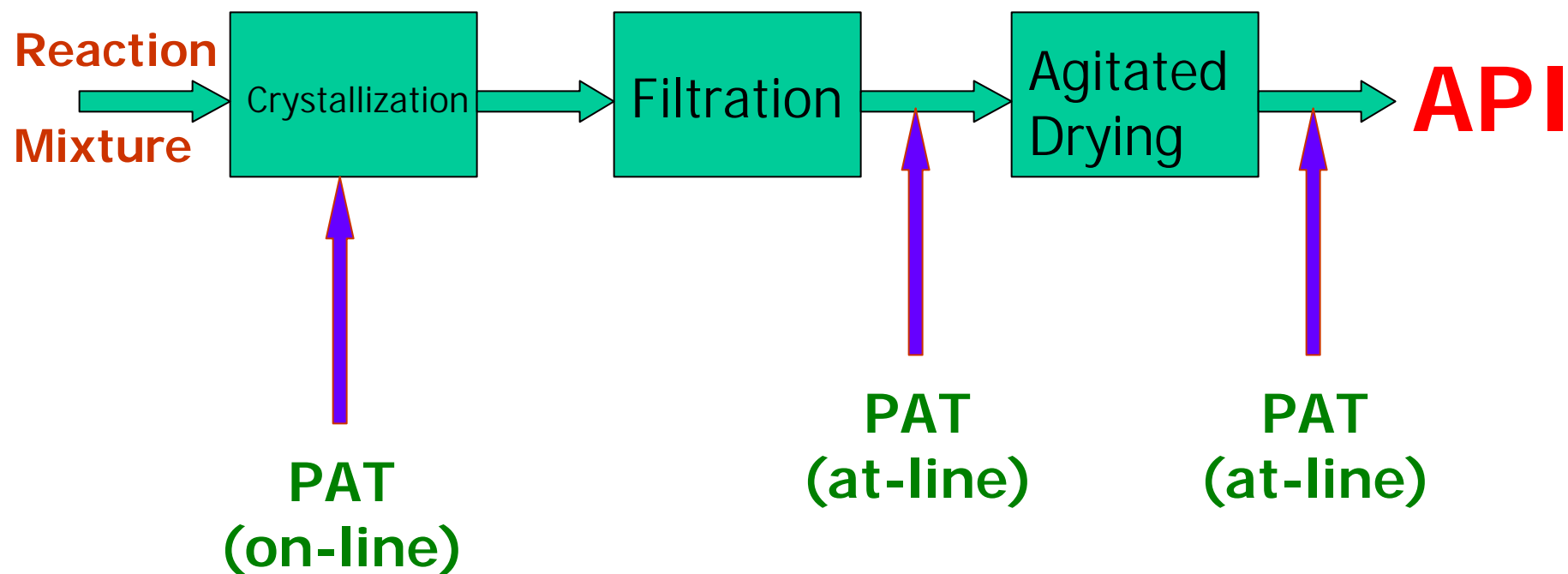


Narrower particle size distributions (PSD) minimize segregation problems during mixing, rendering a more homogeneous distribution of components in the final product

Crystallization Protocol

- 5% Seed
- Controlled Addition of Sulfuric Acid to a Solution of Free Base
- Precipitation of Sulfate Salt

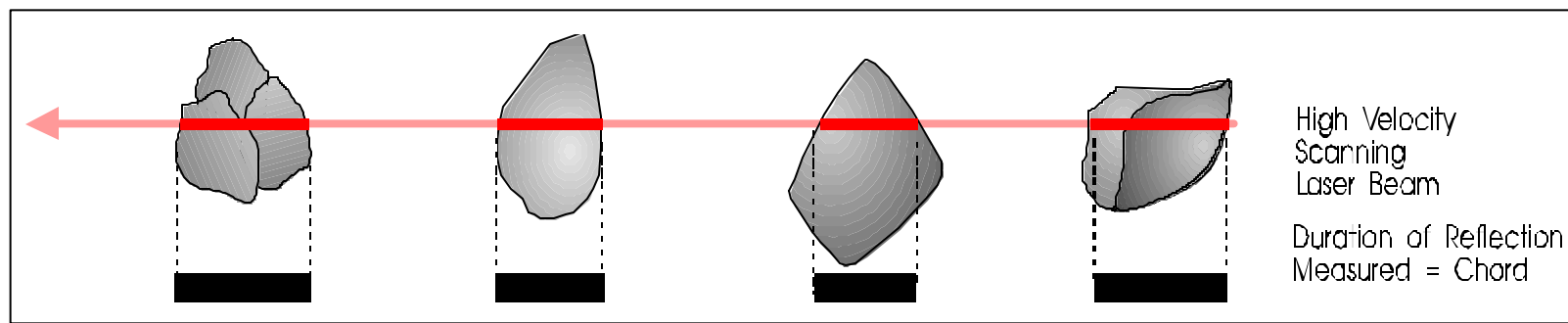
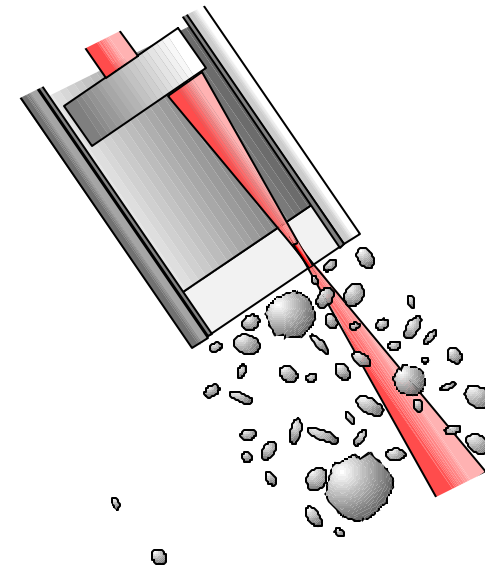
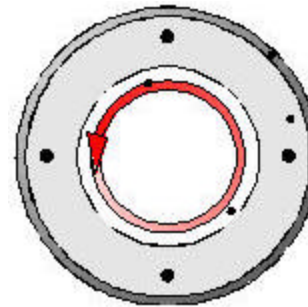
PAT in API Process Development



FBRM[®] (Focused Beam Reflectance Measurement)

