

LLM-105 (DAPO Route) Morphology Study

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1.0 Introduction

The process to manufacture 2,6-diamino-3,5-dinitropyrazine-1-oxide (LLM-105) produces undesirable particle size distribution and morphology. This report focuses on development of the final reaction quench for the nitration of 2,6-diaminopyrazine-1-oxide (DAPO) to LLM-105, with the added goal to consistently produce regularly shaped, cubic particles.

2.0 Background

There are two synthetic routes to LLM-105 being investigated by LLNL with support from Nalas. These routes use different starting materials (dimethoxypyrazine or diaminopyrazine-1-oxide) and processing methods to produce LLM-105. Each route has pros and cons associated with quality and cost. To further investigate the product LLM-105, both synthetic routes continue to be used to produce materials for formulation efforts.

The route utilizing DAPO (referred to as the DAPO process, Figure 1) has fewer steps and produces a more pure product.

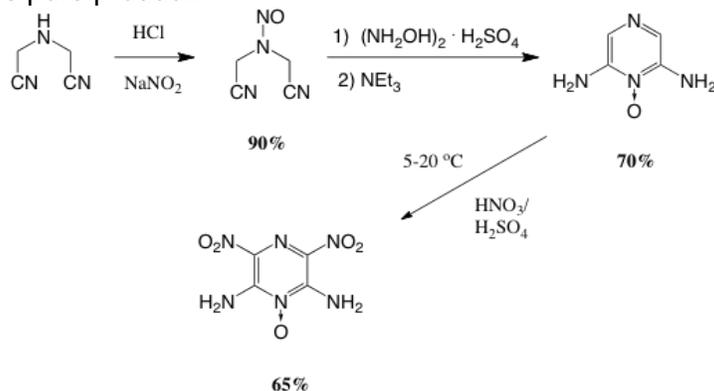


Figure 1. DAPO Process to LLM-105

Small scale experiments to evaluate the reaction quench were undertaken to better understand the LLM-105 particle morphology produced via this route. High aspect ratio particles are undesirable to the formulator. The preferred particle morphology is a cubic shape.

3.0 Morphology Evaluation of LLM-105 from DAPO

3.1 Reaction Quench

LLM-105 was produced using a standard procedure. An HPLC sample was taken 1.5 hours after completing the nitric acid dose; analysis indicated the reaction went to completion.

Preliminary quenching experiments were conducted by taking approximately 850 microliters of the reaction mixture held at 10°C and diluting into 2.5 mL quench solvent in an 8-mL glass vial at room temperature. This procedure provided approximately 200 mg of LLM-105 for each quench experiment based on the theoretical LLM-105 yield from the nitration reaction.

To study the effect of seeding, duplicate vials were set up for each quench solvent. The seed level was approximately 5-6% based on the theoretical yield of LLM-105 in the reaction mixture. Approximately 10 mg LLM-105 were added to each vial followed by 2.5 mL of the quench solvent. In both the seeded and non-seeded experiments a small stir bar was added to the vial and the quench solvent was stirred during and after the addition of the reaction mixture.

In all experiments the reaction mixture was added drop-wise to the quench solvent. In some cases the reaction mixture addition was stopped for 15 to 30 seconds to allow bubbling to subside before completing the addition. In some of the quench experiments, in which bubbling was observed, a red-brown gas believed to be nitrogen oxide was observed.

LLM-105 particle morphology was assessed by taking polarized light microscopy (PLM) images 10 to 15 minutes after the reaction mixture had been added to the quench solvent. Samples were withdrawn using a plastic pipette from the stirred mixture. Where possible, images were taken at three magnifications. In some cases evaporation of more volatile solvents was observed and the precipitation of LLM-105 particles occurred. In these cases a progression of images is presented to show the change in morphology.

3.2 Temperature Cycling

The morphology of LLM-105 was observed after heating and cooling a slurry of two to six mg in a series of select solvents, including 1M aqueous hydrochloric acid, acetic acid, formic acid and trifluoroacetic acid, concentrated hydrochloric acid, acetic acid, formic acid, and trifluoroacetic acid, nitromethane, chloroform, dichloromethane, fluorobenzene, dimethylformamide / water, sulfolane / water, and water.

