Kinetic modeling of crystallization: application in Pharmaceutical industry

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Objectives & Challenges

The **objective** of this Master Project is to:

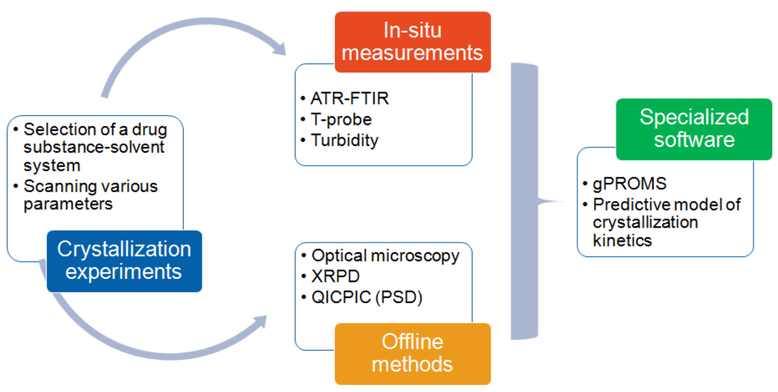
- Build a robust model, which can predict outcomes of pharmaceutical drug substances crystallization under various experimental conditions.
- Establish a generic methodology which leads to such a model, and is transferrable to any drug substance.

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**.

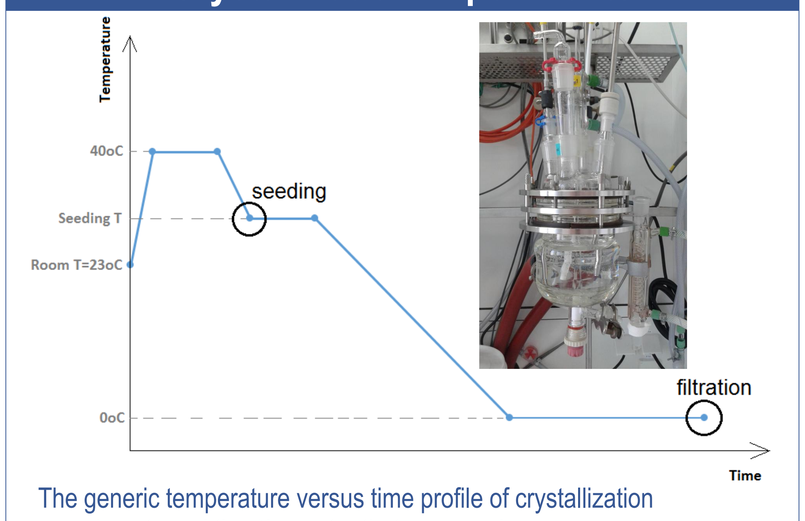
However, various **challenges** are involved:

- Identification of the crystallization mechanisms that are present in the specific substance-solvent system.
- Solve the complex population balance equation and find the corresponding kinetic parameters.

Methodology



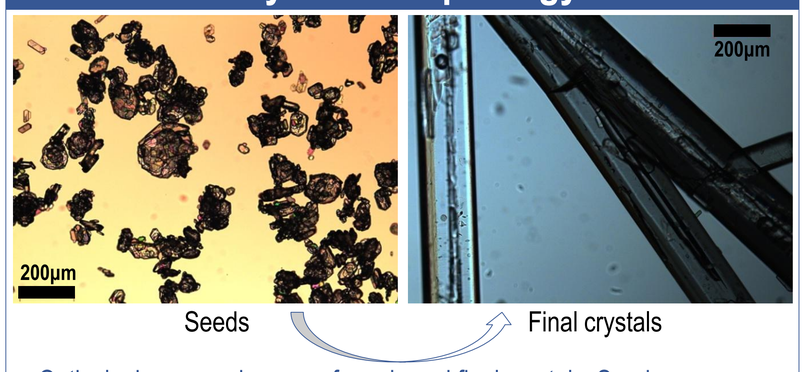
Crystallization Experiments



The generic temperature versus time profile of crystallization experiments and the 1L reactor that was used.