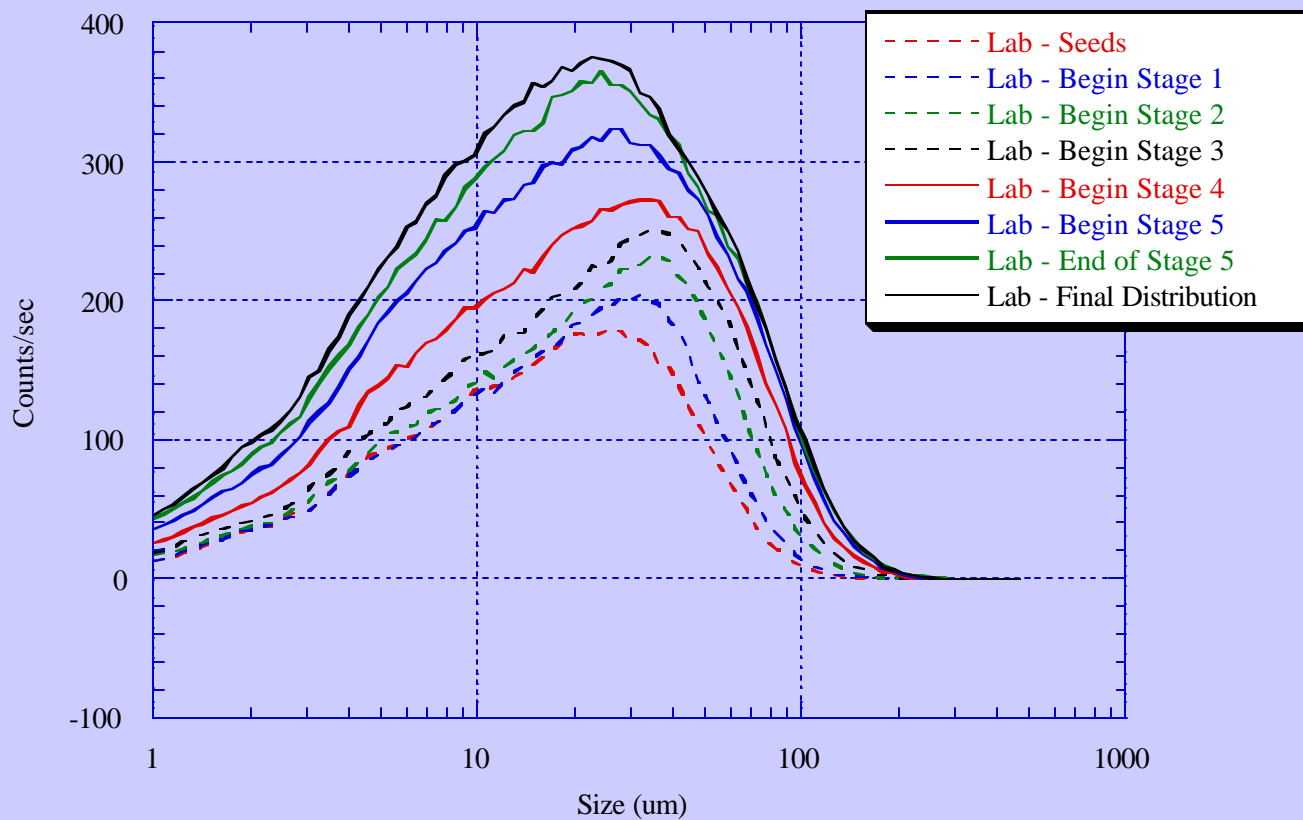
Lasentec[®] FBRM
provide **in-process**
and **real-time**

- Particle size
- High solids concentration
particle count



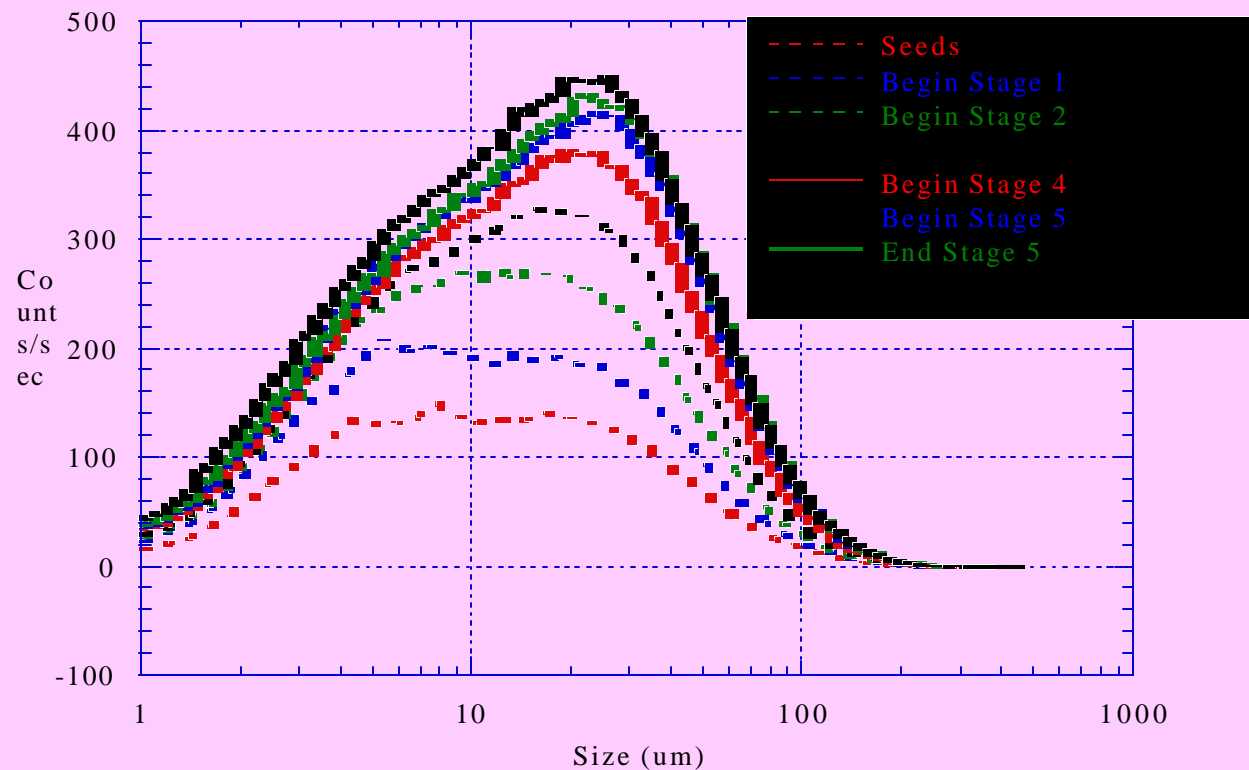
Lab Scale Crystallization (15 L)

Particle Size Distribution



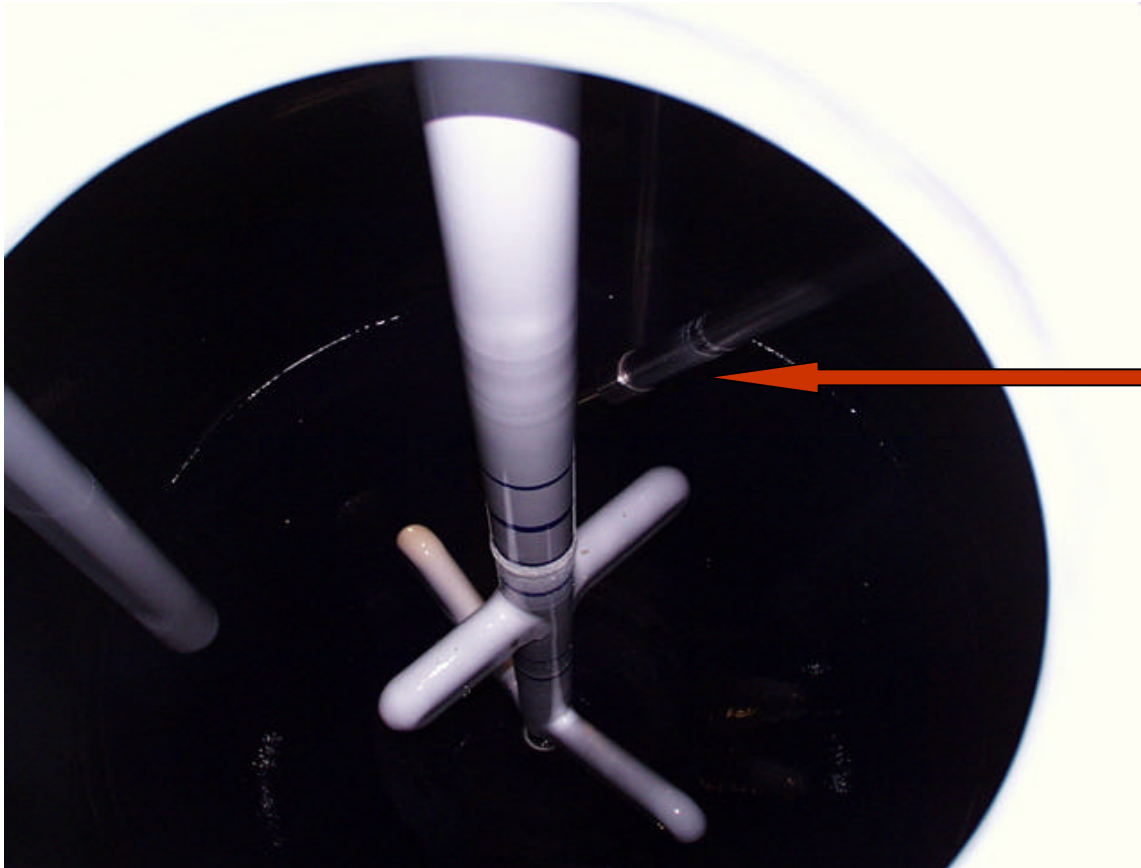
Results at Pilot Scale (1400 L)