The temperature cycle employed was initiated by heating at a rate of 0.5°C/min to approximately 4°C below the solvent's boiling point followed by cooling to 10°C at 0.15°C/min. Exceptions to the maximum temperature for the heat/cool profile included concentrated hydrochloric acid, hexane and dichloromethane, which were heated to approximately 40°C before cooling to minimize boil off. Most of these experiments were slurries for the entire temperature range. Only concentrated hydrochloric acid resulted in the complete dissolution of LLM-105. The particle morphology of the starting material is compared to that of the material resulting from the temperature cycled experiments.

3.3 Analytics

3.3.1 HPLC for purity and potency

An isocratic reversed phase HPLC method was used to determine reaction completion and the presence of any intermediates before proceeding to the quench experiments. The method utilized a Sunfire C18 column, aqueous formic acid and acetonitrile mobile phase run at 1 mL/min. The column was kept at 40°C and data was collected on the UV detector at 310 nm.

3.3.2 Ion Chromatography

Samples (25 mg) were prepared by mixing LLM-105 in a dimethylsulfoxide/water solution followed by centrifugation and sampling the supernatant. Residual ions such as nitrite, nitrate, sulfate, formate, were identified using a HPLC method with conductivity detection.

3.3.3 Optical Microscopy – Particle Morphology

An Olympus BX53 Polarizing Light Microscope (PLM) was employed. The microscope was set up for Koehler illumination with long working distance objectives at 10X (LM PlanFLN NA 0.25, infinity corrected), 20X (LM PlanFLN, NA 0.4, infinity corrected), and 50X (LM PlanFLN, NA 0.5, infinity corrected). A first order red compensator plate was inserted into the optical path while images were captured using a QICAM fast 1394 COLOR camera.

3.3.4 Particle Size

The particle size and particle size distribution were determined using the Malvern Mastersizer 2000 with a Hydro 2000S wet dispersion sample accessory. The optical path and sample cell windows were cleaned to provide a particle free background.

Samples were prepared by weighing 20 to 60 mg into a 20-mL glass vial. Approximately five mL of dispersant (water) were added to the sample and a polypropylene transfer pipette was used to mix the concentrated sample. Five seconds of sonication were employed to provide a fully dispersed sample. A transfer pipette was then used to introduce the concentrated sample into the Malvern Hydro 2000S sample accessory operating at 600 to 1750 RPM.

Measurement data was acquired after a prescribed period of time that allows the entire volume within the sample accessory (approximately 125 mL) to reach an equilibrium dispersion density.

4.0 Screening Experiments Results

4.1 LLM-105 reaction mixture into seeded and non-seeded solvent systems

Following the quenching step, the mixtures were allowed to stir for 10 to 15 minutes before the precipitate was observed under polarized light. In all cases, a phase separation occurred immediately upon addition of the reaction mixture to one of 21 screened quench solvents. Aqueous-based or concentrated acid quench solvents resulted in the precipitation of a yellow solid. Quench experiments involving non-polar organic solvents resulted in two distinct liquid phases.

In the case of concentrated hydrochloric acid, a significant amount of the solids appeared to dissolve before reaching the final slurry concentration. The sulfolane/water (90:10) solvent system resulted in almost complete dissolution of the LLM-105, and became a red-brown colored, slightly hazy solution. It is possible that the nitrogen oxide gases are soluble in the sulfolane water system, providing the change in solution color.

Changes in shape and size are reported in the following tables.

Overall there appears to be no advantage of seeding for the precipitation of LLM-105 using these conditions. It is possible that the solubility difference between the reaction mixture to the quench solvent is sufficiently large that a high degree of supersaturation is obtained; precipitation occurs too rapidly to permit a positive effect from the seeds.

Of particular interest are the experiments that produced different particle morphologies. Quenching in concentrated hydrochloric acid results in blade or needle shaped particles. In a similar fashion concentrated trifluoroacetic acid also provides larger aspect ratio particles of the

rod and blade morphology. Precipitation from concentrated formic acid resulted in the greatest number of cubic shaped particles.

Most aqueous-based quench solvents resulted in regularly shaped, equant particles that were very small. The inclusion of dimethylformamide with water or sulfolane with water resulted in the precipitation of higher aspect ratio blade-shaped particles.

PLM images of the most promising morphology lots are shown below in Figure 2.

