Kinetic modeling of crystallization: application in Pharmaceutical industry

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Objectives & Challenges

The objective of this Master Project is to:

- Build a robust model, which can predict outcomes of pharmaceutical drug substances crystallization under various experimental conditions.
- Establish a generic methodology which leads to such a model, and is transferable to any drug substance.

Prediction of crystallization kinetics and evolution of particle size distribution of pharmaceutical drug substances during research phase, production or during upscale from the lab to the plant can lead to substantial savings of time and resources.

While prediction of x10 and x50 is accurate, satisfactory prediction of x90 would require refinement of the model (i.e., include additional mechanisms of minor contribution).

The computational process that was followed for the parameter estimation, and the obtained values.

The model was constructed with only 4 experiments and 3 computational loops.

The approach of this Project to kinetic modeling.

The model is predictive and robust, at least regarding x10 and x50, also for experiments not included for its construction.

Potential Applications in Pharma

Model prediction of quintiles (x10, x50, x90) for varying agitation (left) and cooling rate (right).

1. Process design: Perform simulations and target the effect of a specific property. Give directions in order to obtain a desired PSD.
2. Scale-up risks: Evaluate the sensitivity of product quality on various processing parameters, and identify those with high risk. Here, simulations suggest that agitation is a potential scale-up risk.
3. Process stretching: Evaluate at which cooling rate there is a high risk to trigger primary nucleation or crystallization of an unstable polymorph (i.e. the concentration profile crosses the purple or grey curve, respectively). Here, simulations suggest that such a risk is not probable, since an enormous cooling rate (380°C/hour) would be required for primary nucleation to occur.

Conclusions

- A robust model was built, which predicts crystallization outcomes under varying conditions (5 varying experimental conditions).
- While prediction of x10 and x50 is accurate, satisfactory prediction of x90 would require refinement of the model (i.e., include additional mechanisms of minor contribution).
- A generic process was established in order to achieve this result.

This process involves only 4 experiments (as inputs to the software) and 3 computational steps.

- The model has several applications in Pharmaceutical industry. It assists to speed up both the early and late phase drug development, by reducing the experimental workload and identifying scale-up risks.

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References