NALAS
Engineering Services, Inc.

Tailoring Particle Size Distribution and Morphology of LLM-105

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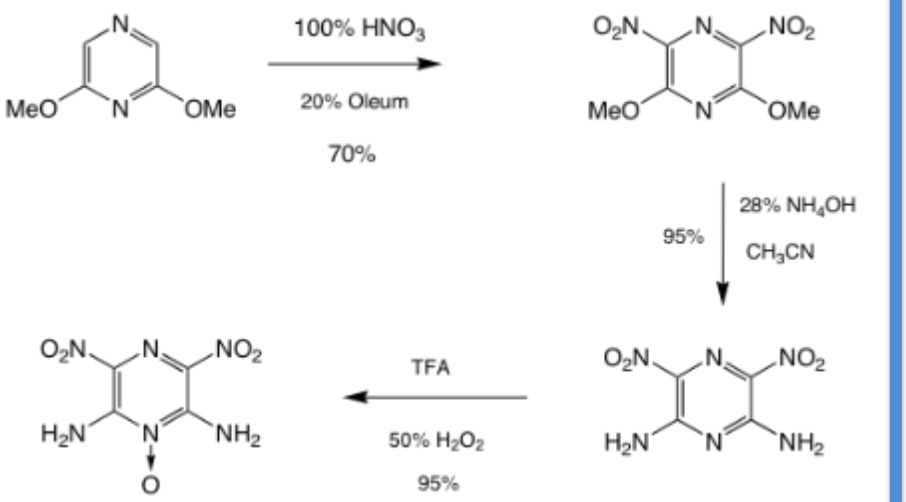
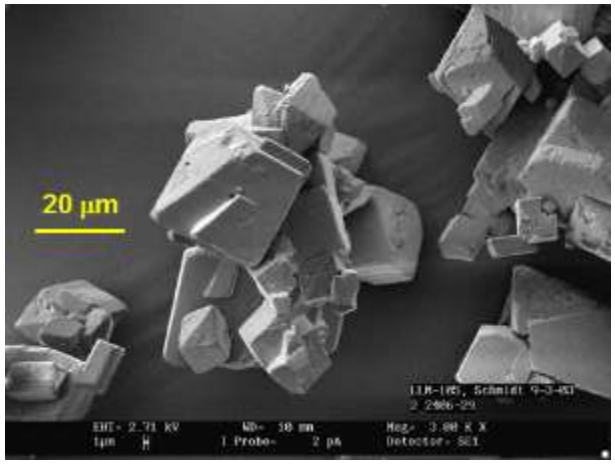
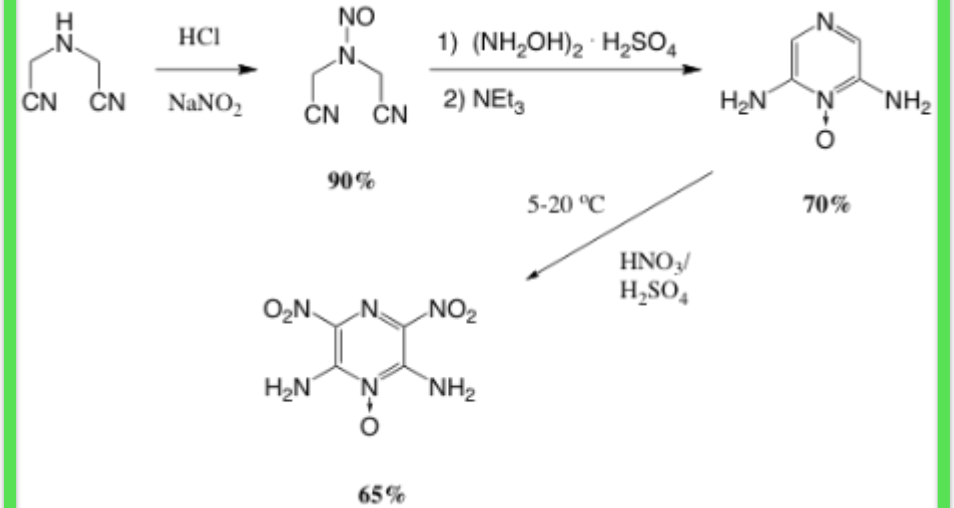
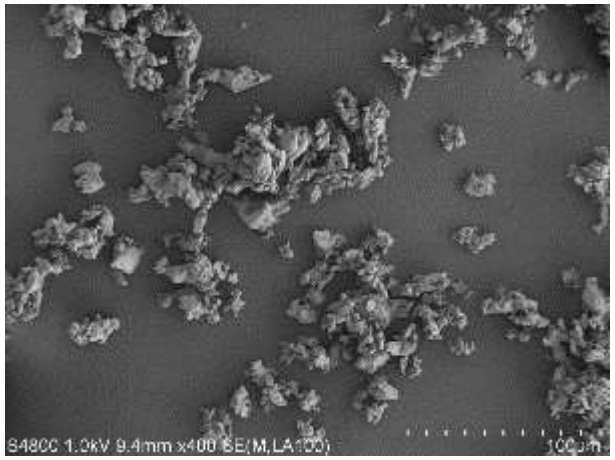
SOLUTIONS THAT SCALE