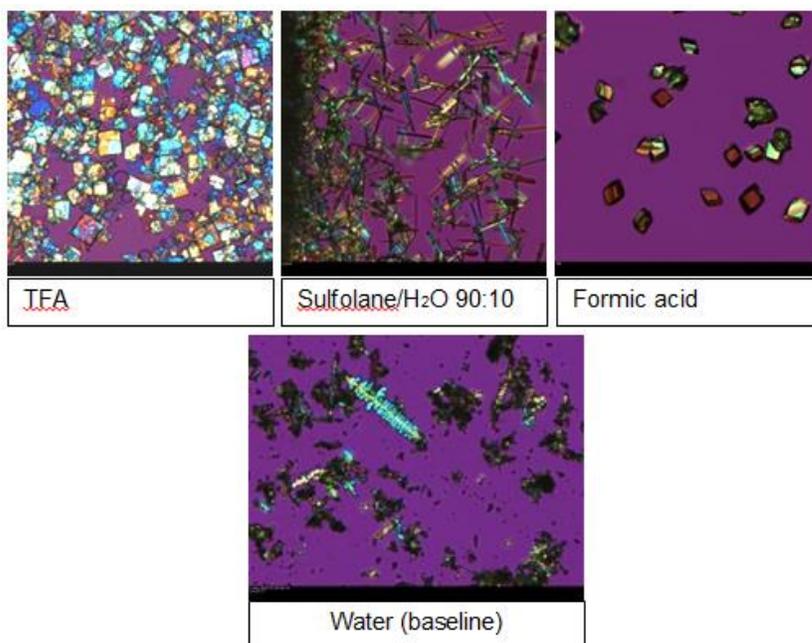


Figure 2. Selected morphologies

4.2 Temperature Cycle

A single temperature cycle to approximately 4°C below the solvent's boiling point was employed to dissolve additional LLM-105 with the expectation that precipitation upon cooling could result in changes in particle morphology. A diverse set of solvents was chosen to explore potential variations in LLM-105 morphology resulting from a process that may include a warm quench and a subsequent cooling step.

These experiments show that small irregularly shaped particles are very common. Higher aspect ratio particles such as rods, blades or other elongated less defined particles were observed from acetic acid, water, fluorobenzene, nitromethane and sulfolane and water (1:1). Particles from concentrated formic acid were largely cubic in shape with some appearing to have a pyramidal shape.

The diversity of physical chemical properties of this set of solvents is quite high, consisting of a large range in boiling point and vapor pressure, for example. It is possible that the varying amount of the higher aspect ratio particles observed in these solvents is dependent on the miscibility of the reaction mixture with the quench solvent and subsequent LLM-105 solubility. Additional heat and cool cycles may eventually drive the product to a more uniform shape independent of the solvent.

4.2.1 Evaporation from a Saturated Solution

Portions of the saturated solutions prepared in the temperature cycling experiments were evaporated to dryness on a specialized microscope slide having an approximate 50-microliter cavity. A similar set of particle shapes was observed. Evaporation from the dilute acids produces very small particles of irregular or no discernable shape.

The solubility of LLM-105 in chloroform, hexane, fluorobenzene, and sulfolane/water (1:1) is very low as the amount of precipitate from the saturated solution was very small. Nitromethane provided long needle shaped particles. Concentrated acids provided a mix of blades, pyramids, and rectangular shaped particles.

5.0 Scale up of formic acid quench

Quench experiments at the screening scale indicate concentrated acids have the largest impact on LLM-105 morphology. Formic acid was chosen to scale up from the screening scale (2.5-mL quench volume in 8-mL vial) to a 100-mL EasyMax™ glass reactor containing approximately 25 mL of acid.

LLM-105 was prepared using standard conditions. The LLM-105 mixed acid reaction mixture was then transferred from the nitration vessel (100-mL EasyMax™ glass reactor) to a second 100-mL EasyMax™ glass reactor containing the quench solvent using an Ismatec pump at the lowest speed, ~0.05 mL/min. Precipitation of LLM-105 during the quench was monitored using PVM (Particle Vision Microscopy) for real-time imaging and FBRM (Focused Beam Reflectance Measurement) for particle size measurement.

