API Crystal Engineering in Early Development

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Abstract

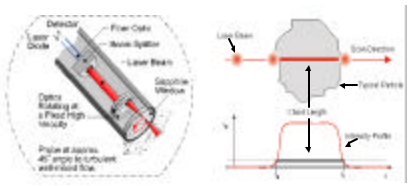
Within Early Development, Chemical Development is charged with producing API with the agreed upon salt and solid state form within given timelines. To accomplish this, unit operations such as crystallization and filtration must be considered and optimized when scaling a process even when dealing with the first kilo-size batches. The optimization involves engineering a filterable solid for typically isolating the most stable solid state form. Two systems that we routinely use to engineer crystallizations, FBRM and PVM, will be introduced and examined through case studies.

Introduction

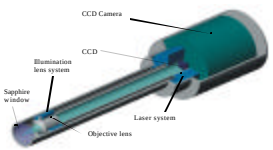
Focused Beam Reflectance Measurement (FBRM) is a powerful tool to track particle size changes through a chord length distribution during a crystallization *in situ* and in real time. A probe is inserted into the system of interest and a focused laser beam on a fast-spinning ring sends light into the system which is backscattered when it bounces off of a particle. The backscattering time is measured and translated into a particle chord length. Thousands of particles are measured and a chord length distribution is obtained that can be tracked throughout a crystallization to record distribution changes that can help one determine the optimal temperature and concentration for batch seeding, the onset of crystallization, crystal growth/breakage, and the crystallization endpoint (or equilibrium).

FBRM

Probe **Measurement Method**



PVM



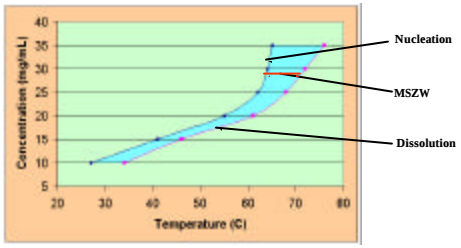
Particle Vision and Measurement (PVM) is *in situ* video microscopy that captures and records pictures of a system in real time avoiding the need for countless stage microscope samples and the ability to save all captured micrographs electronically.

These data can help to confirm the statistics generated from the FBRM. Together, these tools help us to optimize our processes and lead us to higher yielding and very pure API while also monitoring batch-to-batch consistency.

Metastable Zone Width (MSZW)

A crystallization can be dominated by either nucleation or growth depending on how critical variables are controlled. Generally, nucleation will dominate when supersaturation is near to or greater than the upper limit of the metastable region and growth will dominate at low supersaturation in the presence of sufficient crystal surface area. Crystal growth is preferred over nucleation since nucleation can generate a wide particle size distribution, cause agglomeration, and give large batch-to-batch variation. In the example below, FBRM is used to determine the metastable zone width by identifying the temperatures at which known concentrations of product dissolve and crystallize. Optimal seeding occurs within the metastable zone shown in green.

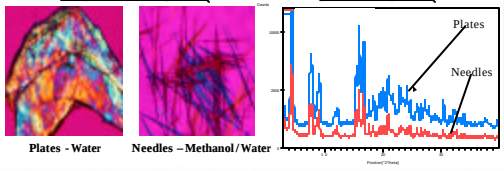
MSZW determination for Compound A in isopropanol



Crystallization Case Study

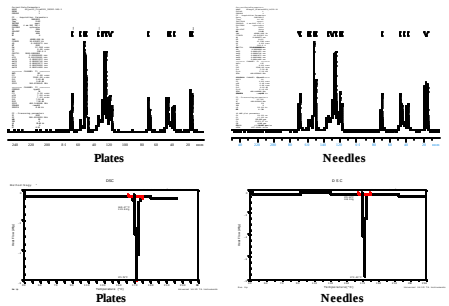
A procedure to make Compound B free base from Compound B di-HCl di-hydrate with the correct solid state form needed to be developed quickly. A 99g experiment in an aqueous NaOH system resulted in a 2.5% solids concentration to effect stirring and a filtration that took three days using two filters! A scalable particle with good filtration characteristics needed to be developed without changing the agreed upon solid state form. The filtration rate and flux increased significantly in a methanol/water system, but the particle morphology had changed. Fortunately, it was still the correct solid state form by pXRD, DSC, and SSNMR.

Morphology Comparison **pXRD Comparison**



Plates - Water **Needles – Methanol/Water**

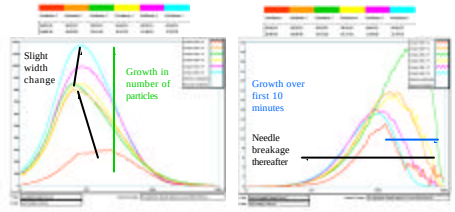
SSNMR Comparison



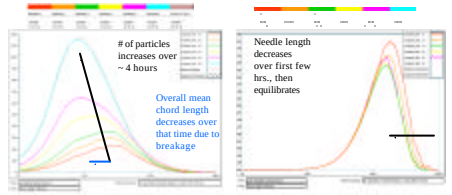
Crystallization Scale-up

With the solid state issue under control, the process was executed at 160g and 670g scale. FBRM and PVM were used to monitor the progress of the crystallization and to determine the variability between batches. Since these crystals have a high aspect ratio, one FBRM statistic was not sufficient to characterize the system. Thus, two FBRM statistics were used, one to monitor the particle chord width and one to monitor the particle chord length. The batches show very similar profiles over time as shown below:

160g Needle Width Analysis **160g Needle Length Analysis**

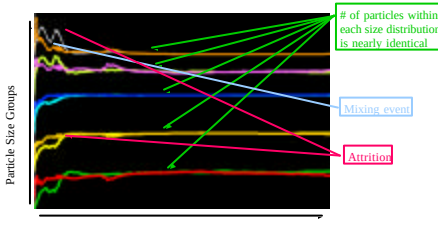


670g Needle Width Analysis **670g Needle Length Analysis**

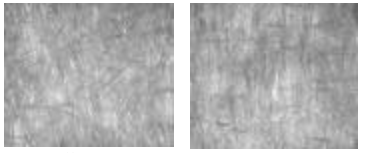


Below, the trend of different particle size groups for both experiments over time are depicted. Throughout most of the experiment, the trends are superimposable. At the beginning of the experiment, two differences in the trend are noted – one from a stirrer malfunction that skewed the data and one from particle attrition once the stirring malfunction was resolved.

Comparison of Chord Length Distribution Trends over Time



Images were collected during the course of both experiments using PVM and visually studied and compared to verify the accuracy of the statistics and trending provided by the FBRM. Below is a comparison of both batches just prior to filtration showing very similar traits.



160g Run 670g Run

Conclusion

FBRM and PVM are valuable tools in analyzing early development API crystallizations. Determining the metastable zone width of crystallization systems along with the ability to record, track, and trend particle chord length provides Chemical Development the information it needs to successfully scale up API crystallizations with batch-to-batch consistency and high quality to provide to our customers..

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