Background - Chemistry









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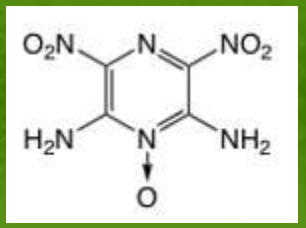
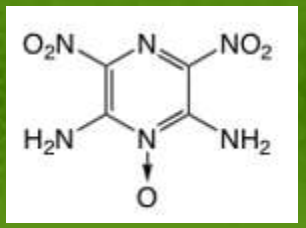
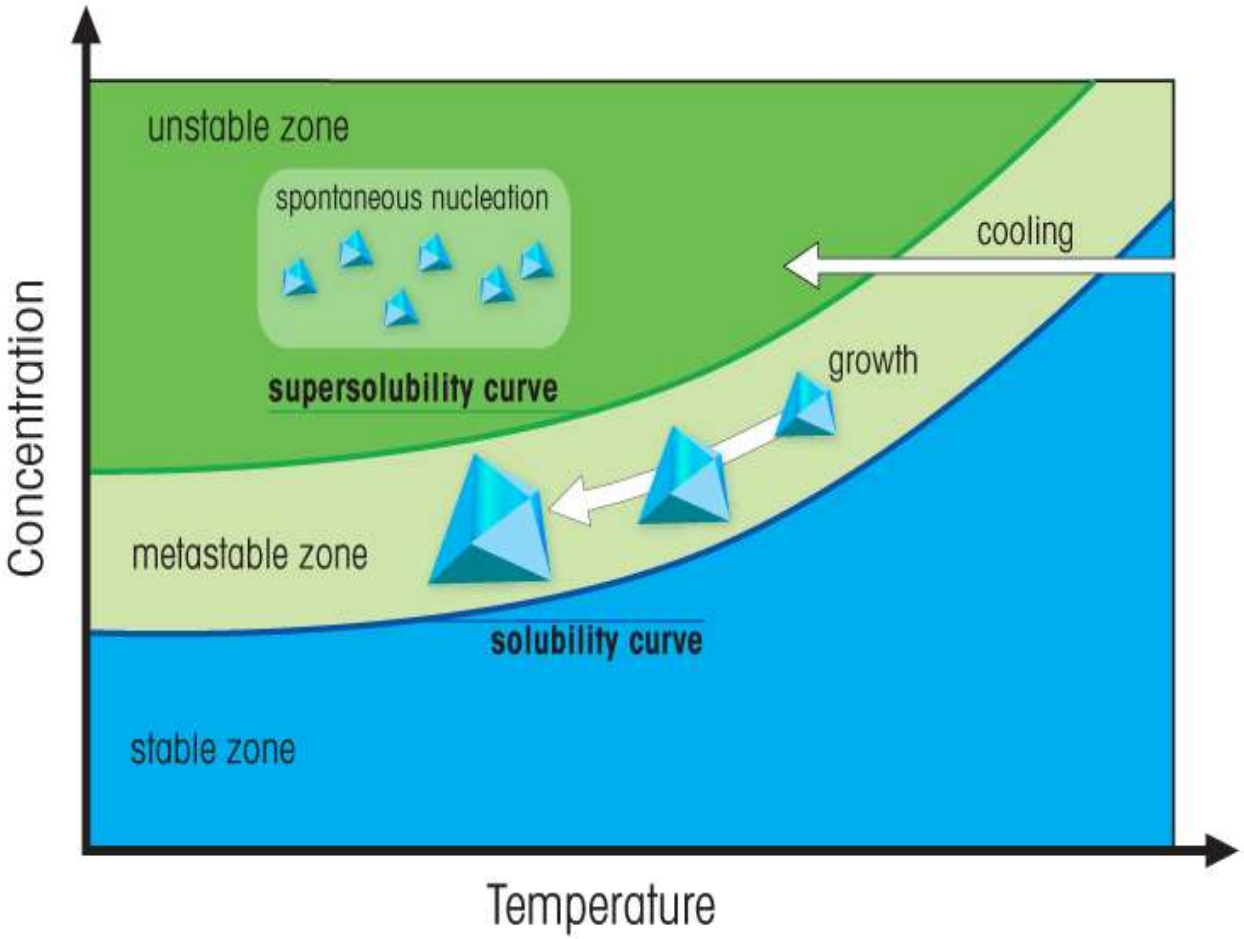
Crystallization Approach



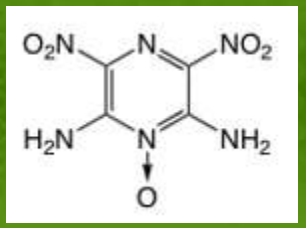
- Polymorph screening
  - Sooner than later!!
- Solubility predictions
  - Yield, impurities, polymorph
- Morphology screening
  - Desired shape-what works best?
- Safety assessment
  - Compatibility, stability, other concerns

Basics of Crystallization





Nucleation and Growth



Crystal nucleation

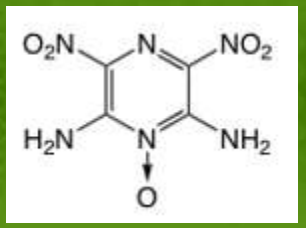
$$B = \frac{dN_T}{dt} = k_b \Delta c^b$$

Crystal growth

$$G = \frac{dL}{dt} = k_g \Delta c^g$$

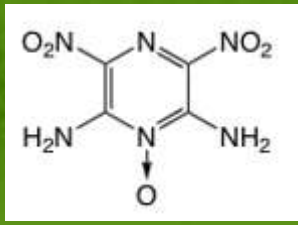
- Supersaturation is the driving force for crystal nucleation and crystal growth
- By controlling supersaturation, nucleation and growth can be controlled, allowing the crystal size to be controlled

LLM-105 Polymorphs



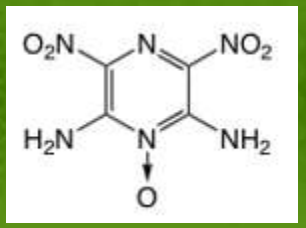
- None reported
- Many recrystallizations
- Due diligence!
  - Polymorph screen resulted in only the known form.