Particle Size Distribution



All stages - Increase in number and size of particles

Lasentec Probe Installation

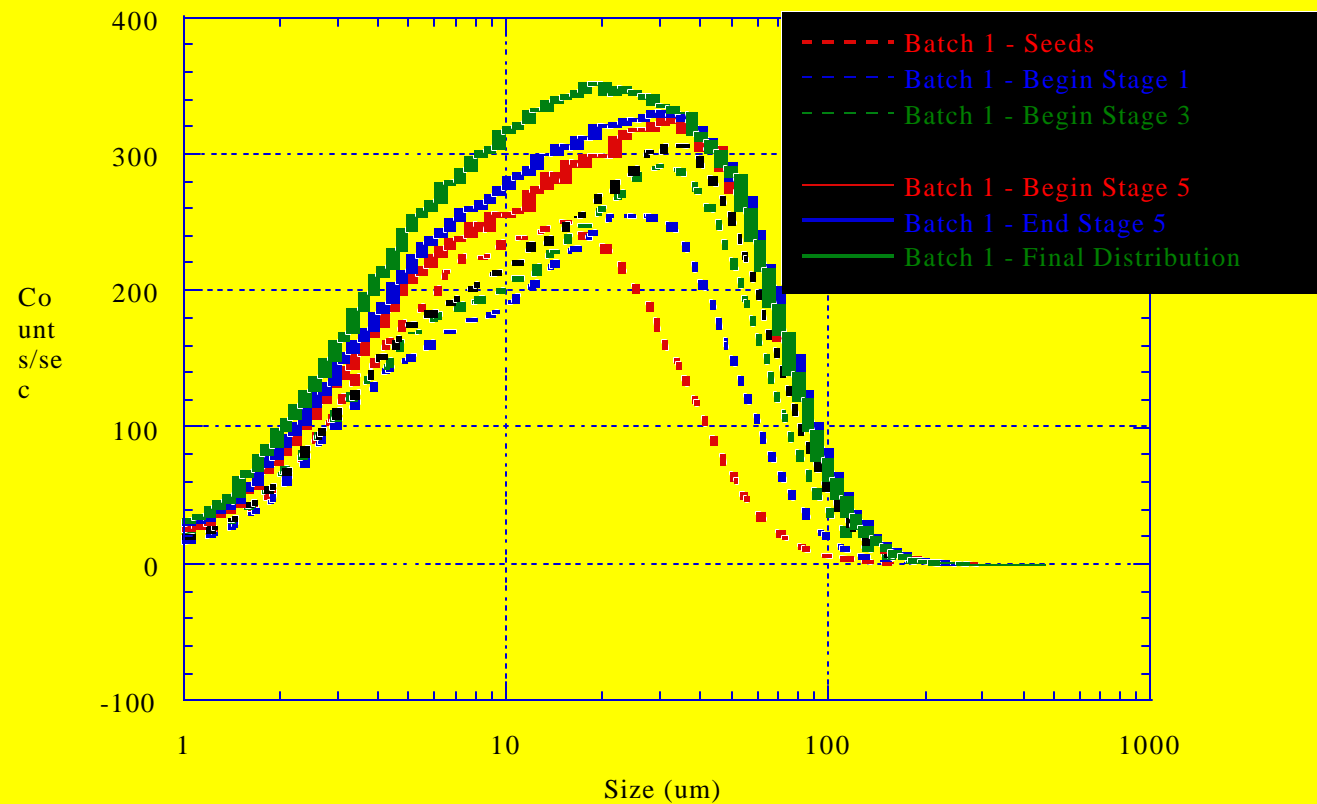


**Probe is in the
area of good
mixing -**

**probe window
constantly
swept with the
batch**

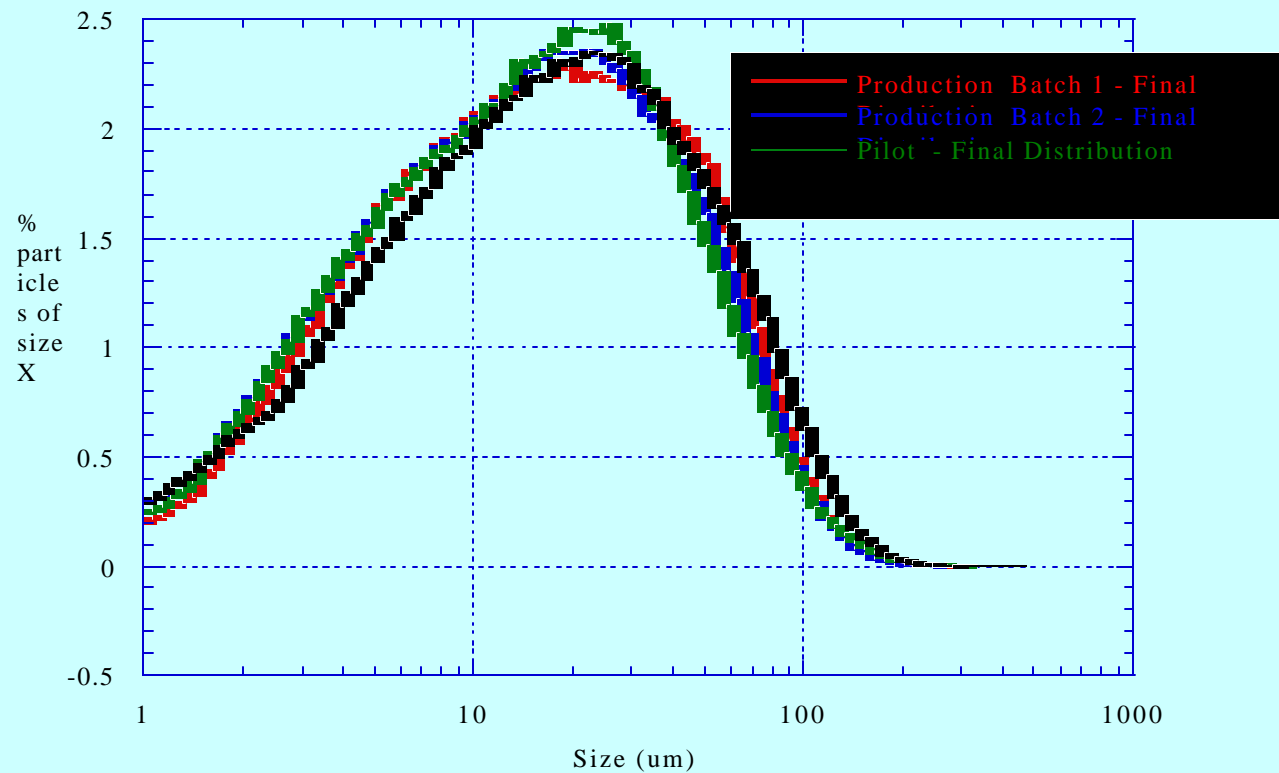
2500 L Crystallizer at Pilot Scale

Production Scale Results (4000 L)



