Improving Process Understanding through Crystallization Modeling

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- Crystallization is frequently employed to produce solid material fit for formulation from chemical synthesis steps

- Oral absorption and formulation performance can be closely tied to particle physical attributes (i.e. particle size and shape)
  - Historically dry milling has been employed to reduce particle size to improve adsorption performance. Significant cost and IH concerns driving a desire for direct crystallization with minimal dry milling required.

- Overall process time cycle and yearly capacity can also be negatively impacted by slowly filtering compounds
  - Filtration performance is frequently correlated to particle size and shape and frequently benefits from larger, more growth dominated crystallization processes.

- Crystallization design plays a key role in balancing many of these particle attribute considerations

Merck's X-Lab

- Merck maintains a dedicated crystallization laboratory to support small molecule crystallization design and development

- Staffed by 9 engineers, the X-lab focuses on support for:
  - Crystallization development support of process design
  - Drug substance processability assessment
    - Solubility screening
    - Wet-milling performance evaluation
    - Evaluation of filtration characteristics
    - Sensitivity to particle breakage
  - Intermediate and drug substance polymorph screening
  - Supply stabilization support and process improvement
  - Crystallization technology development

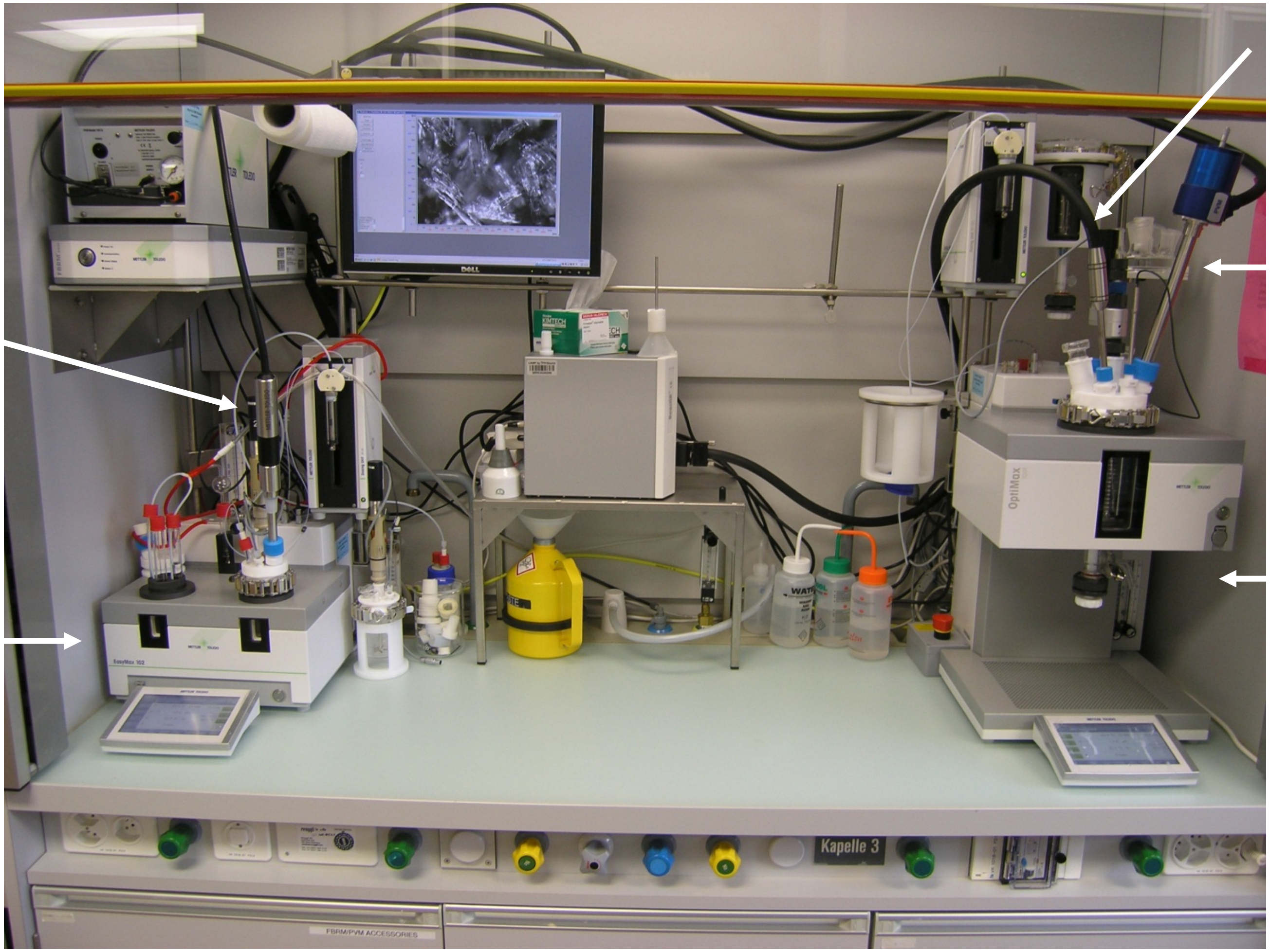
- X-lab operates as a center of excellence with significant subject matter expertise and advanced development and analytical tools.

Equipment Capability

Infrared Spectroscopy (FTIR)

Focused Beam Reflectance Measurement (FBRM)

Particle Vision Microscope (PVM)



Easy-Max
100 mL vessel

Optimax
250 - 1000 mL vessel

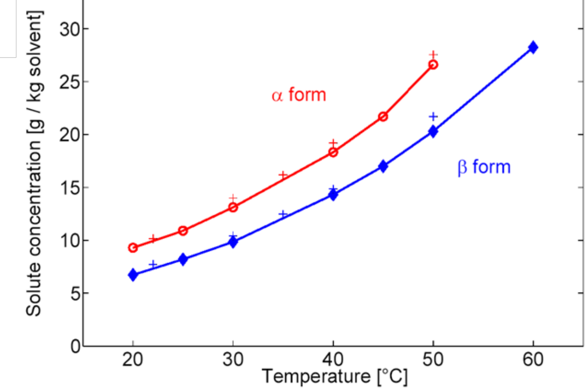
Equipment Capability (cont'd)