Starting Material, LLM-105 Form A Lot: NAL-13K001-016



Test	Method	Result
Appearance	Visual	yellow powder
Appearance	Microscopy (Disperse in water)	small and irregularly shaped particles
Thermal Analysis	Differential Scanning Calorimetry Melting point (endotherm) Decomposition (exotherm) (30°C to 450°C at 5°C/min High pressure pan.)	Melting point: no melt T_{onset} = 347°C, T_{peak} = 348°C, ΔH_{decomp} = 2334 J/g
Particle Size analysis	Mastersizer 2000 (Samples suspended in water)	D[0,1] = 1.775 µm D[0,5] = 6.704 µm D[0,9] = 16.266 µm
Purity	^{1}H and ^{13}C-NMR (Dissolve in d-DMSO)	NMR spectra consistent with structure. >95% purity
Purity	Ion chromatography (IC)	NO_3^- < 0.03 wt % NO_2^- < 0.03 wt % HSO_4^{2-} < 0.03 wt % Cl^- < 0.03 wt % $C_2O_4^{2-}$ < 0.09 wt %

NAL-008-2287 solutions/slurries

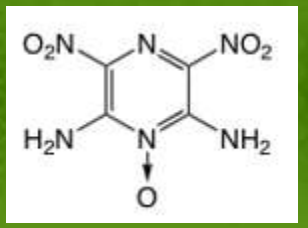


Sample Number	Solvent used	Solvent amount (mL)	Mass of LLM-105 (mg)	Concentration (mg/mL)	Result
1	AcOH	4	18.48		Slurry
2	DMF	4	20.67	5.17	Solution
3	DMSO	1	24.54	24.54	Solution
4	DMSO/EtOH (70:30)	3	20.52	6.84	Solution
5	Formic acid	3	19.34		Slurry
6	Gamma. But. Lactone	4	16.68		Slurry
7	HCl (conc.)	4	19.99	5.00	Solution
8	Sulfuric (conc.)	1	21.56	21.56	Solution
9	MeCN	4	21.83		Slurry
10	TFA	4	19.72		Slurry

Solvents chosen by experimental knowledge of good solubility and COSMOTherm predicted high solubility

Photo of NAL-009-2287. Note: not all of the vials contained the full amount of solvent when this photo was taken (some of the vials were diluted after the photo was taken)

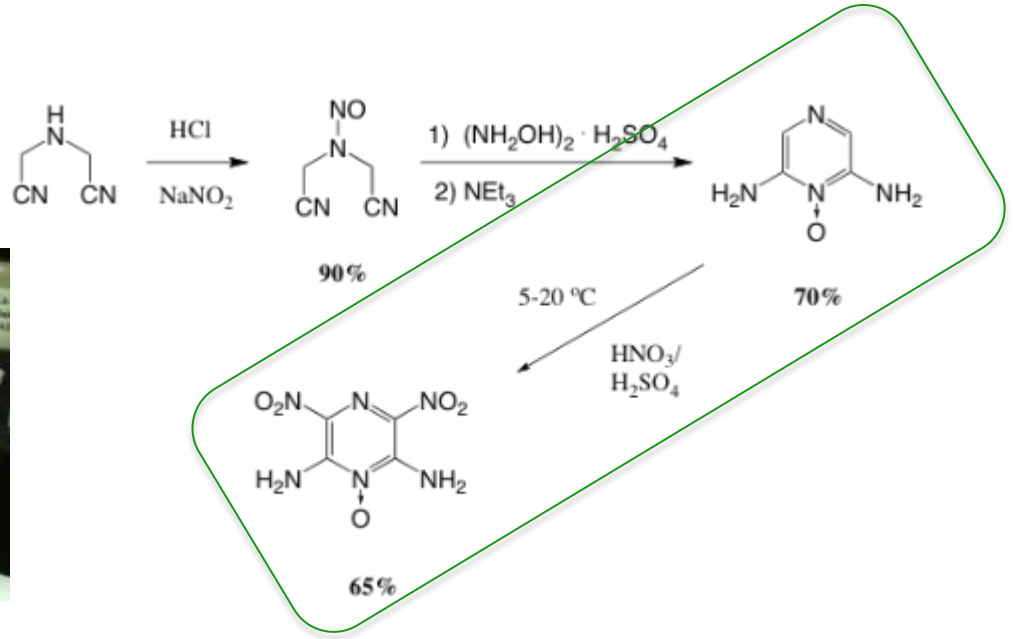
Polymorph Screen Conclusions



- Different morphologies of LLM-105 observed by evaporation using different solvents
- All XRPD patterns match starting LLM-105, no polymorph observed so far.