Scale up experiment 1 (Lot NAL-14H001-031) involved quenching into concentrated formic acid held at 20°C as described above, followed by quenching this mixture into an equal volume of water held at 40°C. The solids were vacuum filtered and air dried in a fume hood behind a blast shield over a period of three days before analysis.

Scale up experiment 2 (Lot NAL-14H001-032) involved a similar reaction mixture preparation followed by quenching into water held at 40°C. The reaction mixture was added to the water at a slow drop-wise rate to minimize any increase in temperature or bubbling. The solids were vacuum filtered and air dried in a fume hood behind a blast shield over a period of three days before analysis.

5.1.1 Pictures and images during the quench

In-situ PVM images taken during the quench into formic acid show a distinct square shape consistent with the morphology observed during the screening experiments. The same square shape persists during the subsequent water quench. The baseline quench into water produces particles that are neither square nor the primary particles as small as those from the formic acid / water quench. PVM images are shown in Figures 3 through 5.

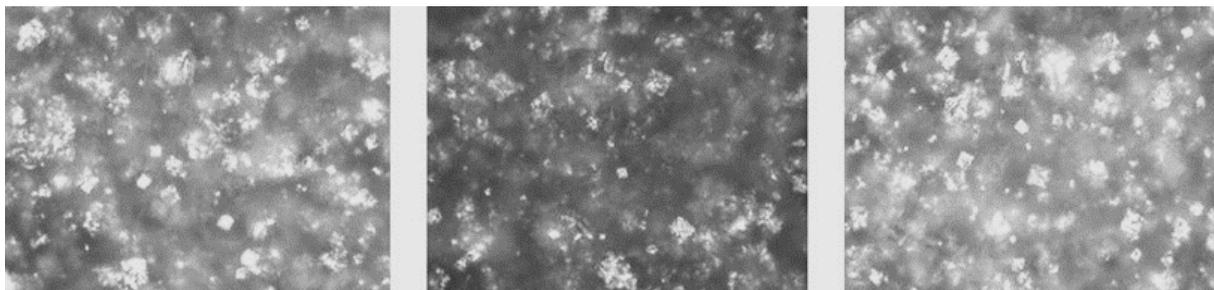


Figure 3: PVM images taken during the formic acid quench.

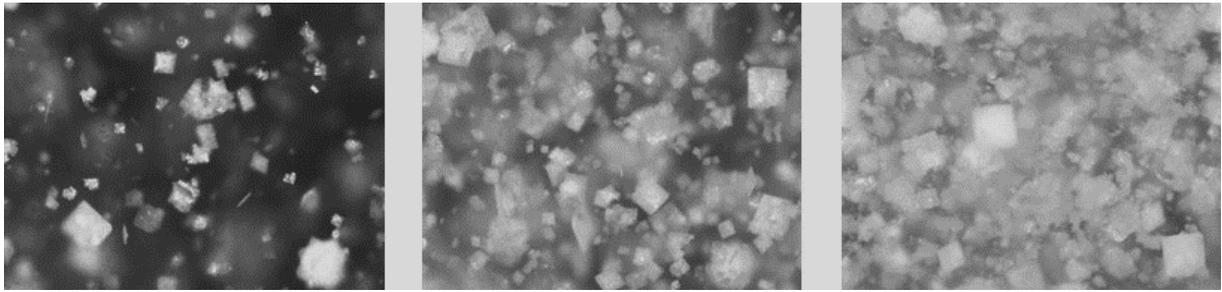


Figure 4: PVM images taken during the water quench followed by the formic acid quench, NAL-14H001-031.