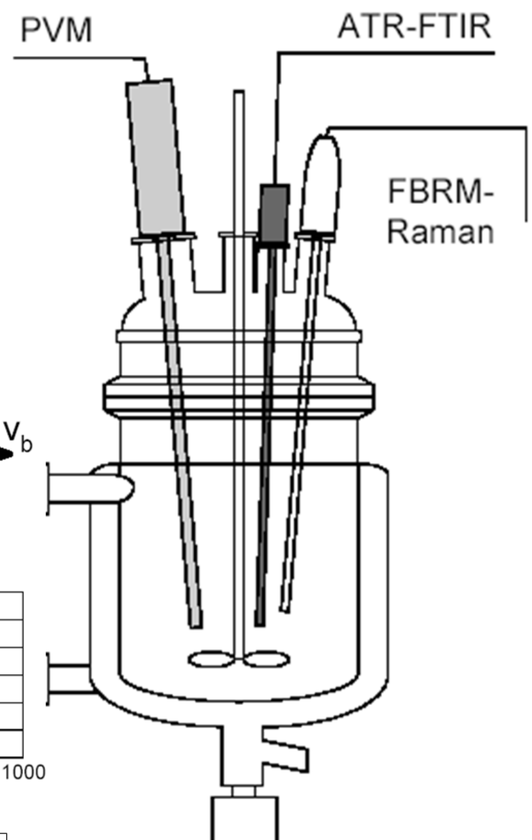
- Particle Characterization
  - SEM
  - Optical Microscope
  - Sympatec
  - Microtrac
  - Surface Area
  - Powder density
- Wet Milling
  - Rotor stator milling
  - Media milling
- Filtration Rate Characterization
  - Rosenmund Pocket Filtration
- Analytical Tools
  - HPLC
  - GC
  - Karl Fischer
  - Crystal 16
- Solid State Characterization Tools
  - XRPD
  - VTI (Vapor Sorption)
  - Differential Scanning Calorimetry (DSC)
  - Thermogravimetric Analysis (TGA)
  - Raman Microscopy
  - On-line Raman

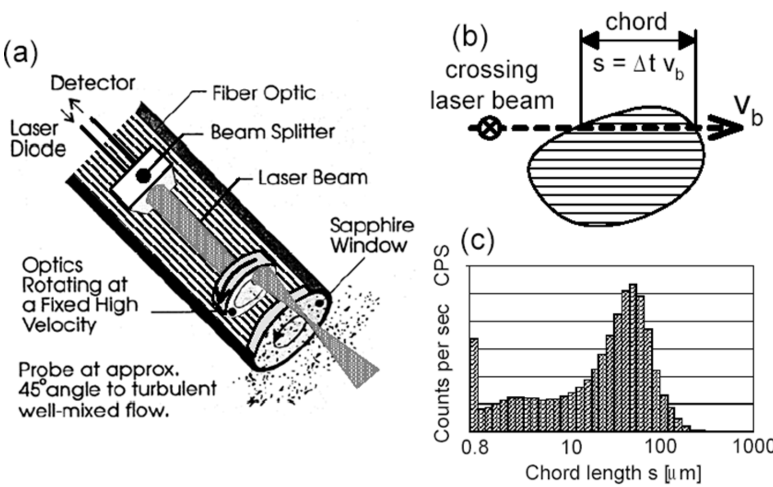
Crystallization Monitoring

In-situ microscopy (PVM)

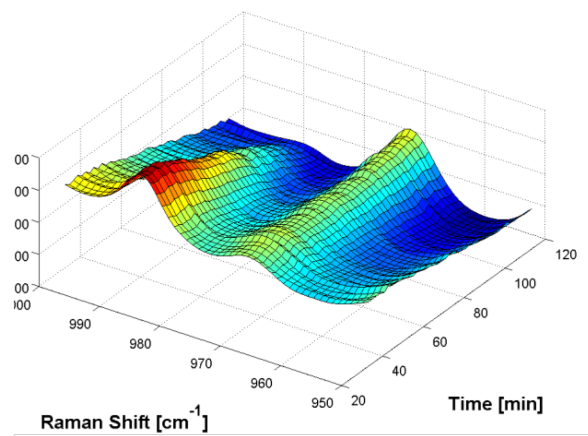
Solubility and solute concentration (ATR-FTIR)







Chord length distribution (FBRM)