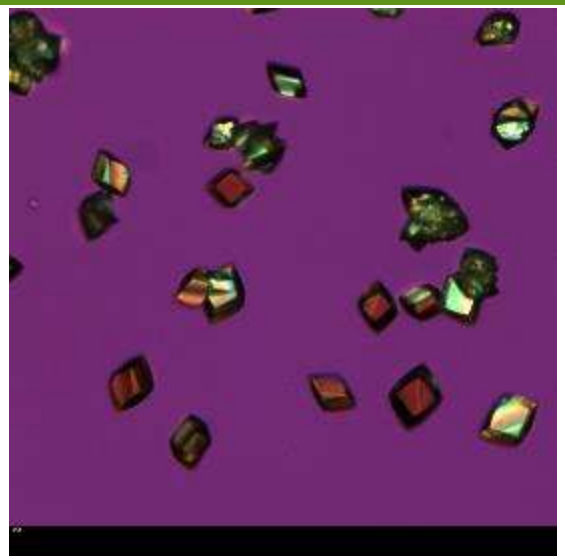
Morphology Evaluation from DAPO

- Add 2.5 mL quench solvent to 8 mL glass vial
- Stir at room temperature (28°C)
- Add 0.8 mL reaction mixture to quench solvent (~200 mg LLM-105)
- View particle morphology by Polarized Light Microscopy
- Analyze product by HPLC, and check solid form with XRPD.

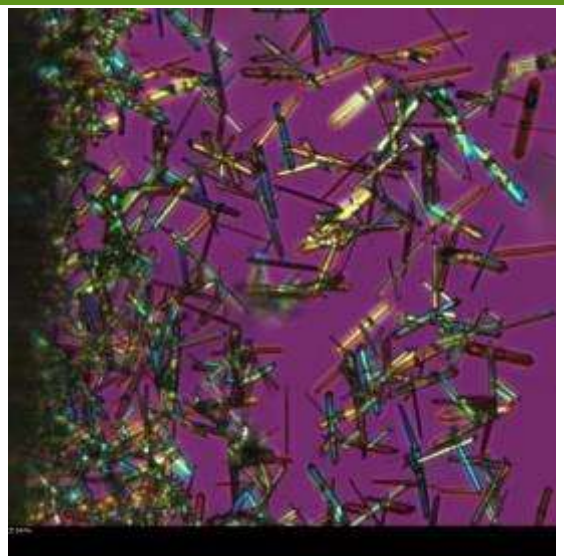


SELECTED IMAGES

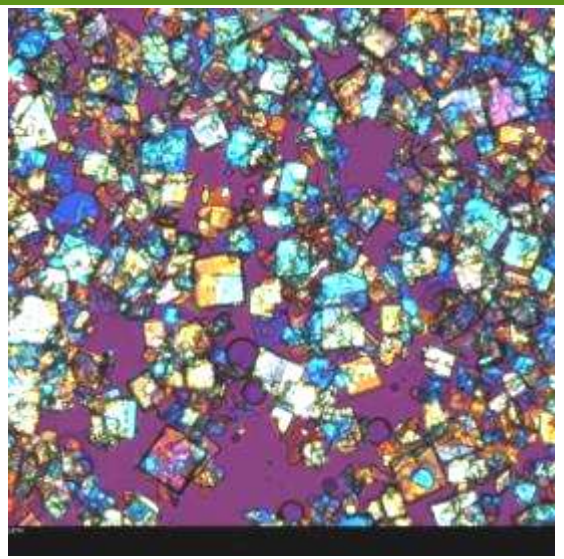
Selected Images



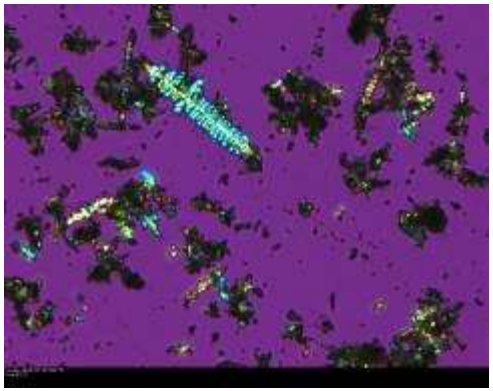
Formic Acid



Sulfolane



TFA



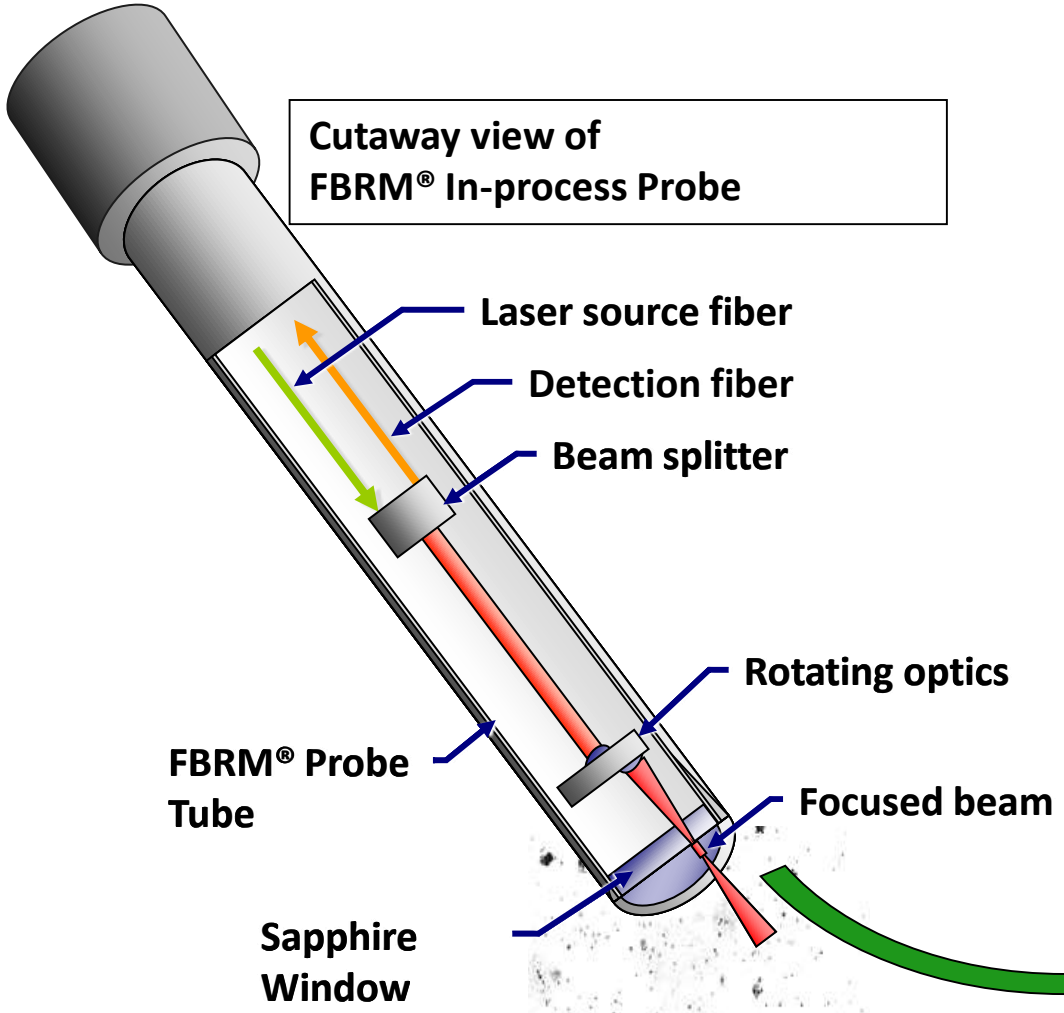
Water (baseline)