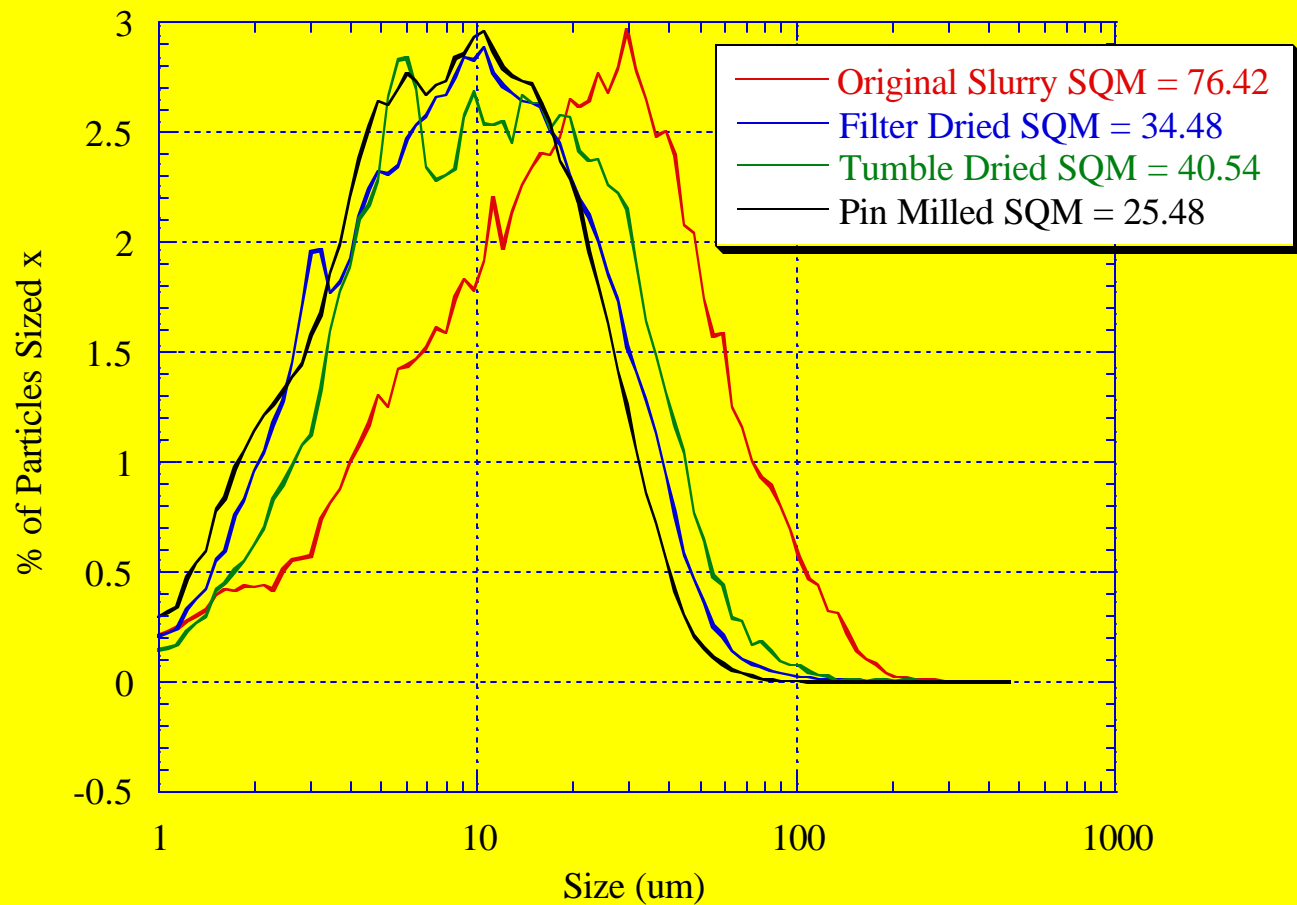
Seamless Scale Up

Particle Size Distribution



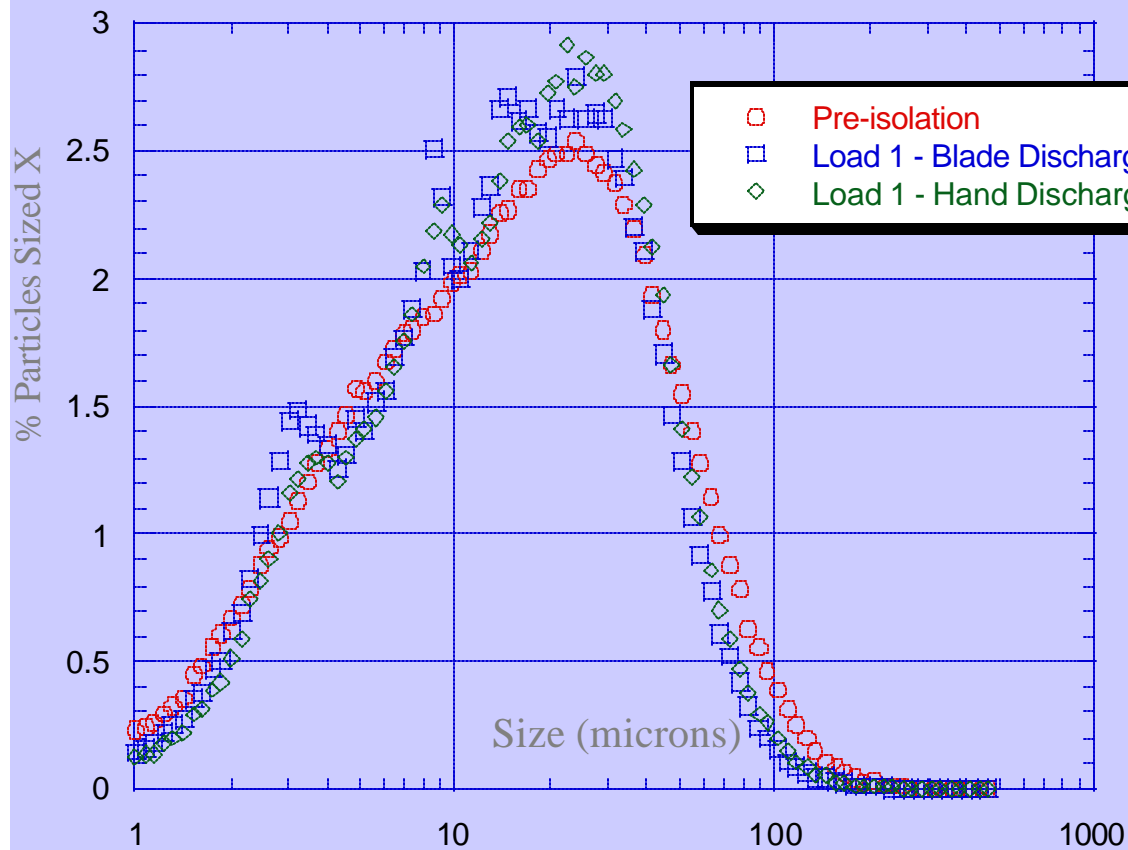
Similar Results at Lab, Pilot, and Manufacturing Scale