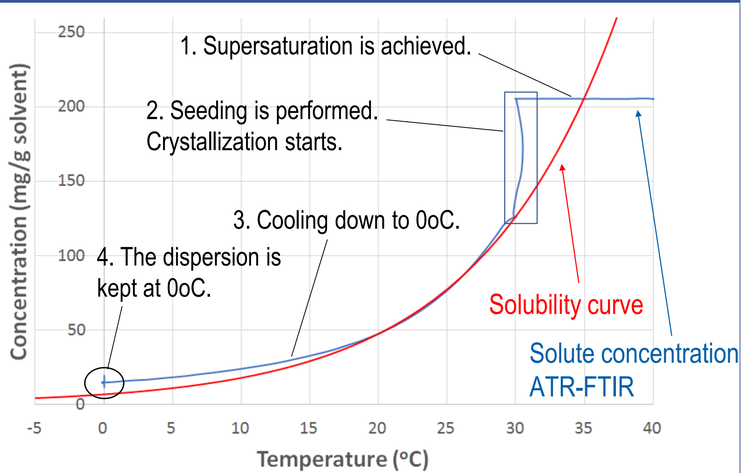
A 1L double-jacketed glass reactor was used, in which ATR-FTIR, temperature and turbidity probes are inserted. Each crystallization experiment is unique and **5 experimental parameters are altered**: initial solute content, agitation, seed load, seeding temperature and cooling rate (after seeding).

Crystals morphology



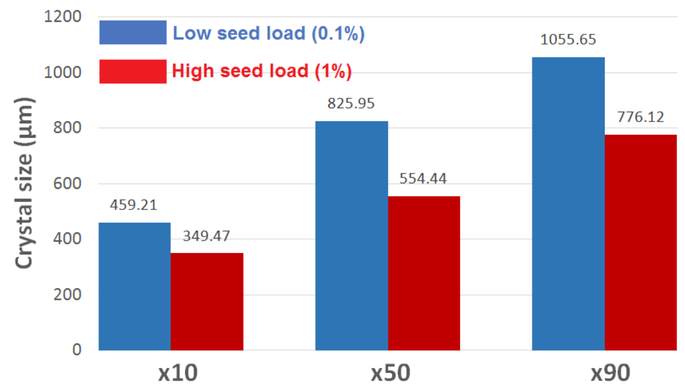
Optical microscopy images of seeds and final crystals. Seeds grow significantly from "spherical particles" (average d=116μm) to elongated plates with their main axis exceeding 1mm in many cases.

ATR-FTIR data



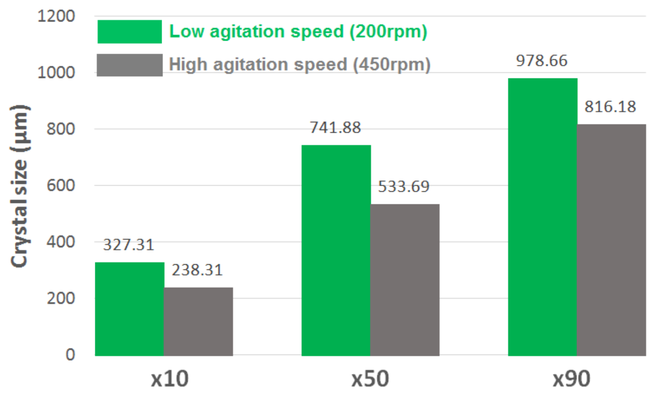
Typical profile for this Project of in-situ solute concentration measurements with ATR-FTIR versus temperature. Solubility data are plotted for comparison. The measured concentration curve follows the expected trend (as explained on the graph).

Mechanisms Identification



Quintiles (x10, x50 and x90) of final crystals for experiments that differ only in terms of seed load.

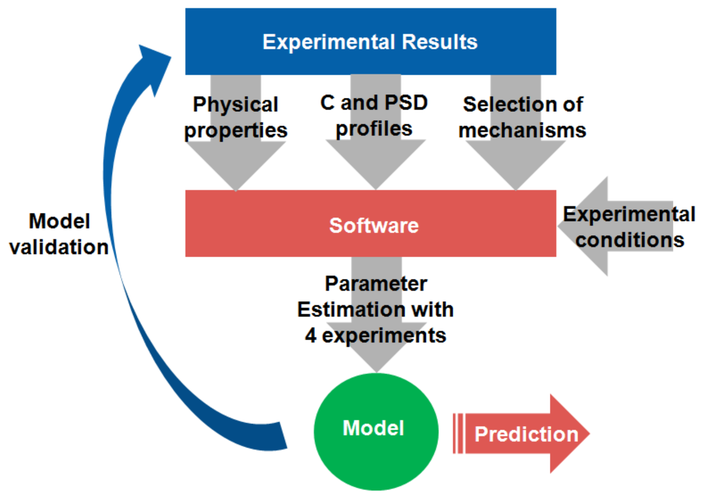
Low seed load leads to significantly bigger crystals, which implies that **crystal growth is the dominant mechanism of the system**: fewer seeds mean more solute available per particle, which results in bigger crystals.



Quintiles (x10, x50 and x90) of final crystals for experiments that differ only in terms of agitation speed.

Higher agitation speed results in significantly smaller quintiles, revealing the importance of this factor. This suggests that **secondary nucleation by attrition is also a mechanism of the system**.