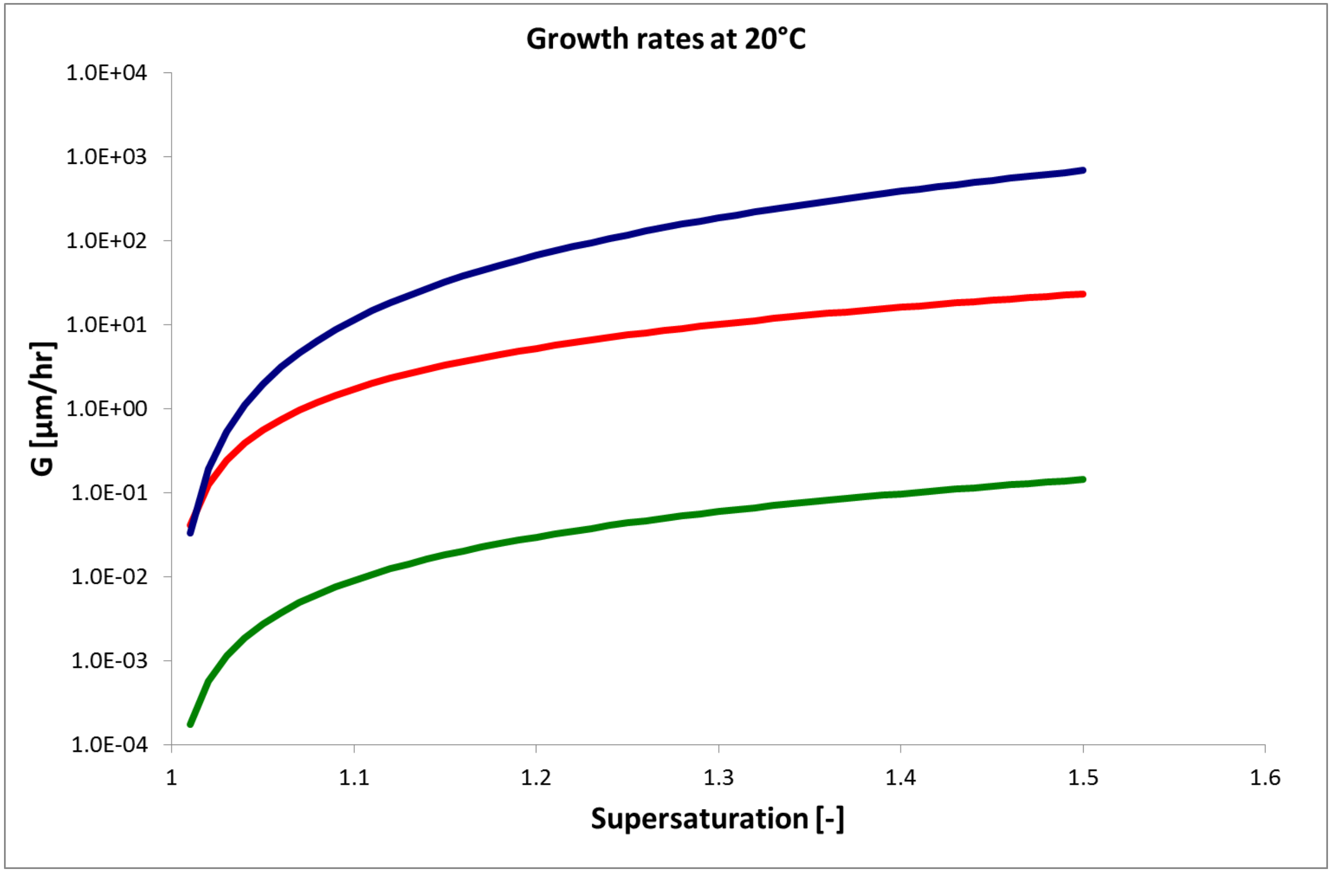


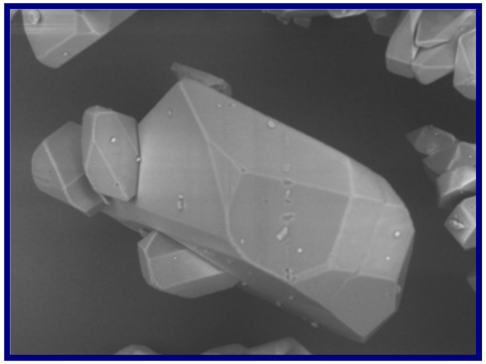
Polymorphic form (Raman)

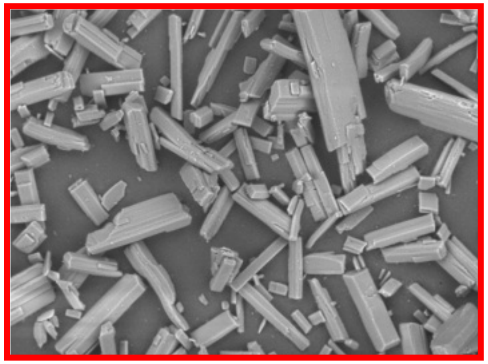
Drivers for Modeling

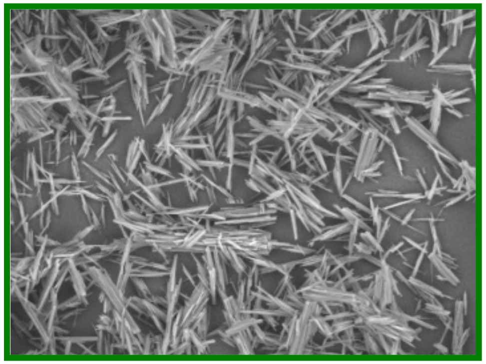
- Preliminary assessment of a compound's propensity for growth
  - Quick regression of growth parameters gives preliminary read regarding whether crystallization kinetics are:
    - Fast posing potential challenges with need for rapid micro/meso-mixing
    - Slow creating potential time cycle challenges
- Rapid screening of batch crystallization conditions
  - Numerous alternative crystallization modes can be simulated in-silico, with only minimal lab-scale pre-investment required
- Optimization of target process parameters/recipes
  - Advanced process optimization algorithms enable more efficient process design and opportunities for increased process robustness
- Batch-to-Continuous Process Development
  - Lab-scale continuous crystallization capabilities are severely limited with existing lab infrastructure
  - Simulation offers an attractive tool for design optimization that is both time and resource efficient and can be based on existing batch process information

