API Crystal Engineering in Early Development

Steve Fabian, Jeffrey Grimm, Fuqiang Liu, Stephen Manzo, Christopher Nilsen, and Kirk Sorgi


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 tolerable 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 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

CPTOSS,BL4mm,RT,ct=3.5ms,spin=5000Hz

Nucleation

Dissolution

MSZW determination for Compound A in Isopropanol

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. To accomplish this, unit operations such as crystallization and filtration must be performed with the agreed upon salt and solid state form within given timelines. To determine the optimal temperature and concentration for batch seeding, the batches show very similar profiles over time as shown below:

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 length and one to monitor the particle chord length. The batches show very similar profiles over time as shown below:

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.

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 provide 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.

Acknowledgements

The authors wish to acknowledge the following scientists for their help with this work:

Nagy Fawzy

Wenhua Wu

ShinHong Kang

Jiayi Wu

Dawei Xu

Lian Huang

Naga0 Fabian

Esimma Hsiung