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# Digital Design of a Crystallization Process: Why particle size and shape measurement matters!

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SUMMARY

Population balance modelling is a widely used tool to understand the mechanism and kinetic parameters of crystal growth at the bench, to facilitate scale-up to Production. In this work, we present recommendations for particle size and shape analytical methods to improve the predictive capability of 1D and 2D population balance models for crystallisation of contemporary active ingredients. For 1D models, we report that the optical model for laser diffraction, a common technique for measuring particle size distribution, can significantly impact the growth parameters resolved from the model. For 2D models, particle image analysis of powders and single crystals give valuable length and width data to predict how the aspect ratio of particles evolves. Future work will be directed towards applying these tools when scaling a crystallization process.



## INTRODUCTION

Crystallization is the most widely used method for separating an active ingredient from a reaction product mixture. It functions to control purity, crystal form, particle morphology, and particle size distribution (PSD) (Bötschi et al). The application of population balance modelling (PBM) to aid crystallization process understanding and development has been growing with improvements in process analytical tools (PAT) and numerical software packages.

There are numerous sources of error associated with the measurement inputs for PBMs that directly impact the estimation of crystallization rate parameters, and hence the predictive capability of the model. In turn, both measurement and model influence one another and can be co-optimised to better understand the process. Using an agrochemical case study, our work details method development for PSD measurements and the direct impact on the output of a mechanistic model of a crystal growth process.

## MATERIALS AND METHODS

Crystallization experiments were conducted using a Mettler Toledo Easymax reactor (<100 mL) with in-situ IR and offline HPLC for solute concentration. Particle size and shape analysis was conducted using a Mastersizer 3000 and Morphologi G3 from Malvern Panalytical and a bespoke immersion cell for single crystal work. These data were used to develop a mechanistic model of the crystallization process using gPROMS Formulated Products from Siemens PSE.

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## RESULTS AND DISCUSSION

Our results show the effects of measurement error for particle size and shape measurements during crystallization model calibration activities across several applications. We provide recommendations for Standard Operating Procedures (SOPs) and workflows when performing particle size and shape analysis to ensure the data is of sufficient quality for developing a mechanistic model. Specifically, we demonstrate the significant impact of the optical model used for laser diffraction measurements on mechanistic modelling parameters.

We also detail a new workflow using single crystal microscopy growth data to calibrate a 2D morphological crystallization model for the prediction of particle size and shape. With these models, we explore the crystallization design space for our agrochemical system (Figure 1) and show the potential for improving particle properties for downstream processes and end performance. Our results aid in identifying robust process conditions which provide bounds on the minimum aspect ratio of the product material based on seeding strategy.

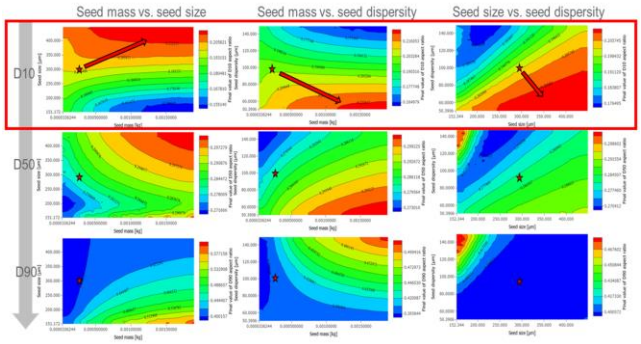


***Fig. 1.*** *Impact of seeding on the final product aspect ratio.*

## CONCLUSIONS

Optical model selection for laser diffraction measurements has significant impact on the ability to predict crystallization kinetics. Mie optical method provided significantly better product PSD predictions when compared to the Fraunhofer method.

Malvern Panalytical Morphologi (PSD by microscopy image analysis) can also be used to obtain seed PSD with the ability to filter out artefacts. For needles, the length, width, and aspect ratio distributions for particle shape and size can be extracted and used to build a 2D population balance model.

Single crystal growth measurements can be used to directly extract growth kinetics, where other mechanisms may influence "growth only" desupersaturation measurements. Growth/dissolution cycles can be used to build a 2D population balance, by decoupling surface integration and mass transfer limitations.

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