Growth Parameter Libraries





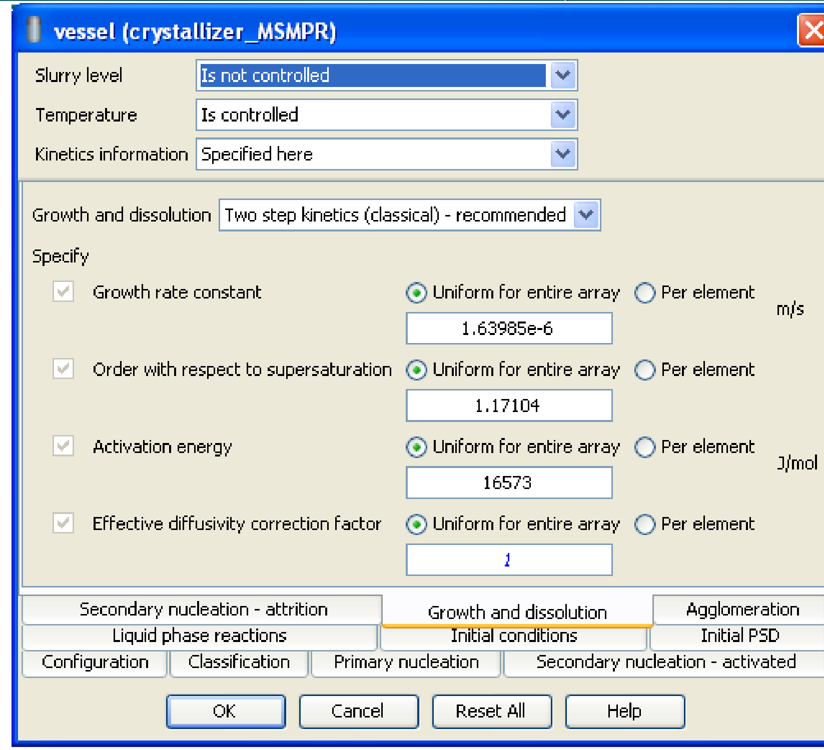


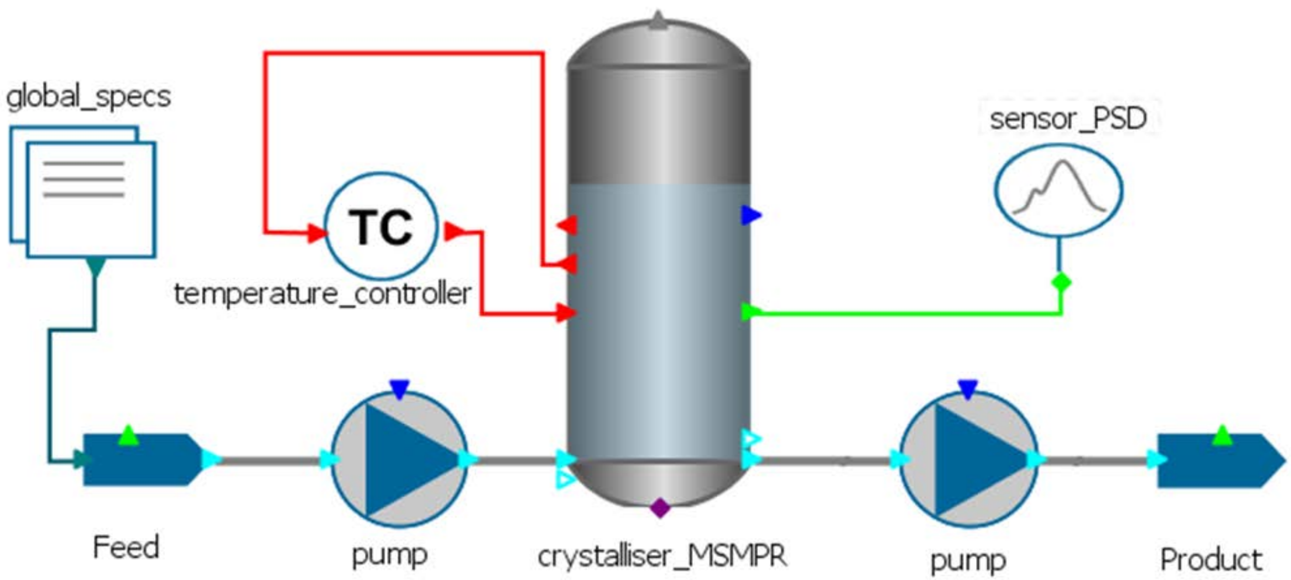


- Heavily seeded, isothermal crystallizations are executed to gain understanding of a compound's propensity for growth (vs. secondary nucleation for example)
- Comparison of growth rate to historical database enables rapid assessment of expected process cycle times and potential processing challenges (e.g. need for rapid mixing)

gCrystal Environment

- Flow sheeting environment for building the crystallization
- Options for temperature, level and pressure controllers, as well as numerous sensors/ analyzers (ie. PSD)
- A convenient graphical user interface for parameter entry with numerous crystallization kernels built in



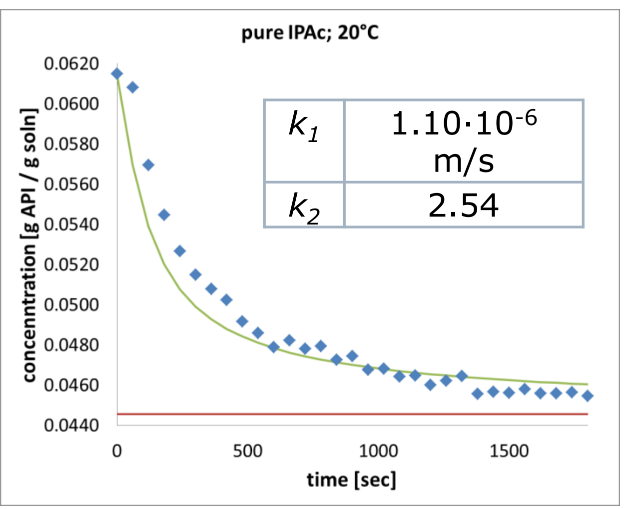


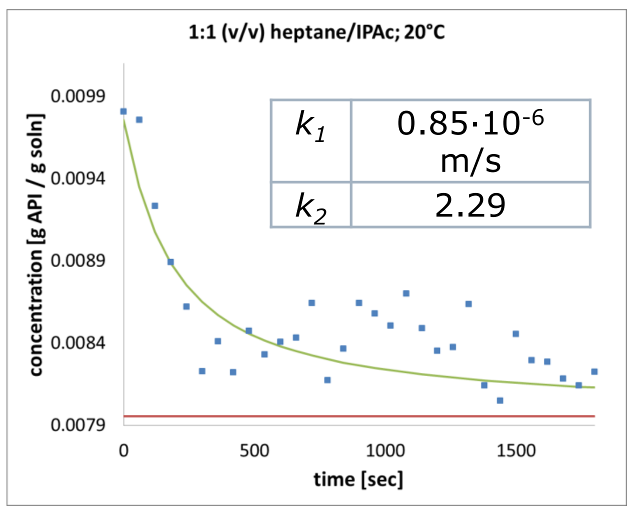
Propensity for Growth

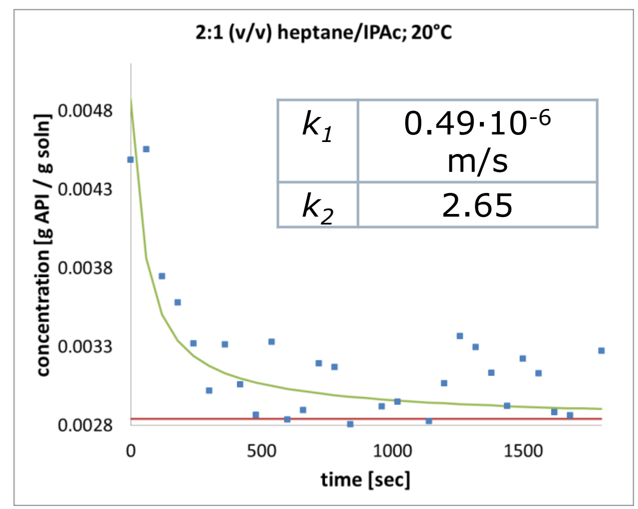
- Seeded isothermal crystallization experiments with a high seed loading in varying solvent mixtures

- Growth parameters estimated using gCrystal
  - gCrystal's graphical user interface and straightforward regression techniques simplifies growth parameter acquisition

- Understanding of growth kinetics helps guide additional crystallization development

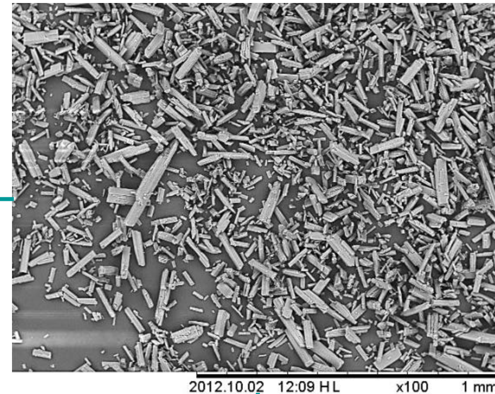






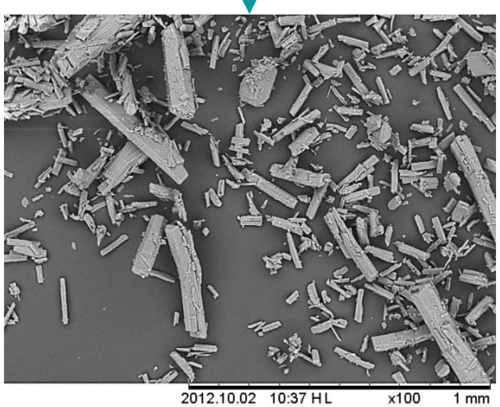
$$G = k_1(S-1)^{k_2}$$

Particle Size Prediction



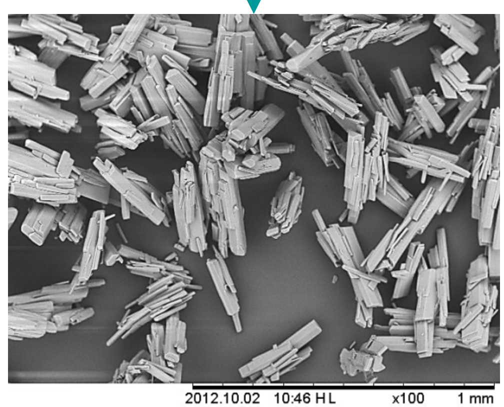
0.4% seed @ 65C
Age at seed point
Staged cool down