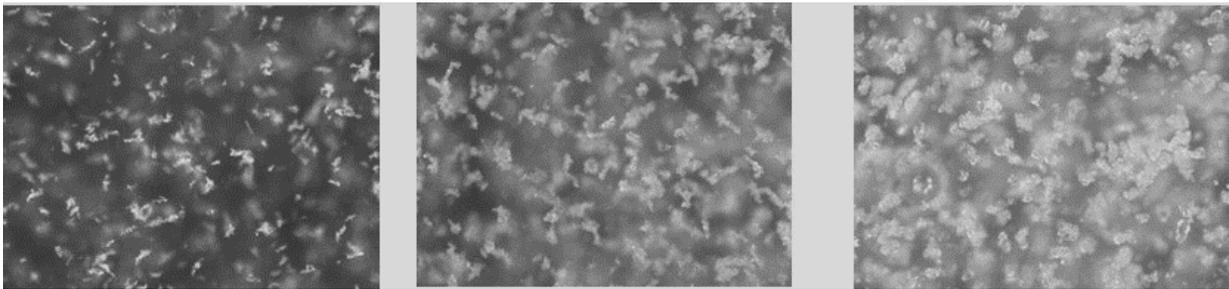


Figure 5: PVM images taken during the water quench, lot NAL-14H001-032

The polarized light microscopy images from these experiments are consistent with the observations noted from the in-situ PVM images. Formic acid and formic acid/water provide regularly shaped square particles. The addition of the water quench following the formic acid quench appears to facilitate the particle size reduction from the large square plates to much smaller primary particles. The large square particles in the water quench following the formic acid quench appear to be polycrystalline, comprised of many small crystalline particles. PLM images are shown in Figures 6 through 8.



Figure 6: PLM images of LLM-105 sampled directly from the formic acid quench

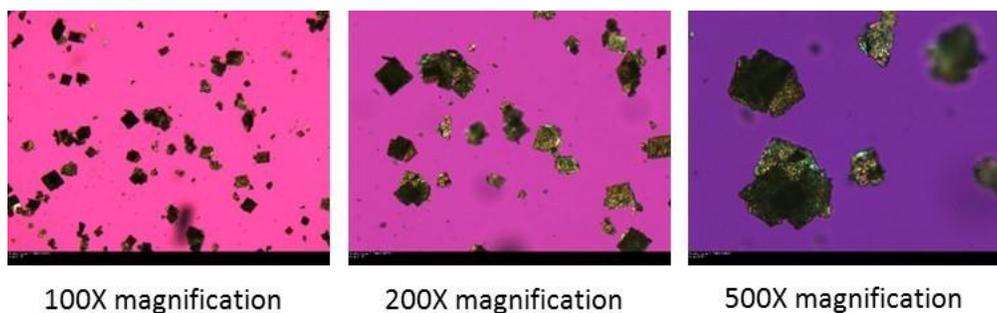


Figure 7: PLM images of LLM-105 quenched in formic acid quench followed by water. Samples were taken directly from the water quench.

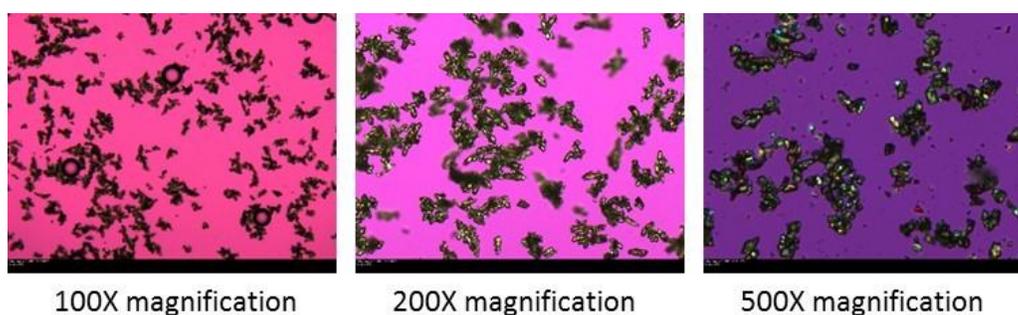


Figure 8: PLM images of LLM-105 sampled directly from the baseline water quench.

5.1.2 Purity and Potency of the isolated product

The isolated yield, purity, and potency were comparable between LLM-105 lot NAL-14H001-031 (formic acid quench, then water quench) and LLM-105 lot NAL-14H001-032 (water quench). The results are presented in the following Table I.

Table I: Isolated yield, HPLC Purity, HPLC Potency, and Weight % Sulfate in LLM-105 lots NAL-14H001-031 and NAL-14H001-032

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%

The only difference observed between these two lots is the presence of a small amount of formic acid in lot NAL-14H001-031 from Experiment 1. Evidence of formic acid is observed in the ion chromatogram as broad signal in the 3- to 4-minute retention time and in the proton NMR spectrum as a weak signal at 8.1 ppm.