Effect of Agitated Drying

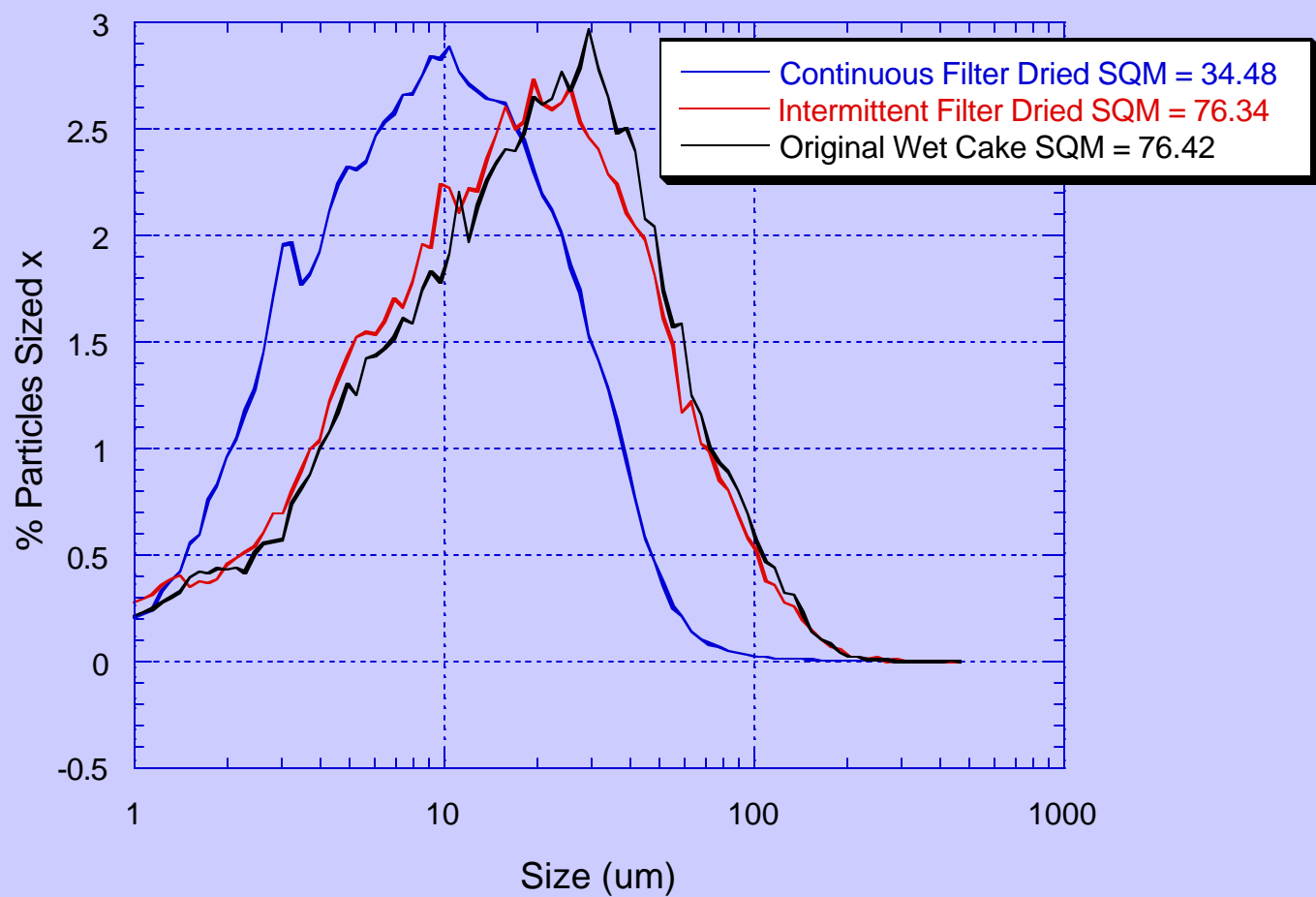


Following the Process - at line

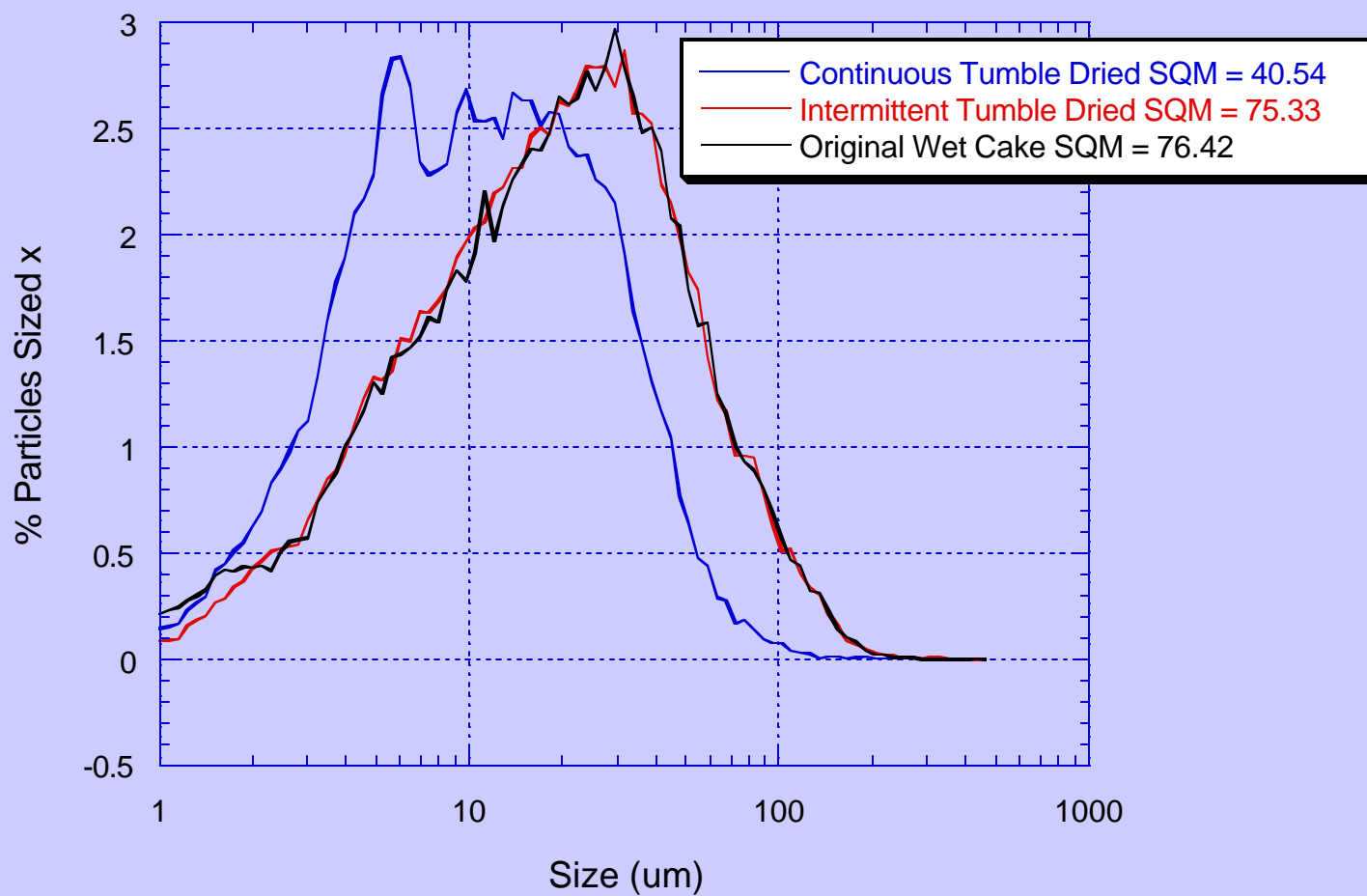
Isolation on Centrifuge



Monitoring in Filter Dryer - at line

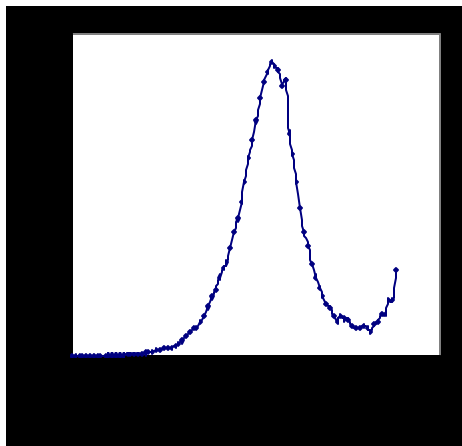
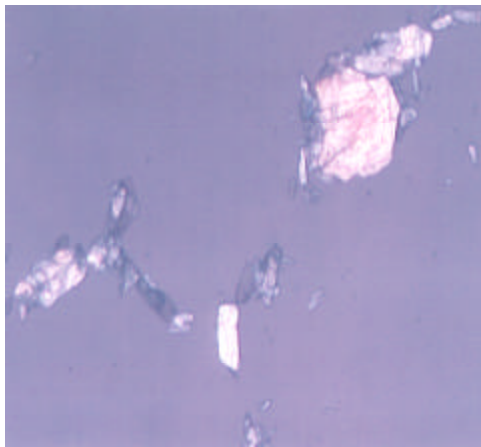