Secondary Nucleation
then Growth



20% seed @ 70°C
Age at seed point
Staged cool down

Growth &
Agglomeration Only



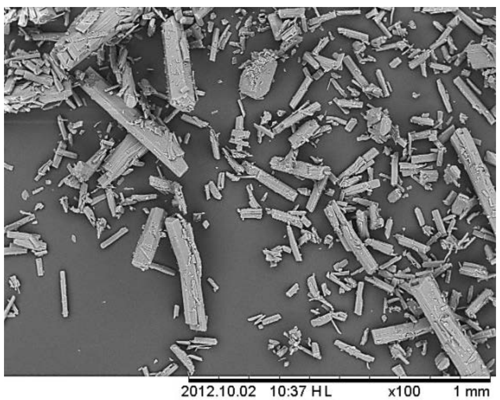
5% seed @ 71°C
Staged cool down

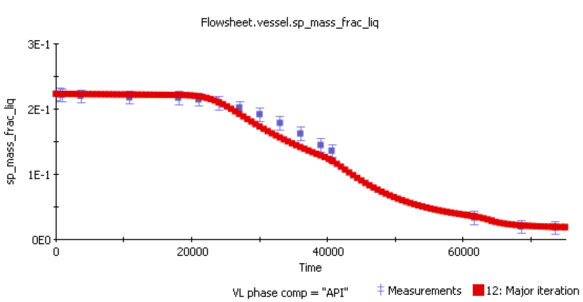
Growth &
Agglomeration then
Secondary nucleation

Solution Phase Regression

0.4% seed @ 65C
Age at seed point
Staged cool down

Secondary Nucleation
then Growth





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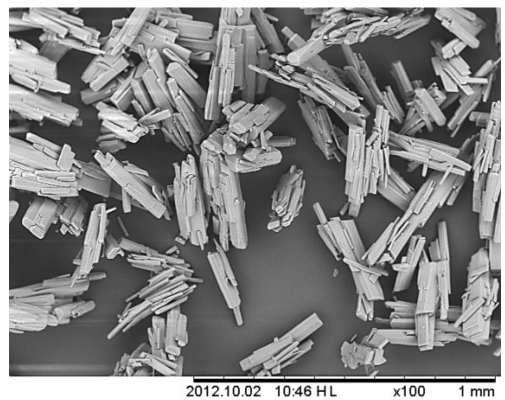

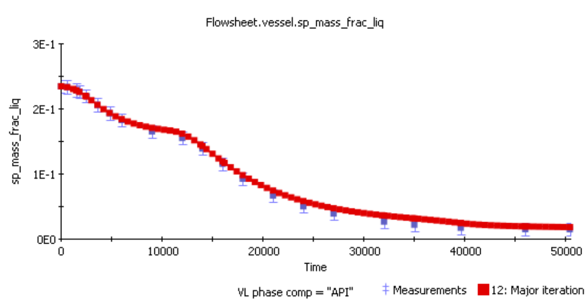

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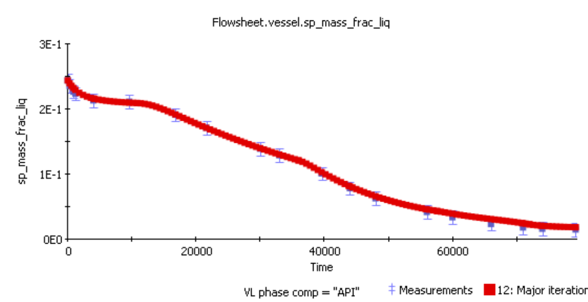
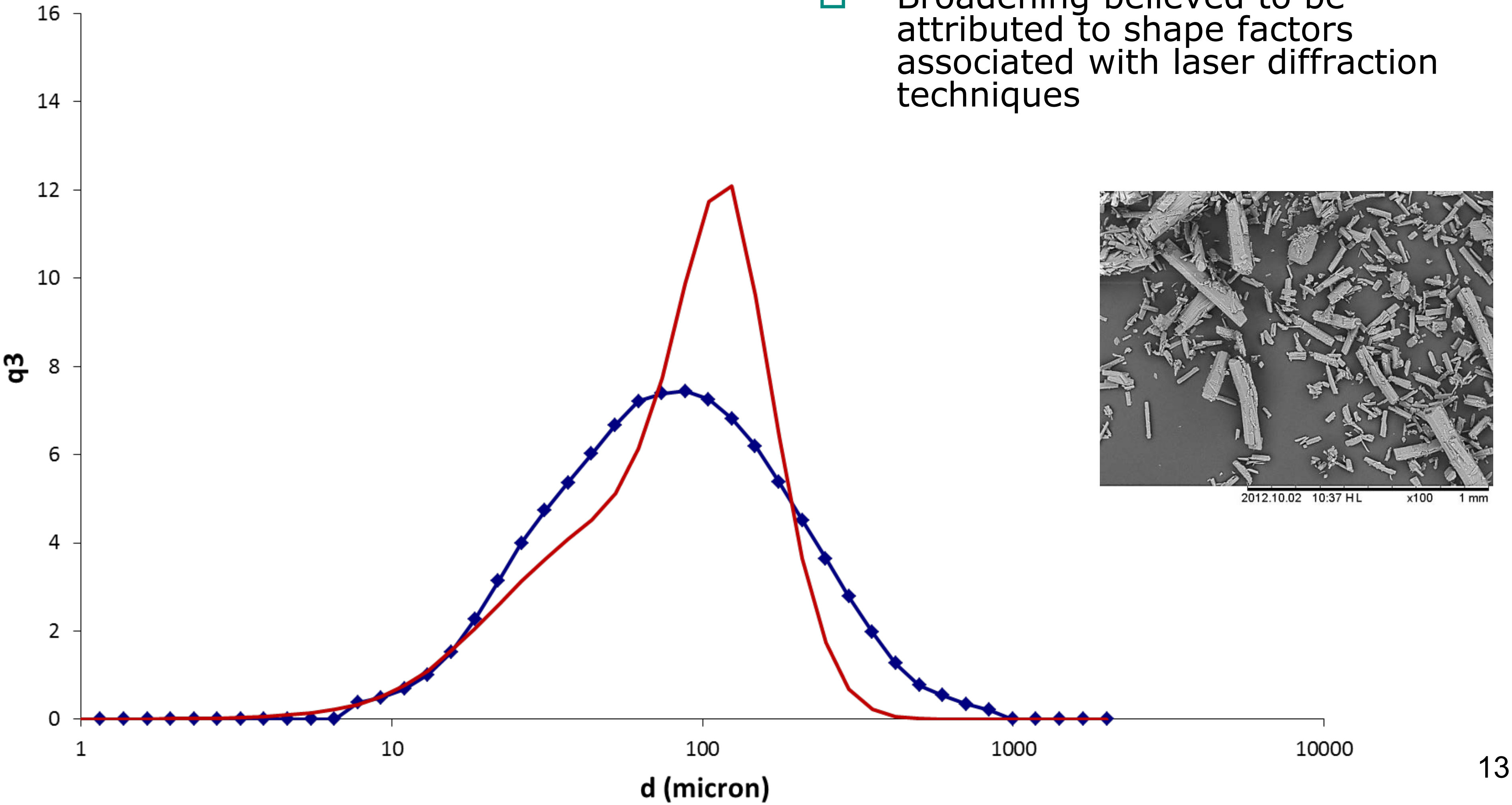