SCALE UP - QUENCH

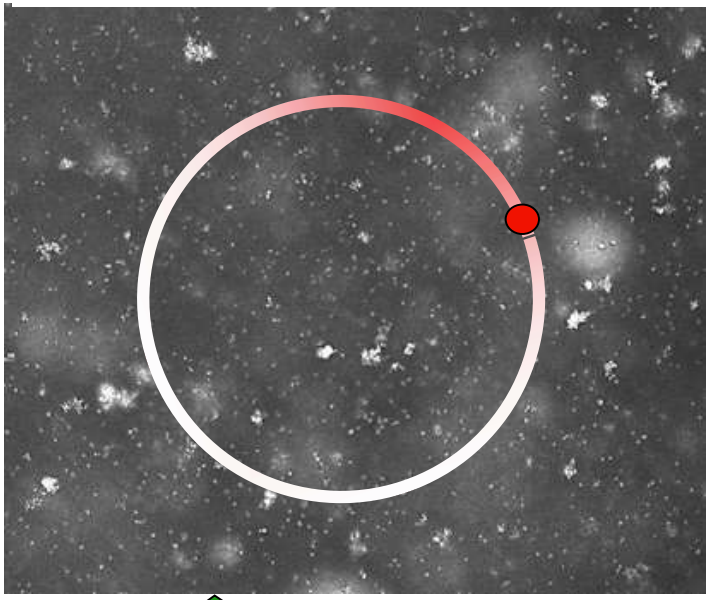
Particle Analyzers

- Focused Beam Reflectance Measurement
- Particle Vision Measurement

The FBRM® and PVM



PVM® image illustrating the view from the FBRM® Probe Window



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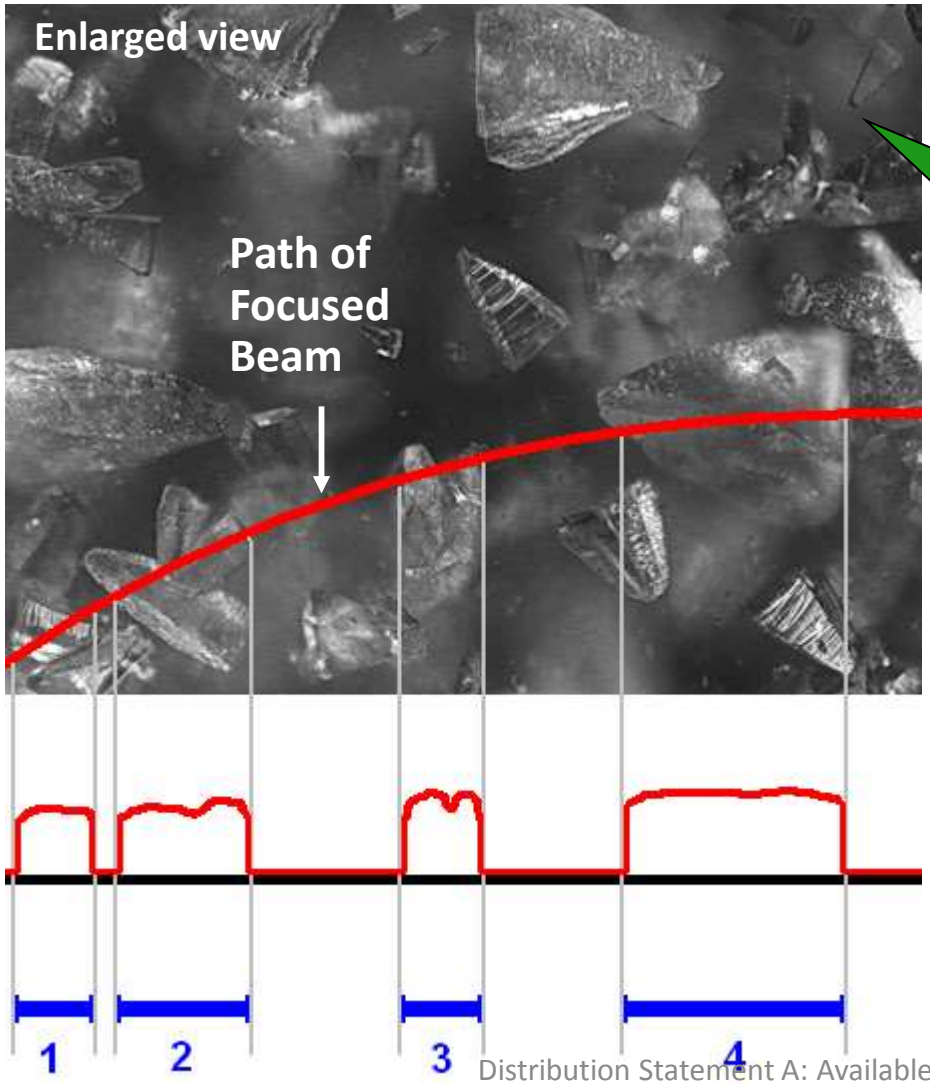