Monitoring in Tumble Dryer - at line



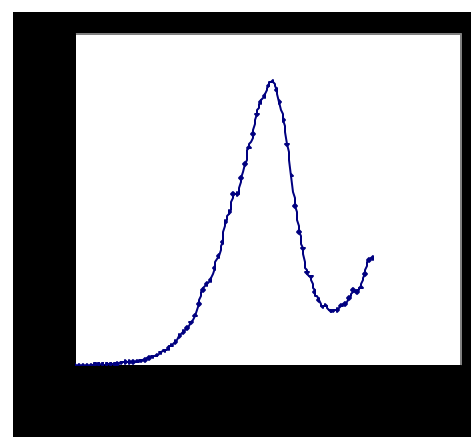
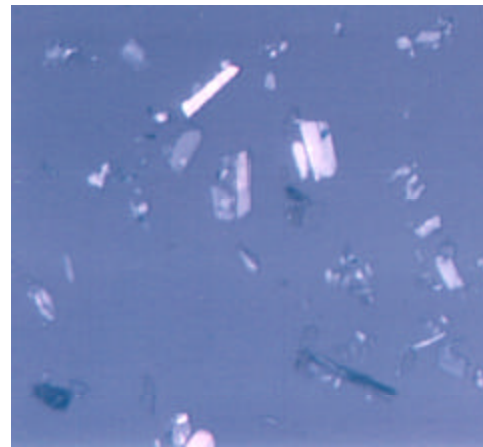
High Shear Drying

T=0 min



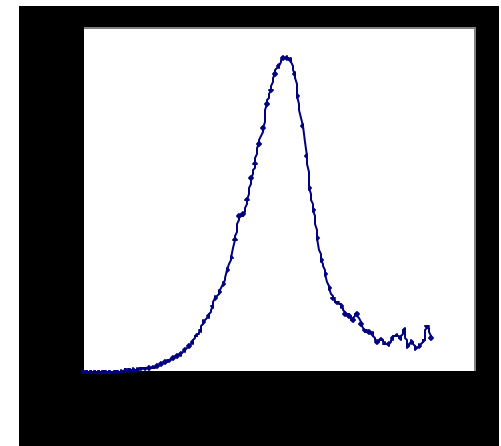
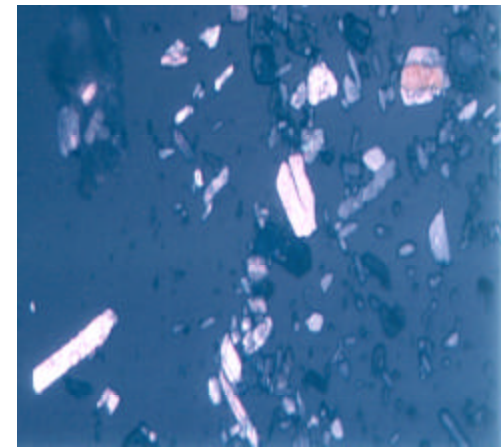
Median=41.70

T=120 min



Median=30.92

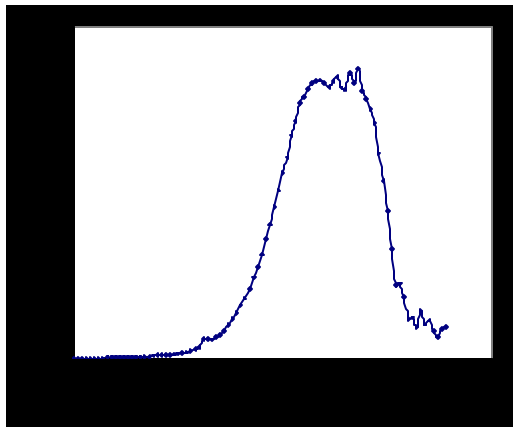
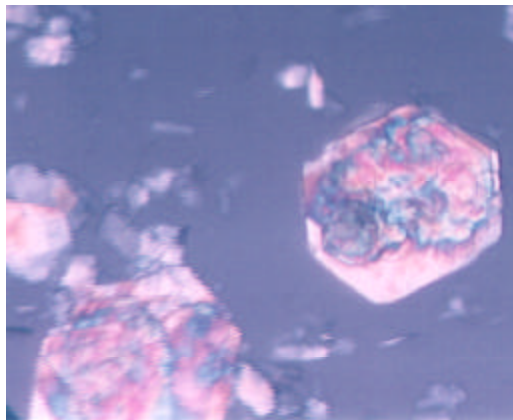
T=200 min



Median=32.80

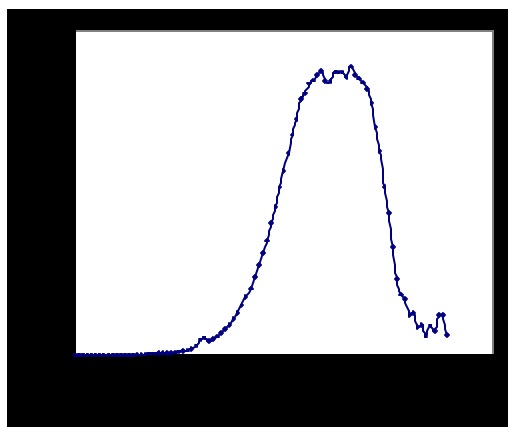
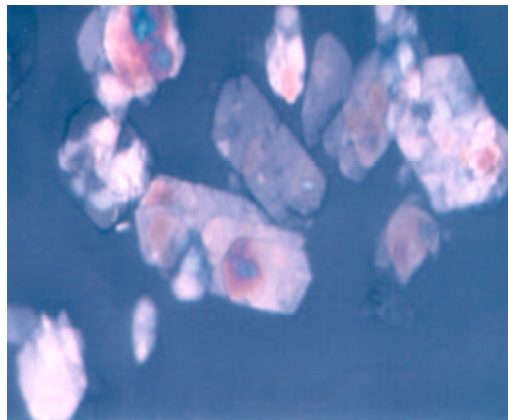
Low Shear Drying