Public

Experiment 1

	D10	D50	D90
Model prediction - Growth & 2nd Nucleation	22.5	82.5	158.6
Experimental Data -	22.5	72.5	224.1

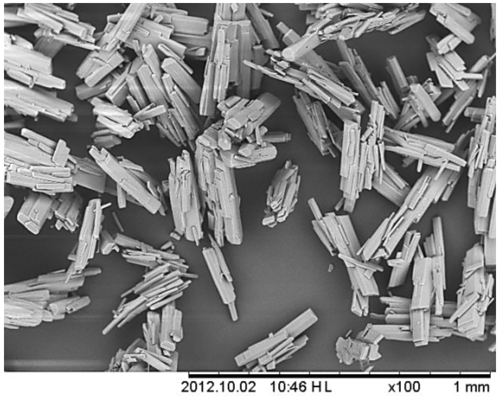
- Distribution broadening prevents accurate prediction of D90 results
- Broadening believed to be attributed to shape factors associated with laser diffraction techniques

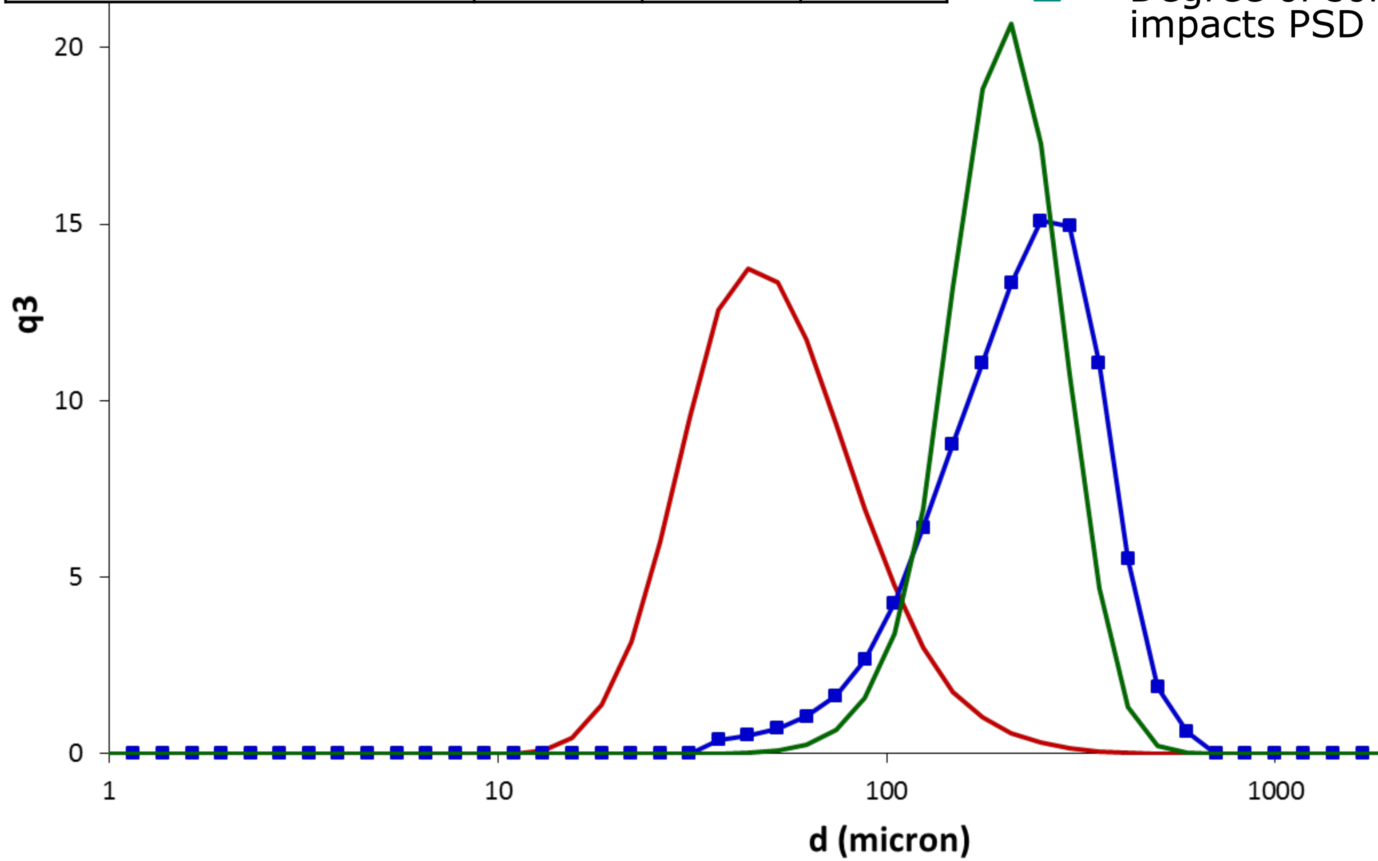


Experiment 2

	D10	D50	D90
Model prediction - Growth only	25.2	45.7	93.3
Model prediction - + Agglomeration	115.3	183.4	275
Experimental Data - No sonication	100.0	207.1	338.9

- SEM micrographs indicate minimal secondary nucleation
- Growth only model does not accurately predict the data
- Addition of agglomeration kernel improves PSD prediction significantly
- Degree of sonication during analysis impacts PSD significantly