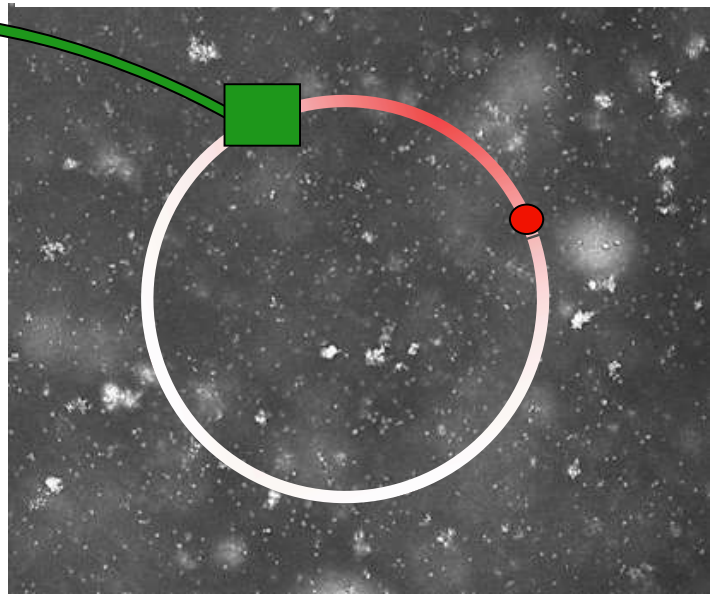
The FBRM® and PVM



PVM® image illustrating the view from the FBRM® Probe Window



Probe detects pulses of Backscattered light

And records measured Chord Lengths

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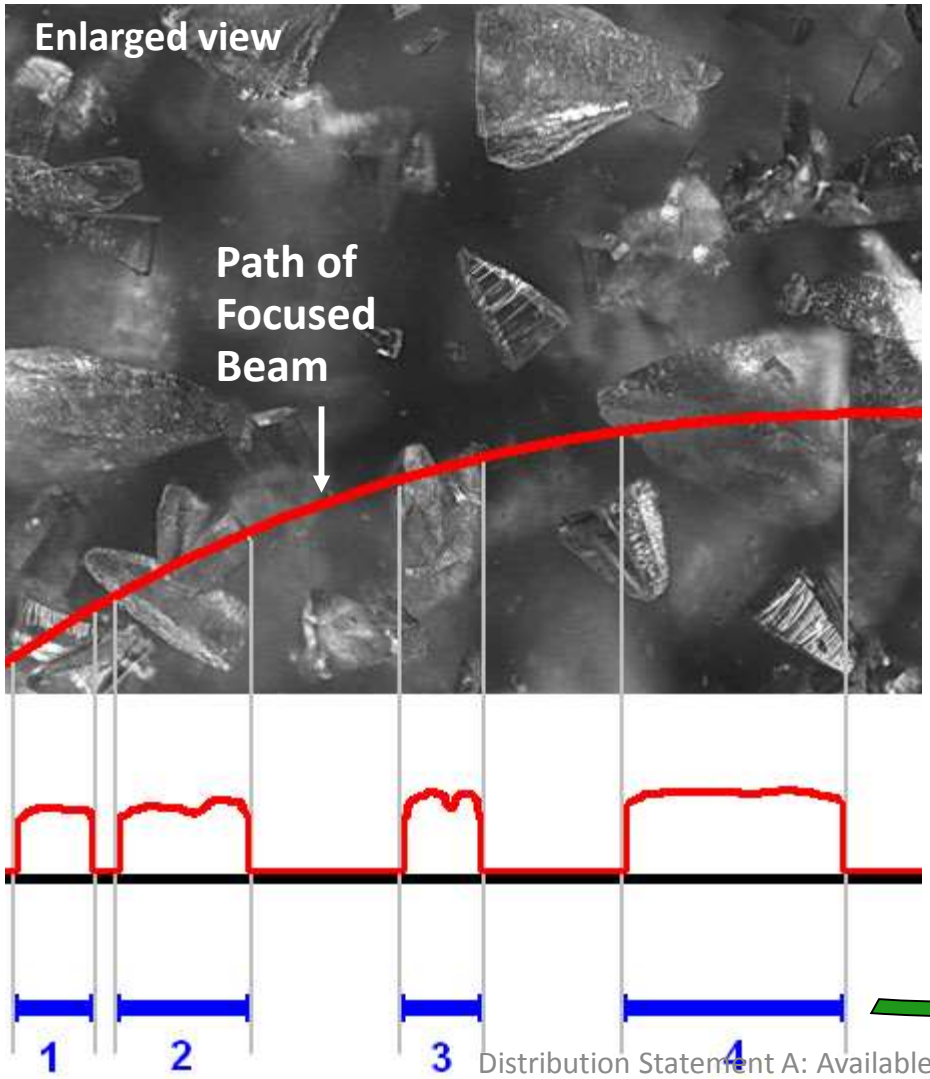
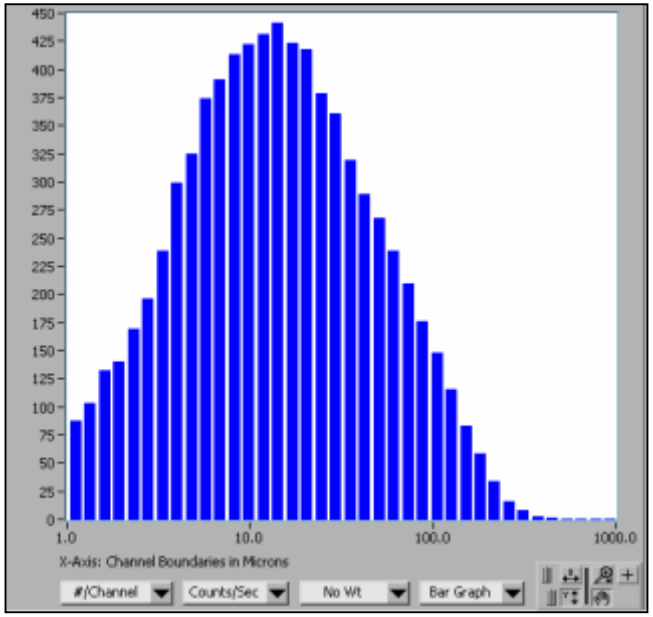
The FBRM® and PVM