T=0 min



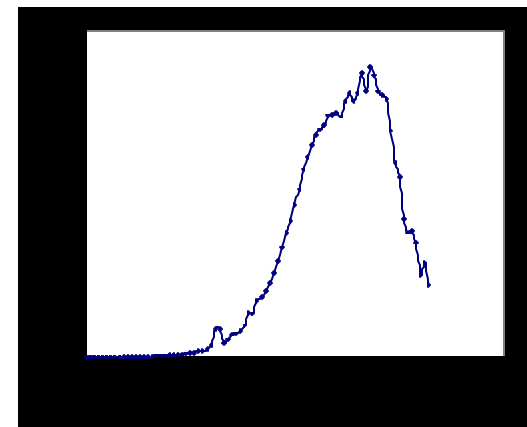
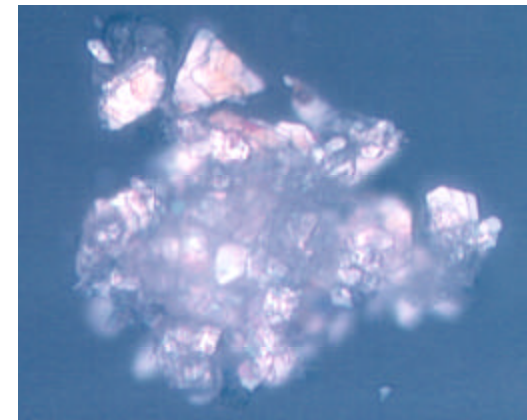
Median=61.27

T=200 min



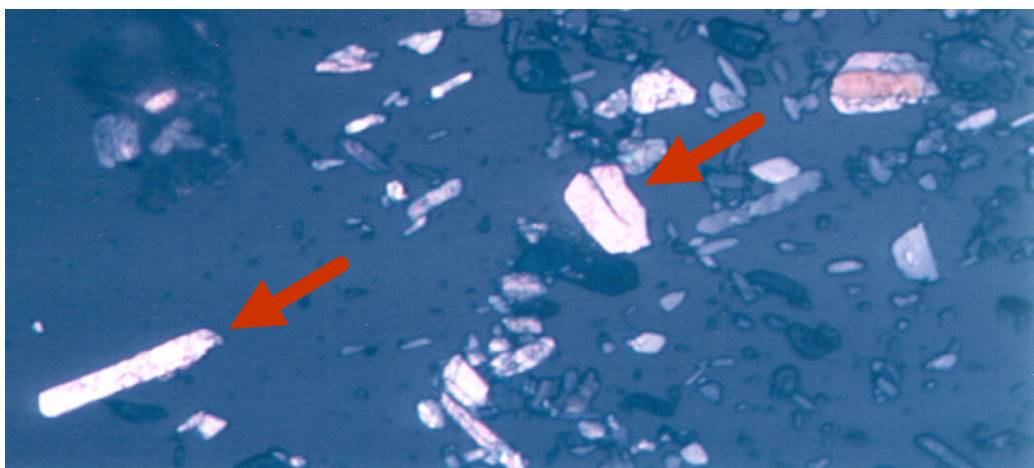
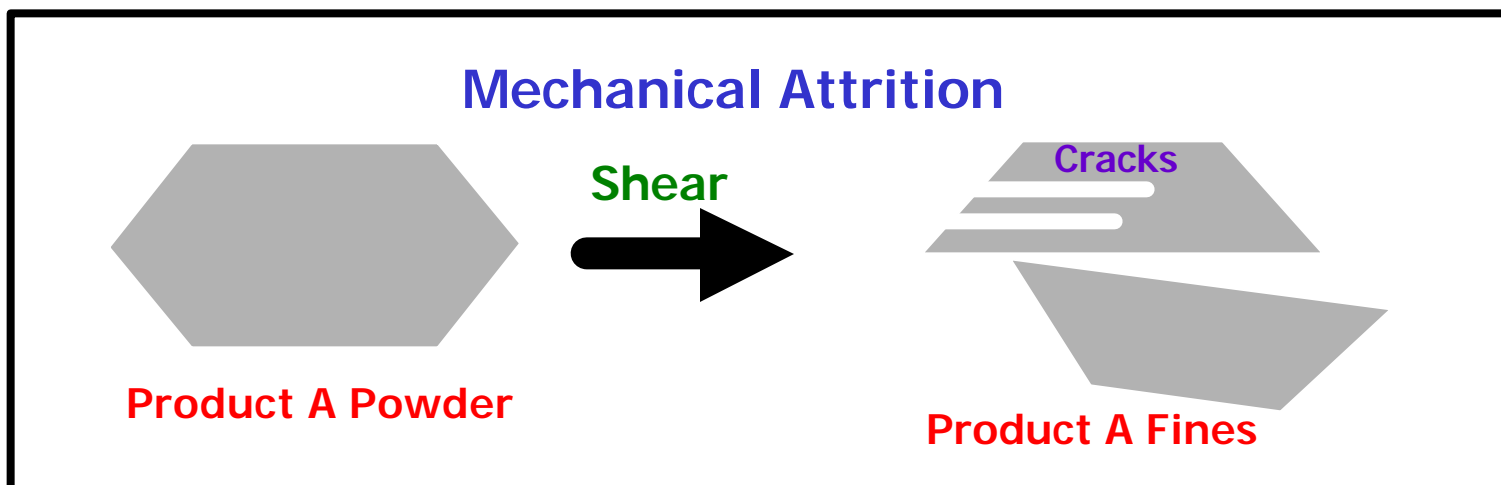
Median=60.70

T=700 min



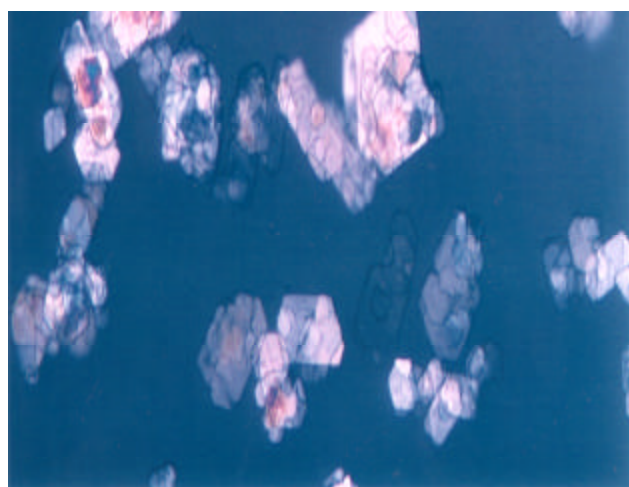
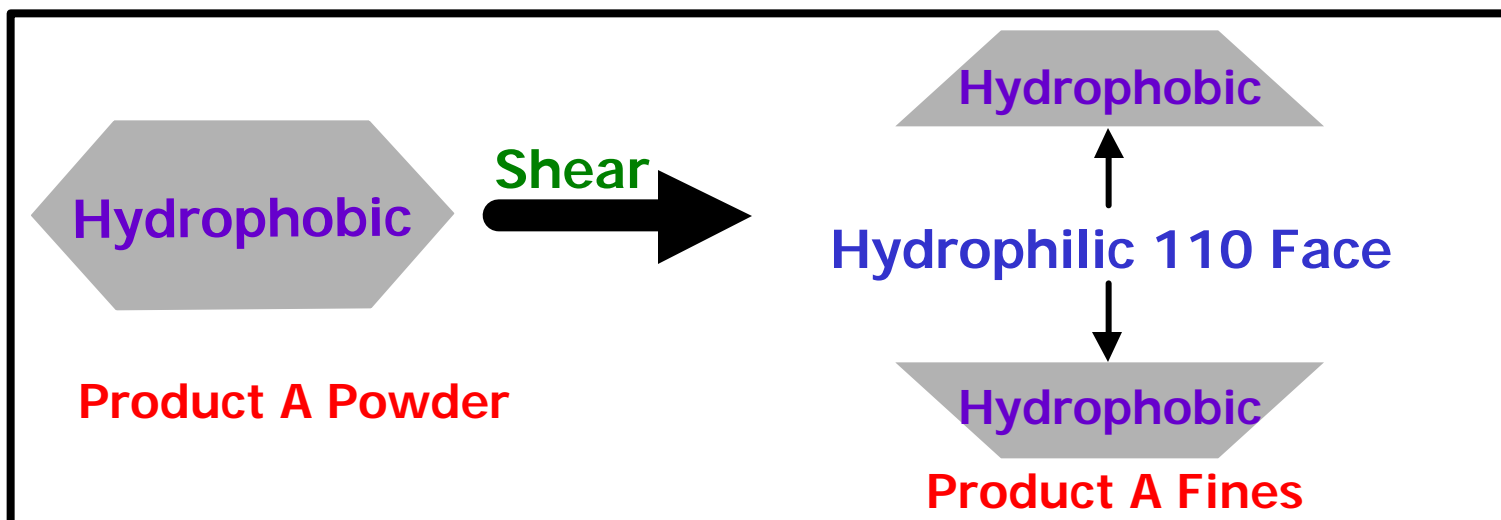
Median=56.10