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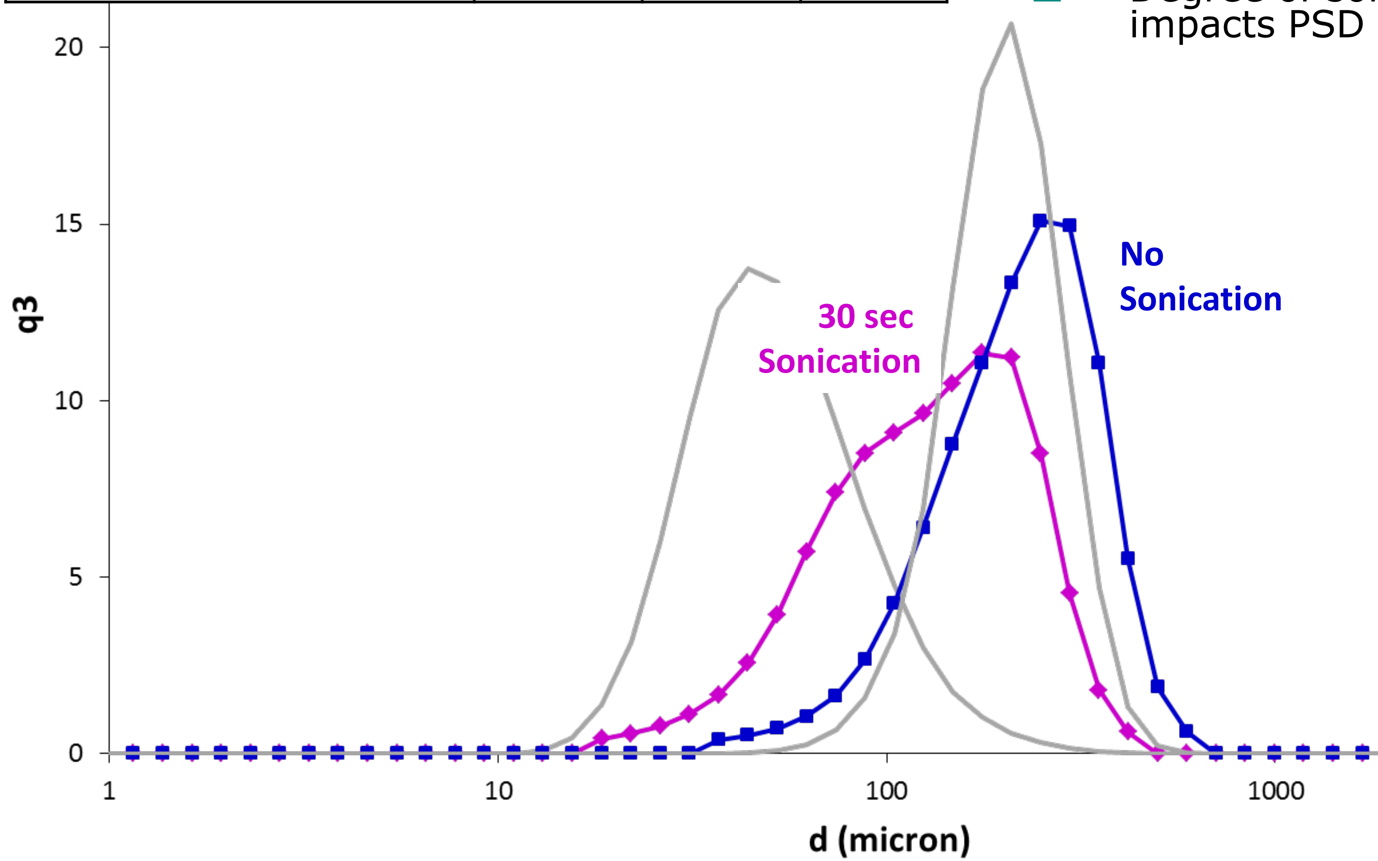