Thousands of Chord Lengths are measured each second to produce the FBRM® Chord Length Distribution :

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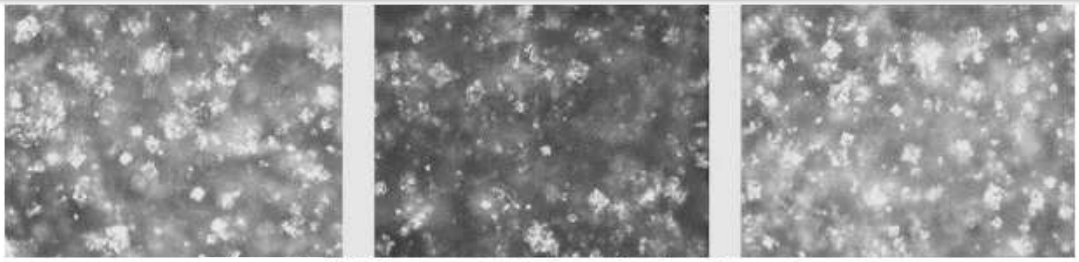
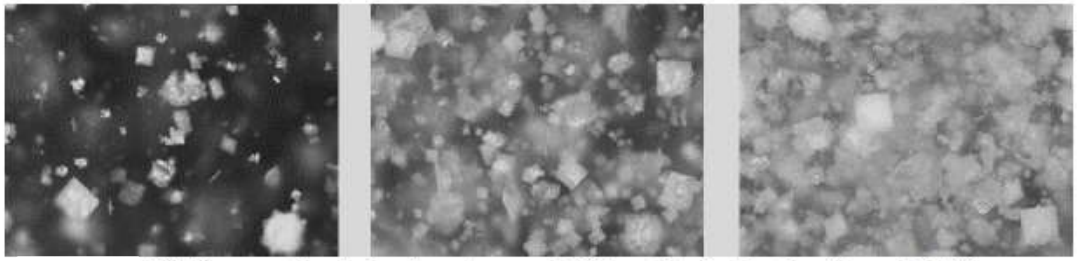
PVM



PVM images taken during the formic acid quench.

Formic Acid “quench”

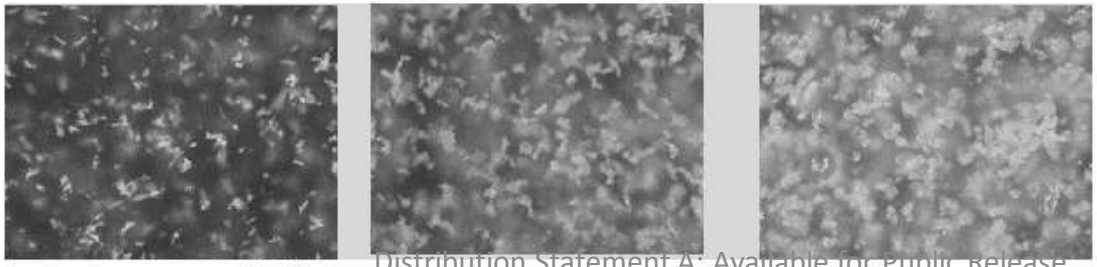
The same square shape persists during the subsequent water quench shown below.



PVM images taken during the water quench followed by the formic acid quench, NAL-14H001-031.

Followed by Water “quench”

The quench in just water produces particles that are neither square nor the primary particles as small as those from the formic acid / water quench.



PVM images taken during the water quench, lot NAL-14H001-032.