Impact of Agitation on PSD

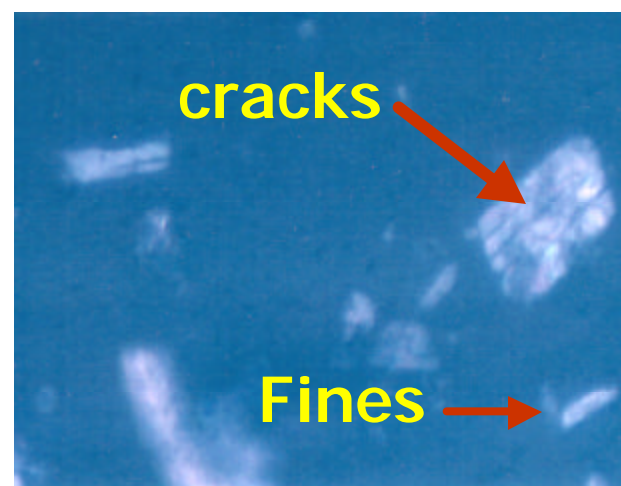


**Filter Dried
with Agitation**

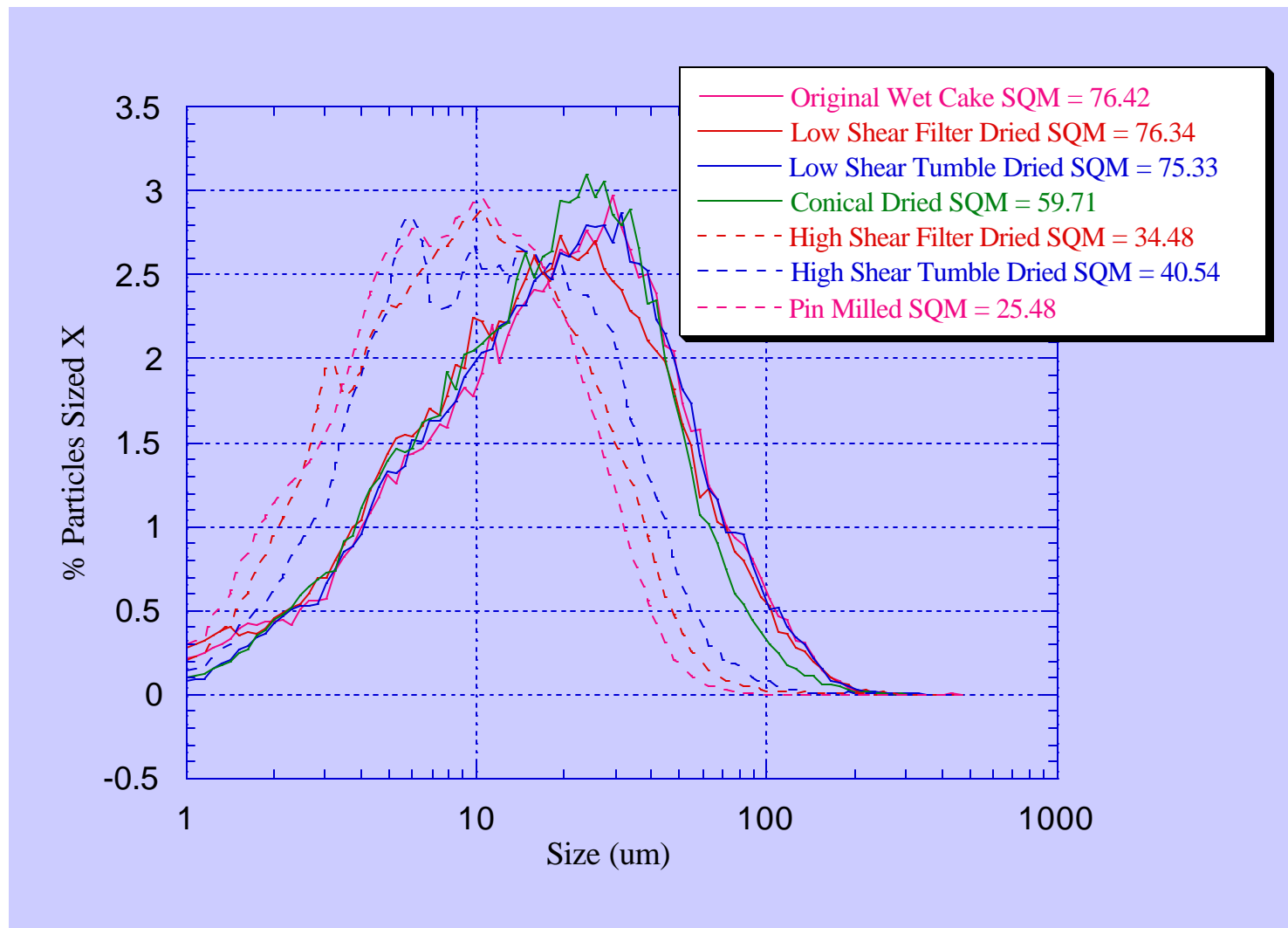
Impact of Shear Force on PSD



Shear →



Dryer Dependence, Unraveled!



Summary

In this case study, we demonstrated that PAT

- can be used in crystallization process development
- can improve confidence during scale up
- can be applied in monitoring of downstream operations
- can be used for better PSD control during crystallization & downstream process
- can be used for better control of API attributes leading to consistent performance of formulation process and drug product performance

PAT Regulatory Overview

- Better assurance of quality through improved control of particle size and particle size distribution
- Particle size is scale and site independent
 - have we demonstrated adequate process validation?
- FBRM Technology may be applied to other BMS products where particle size is a critical performance measure to provide Regulatory relief

PAT Regulatory Strategy

Regulatory Overview - Contd.

- **'In-Process' acceptance criteria**
 - Could this replace existing final release particle size test?

- **Validation of PAT**
 - How do we validate FBRM?

PAT Regulatory Strategy

Confidence Factors

- Consistent Impurity Profiles
 - through better control of filtration and washing
- Particle Size and Particle Size Distribution
- Process Consistency of API & Dosage Form



PAT Regulatory Strategy

Filing Mechanism

- New Molecular Entity - NDA
- Marketed Product - SNDA
- Pending (under review) Application -
Amendment to the NDA in consultation
with the FDA

PAT Regulatory Strategy

Filing Requirements

- Impurity Profile
- Physical Characteristics
- Validation of PAT process
- Particle size and particle size distribution acceptance criteria

PAT Regulatory Strategy

Filing Requirements - Contd.

- Description of the Process
- Demonstrate Material Equivalency for SNDA
- Stability Data: ***none different from current practice***
 - For SNDA - Stability Commitment only
 - For NDA - Commercial Scale/Pilot Scale Batches



21 CFR Part 11 Requirements and PAT

- Audit trail with date and time
- Data available for review and copying
- Device checks
- Security
- Computer Validation



21 CFR Part 11 Considerations for PAT

- Promote the use of technology
- GMP's developed for paper process
- Data retention requirements
- Reprocessing of data