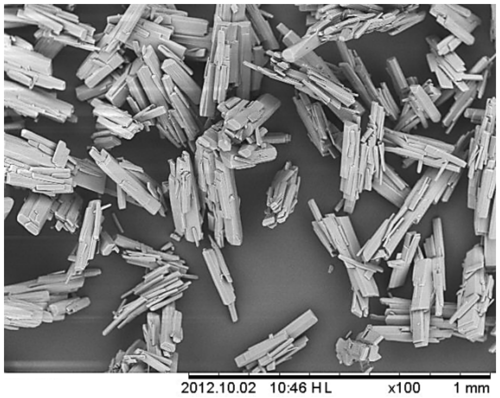

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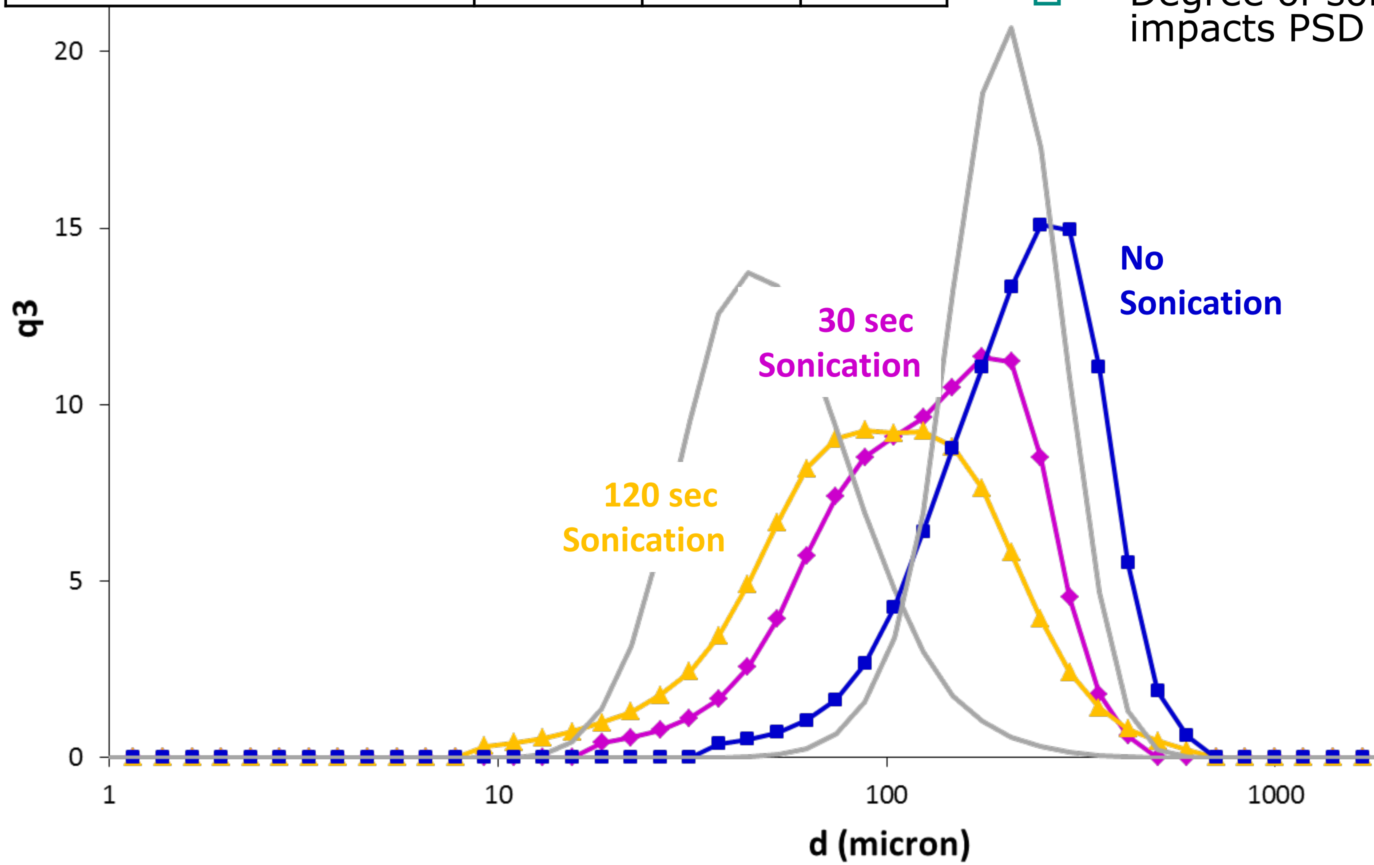
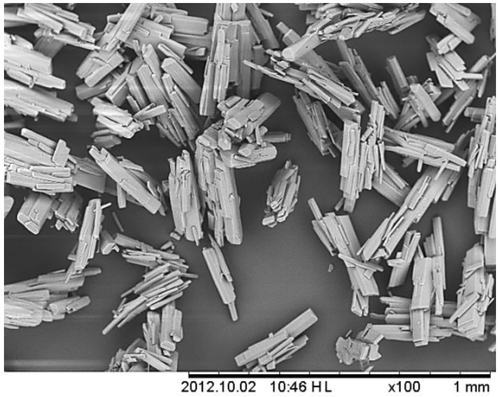
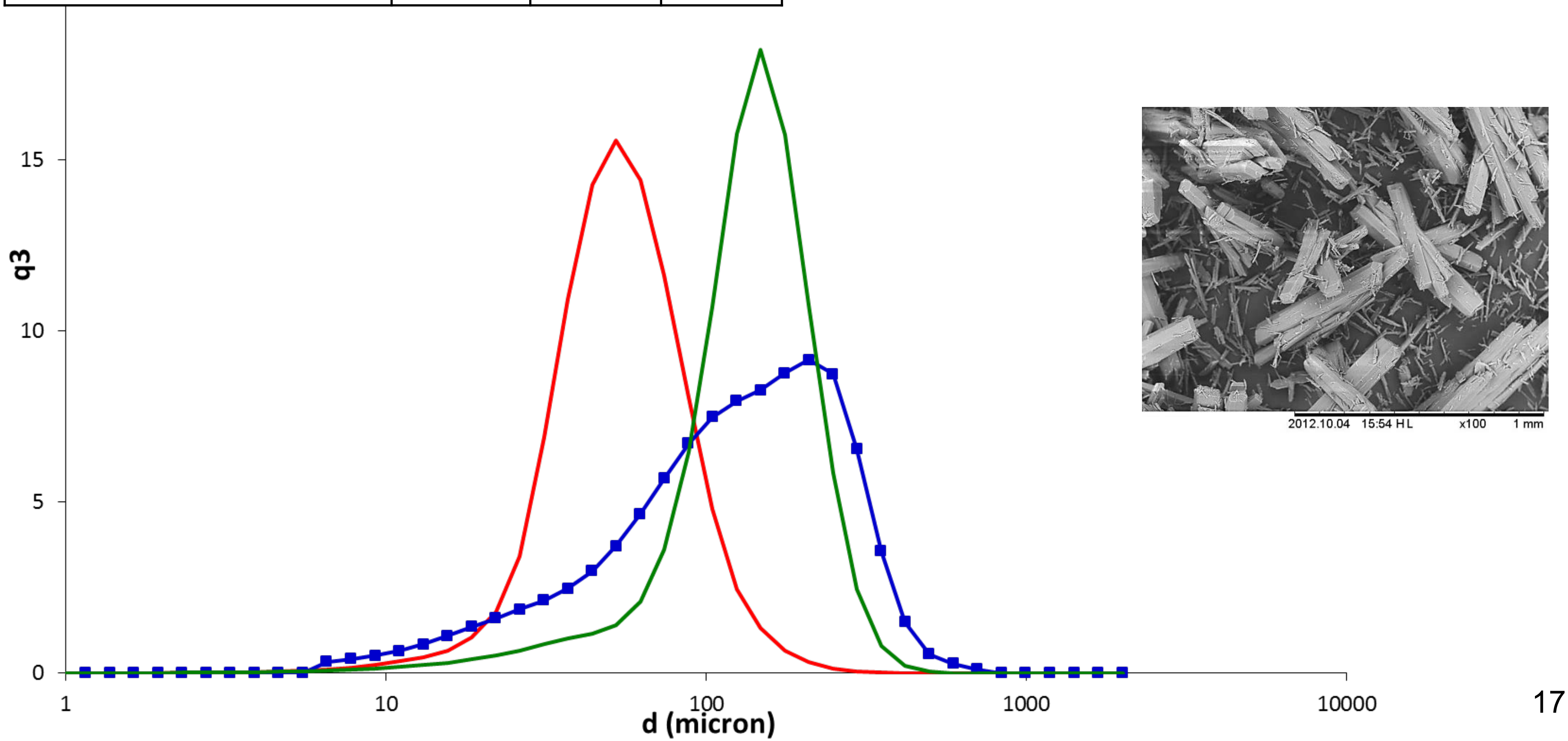




Experiment 3

	D10	D50	D90
Model prediction - Growth and 2nd Nucleation	32.3	58.1	104.8
Model prediction - + Agglomeration	64.9	129.2	206.5
Experimental Data -	29.2	118.0	264.3

- SEM micrographs indicate significant secondary nucleation, at the end of the crystallization
- Growth and 2nd nucleation only model does not accurately predict the data
- Model is not accurately capturing bimodal behavior



Next Steps

- Agglomeration
  - Agglomeration parameter regression was not functioning properly at the time of original investigation. Quantitative prediction of the agglomeration parameter should improve further agglomeration kernel performance.
  - Impact of degree of sonication employed during analysis impairs agglomeration regression. Re-evaluation with a compound less prone to agglomeration is currently underway.

- Shape effects in laser diffraction measurement
  - Re-execute population balance model evaluation with more block like material
  - Current investigations are planned towards repeating particle size measurement with alternative techniques less sensitive to particle shape (i.e. Coulter counter)
    - Techniques such as coulter counter are less frequently used within the industry and therefore do not likely serve to address the issue
    - Can data generated as output from gCrystal be treated so as to predict the broadening attributed to such shape effects? we shall see…

Conclusions

- Propensity for growth
  - Growth kinetics are rapidly and easily estimated using the gCrystal software environment and helpful in assessing a particular substance’s crystallization tendencies.

- Particle size distribution prediction
  - Population balance models for prediction of particle size distribution can reasonably predict D50, provided the appropriate kernels are active and regressed, and alteration of the simulation parameters are rapid
  - Measurement error attributed to laser diffraction measurement techniques appears to be limiting the quantitative prediction from a particle size perspective, but qualitatively, model is well suited for determining mean size and active crystallization mechanisms.