Baseline Water “quench”

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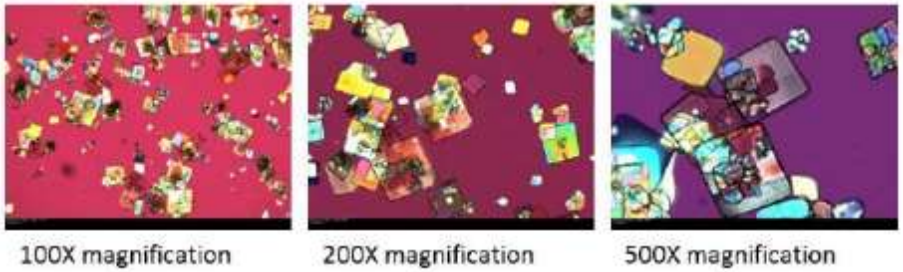
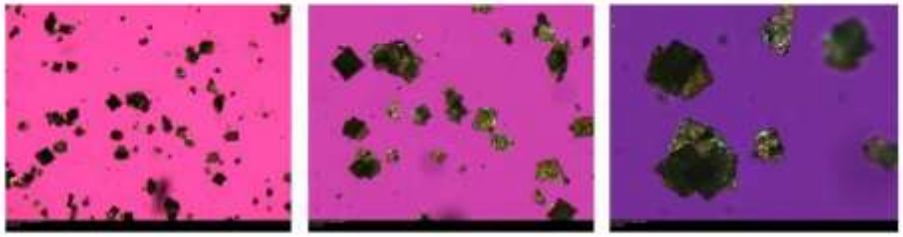
PLM



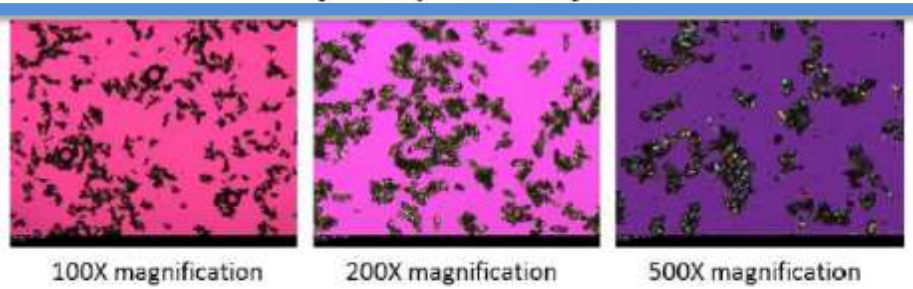
Polarized light microscopy images sampled directly from the formic acid quench.

Formic Acid “quench”



Polarized light microscopy images from the formic acid quench followed by the water quench. Sampled directly from the water quench.

Followed by Water “quench”



Polarized light microscopy images sampled directly from the water quench.

Baseline Water “quench”

HPLC – Purity and Potency

Experiment / Lot	Quench	Isolated Yield	HPLC Purity	HPLC Potency	Weight % Sulfate
Experiment 1 NAL-14H001-031	Formic acid, then water	48%	100%	101%	0.1%
Experiment 2 NAL-14H001-032	Water	48%	100%	101%	<0.03%

Particle Size

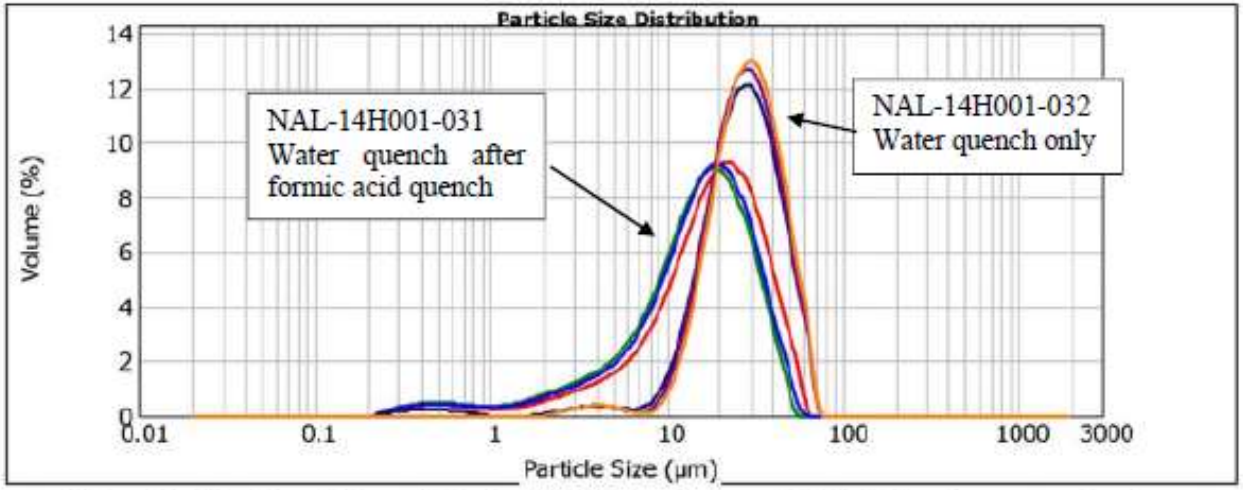


Figure 26: Overlay of the particle size distribution (volume %) for both scale up experiments.

Material	Samples	d(0.1) (microns)	d(0.5) (microns)	d(0.9) (microns)
NAL-14H001-031 Quench into Formic acid then water	3	4.0	16.6	34.6
NAL-14H001-032 Water quench	3	14.5	27.9	49.1

Conclusions and Thank You!

- Developed data supporting single form of LLM-105
- Developed data supporting tailored morphology across quench systems
- Still evaluating particle size distribution control while maintaining purity
- Safety assessment ongoing
- Grazie!!