5.1.3 Particle size of the isolated product

Samples of each scale up experiment were prepared in triplicate and analyzed on the Malvern MasterSizer 2000. The following table (Table II) and plot (Figure 9) show that the particle size distributions are similar having $d(0.9)$ values of less than 50 microns. Lot NAL-14H001-031, employing the formic acid quench followed by water quench, shows a broader distribution and smaller size. Both data sets are consistent with the particles observed using polarized light microscopy.

Table II: Particle size analysis for both scale up experiments. The data are an average of three separate sample preparations.

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

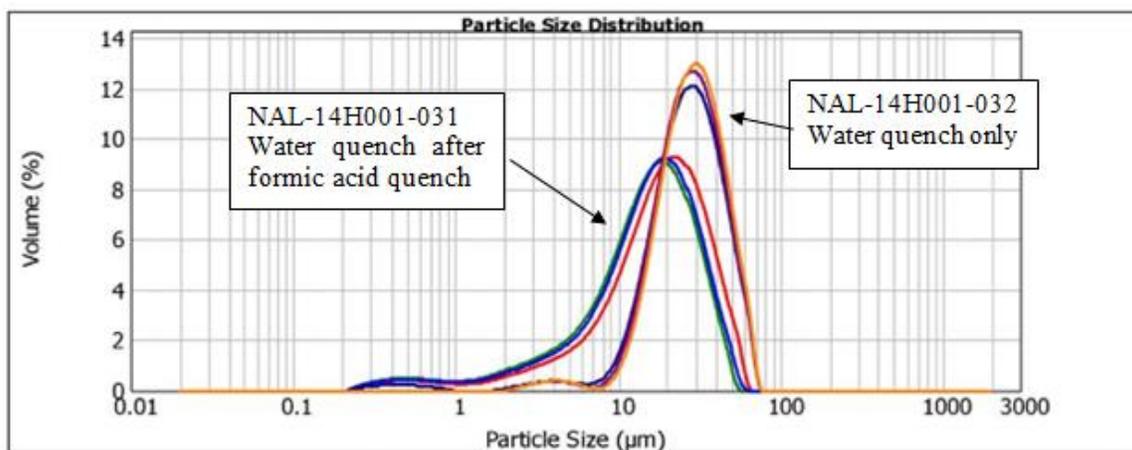


Figure 9: Overlay of the particle size distribution (volume %) for both scale up experiments.

5.1.4 Powder XRD and PLM images of the isolated product

The powder x-ray diffraction pattern for both lots of LLM-105 are consistent with the reference calculated powder pattern from the single crystal structure of LLM-105 (Cambridge Crystal Structure Database Refcode YEKQAG).

PLM images of the air dried LLM-105 show that formic acid followed by a water quench results in small particles and large polycrystalline chunks that easily break up into the smaller primary particles. The particles produced from a single water quench appear to precipitate as agglomerates or twins of a slightly larger size.

6.0 Conclusions

Different solvents were found to provide significantly different LLM-105 particle morphology. Consistent with previous work, the presence of dimethylformamide or sulfolane produced elongated blade or rod shaped particles. The most promising solvents include the concentrated acids and specifically formic acid, which provided the most consistent and cubic particle shape in this study. Seeding the quench does not have a significant impact on the

morphology or particle size. A single temperature cycle in various solvents resulted in the precipitation of regularly shaped equant particles from most of the solvents selected. Large needles precipitated from concentrated hydrochloric acid while dilute formic acid, hexane, nitromethane, and water produced some fraction of rod shaped particles. Short blade-shaped particles were observed from fluorobenzene, and mixtures of dimethylformamide/water and sulfolane/water. Evaporation of aqueous-based solvent systems should be avoided as it may lead to the formation of elongated particles rather than the preferred equant or cubic shaped material.

Scale up of the formic acid quench followed by a water quench provided LLM-105 of excellent purity and potency with small regularly shaped particles. Optimization of the formic acid/water quench system may provide a smaller particle size distribution free of formic acid or sulfate. The 6-gram scale batch of LLM-105 that was quenched directly into water was also high purity and potency with no sulfate. The particle size distribution of this batch was slightly larger than the formic acid quenched lot.

Future work includes evaluating further scaleup and stability testing of the crystallization media.