Model Construction



The approach of this Project to kinetic modeling.

Crystal Growth rate

$$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_{int}(L) - C_{sat}}{C_{sat}}\right]^g$$

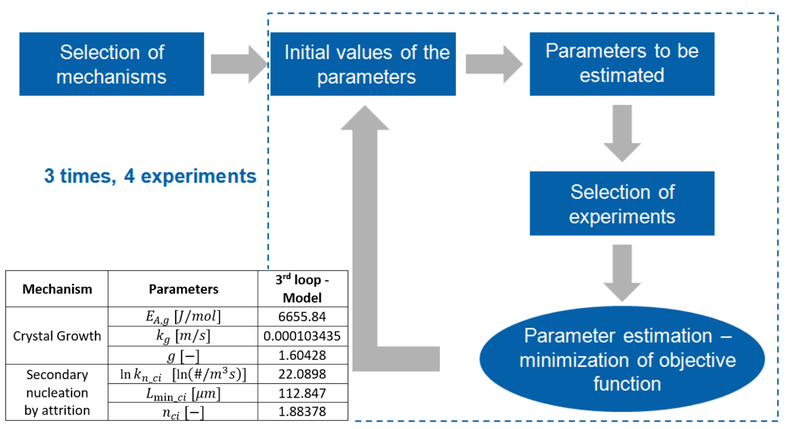
- k_g proportional factor to crystal growth
- $E_{A,g}$ activation energy, T-dependency
- g supersaturation dependency

Secondary nucleation Rate by attrition

$$J_{sec\,ci} = \exp\left(\ln k_{n\_ci}\right)\sigma^{n_{ci}}\frac{N_Q}{N_P}k_v\rho_c\varepsilon\int_{L_{min\_ci}}^{\infty} n\ L^3\,dL$$

- k_{n_ci} proportional factor
- n_{ci} supersaturation dependency
- L_{min_ci} crystal size above which crystals are prone to attrition

The six kinetic parameters which have to be estimated [1,2].

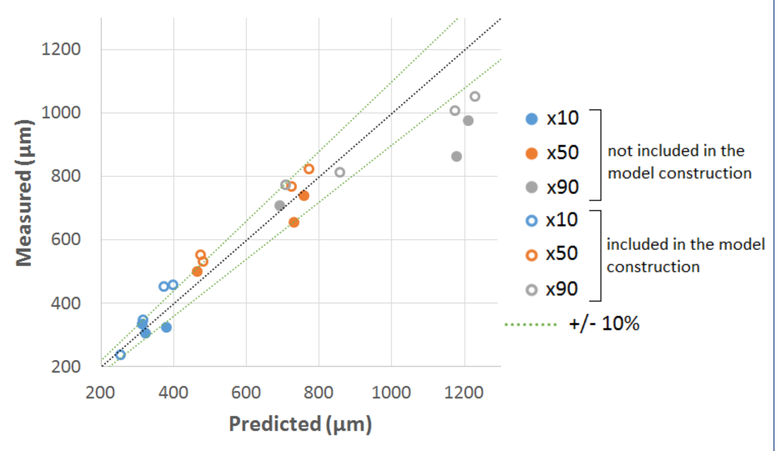


Mechanism	Parameters	3rd loop - Model
Crystal Growth	$E_{A,g}$ $[J/mol]$	6655.84
	k_g $[m/s]$	0.000103435
	g $[-]$	1.60428
Secondary nucleation by attrition	$\ln k_{n\_ci}$ $[\ln(\#/m^3 s)]$	22.0898
	$L_{\min\_ci}$ $[\mu m]$	112.847
	n_{ci} $[-]$	1.88378

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.

Model Performance

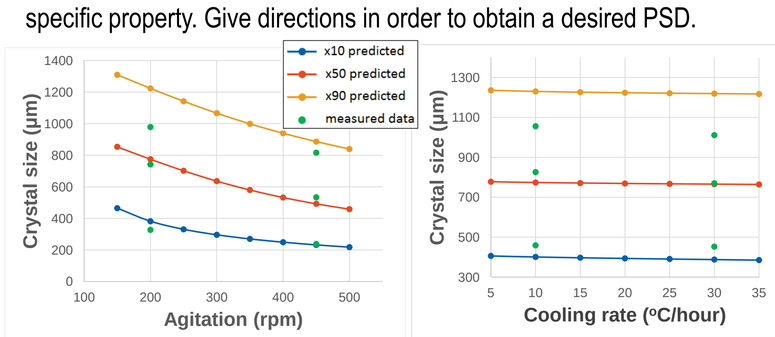


Measured versus predicted quintiles (x10, x50, x90) of final crystals. Prediction was made based on the final model

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

Potential Applications in Pharma

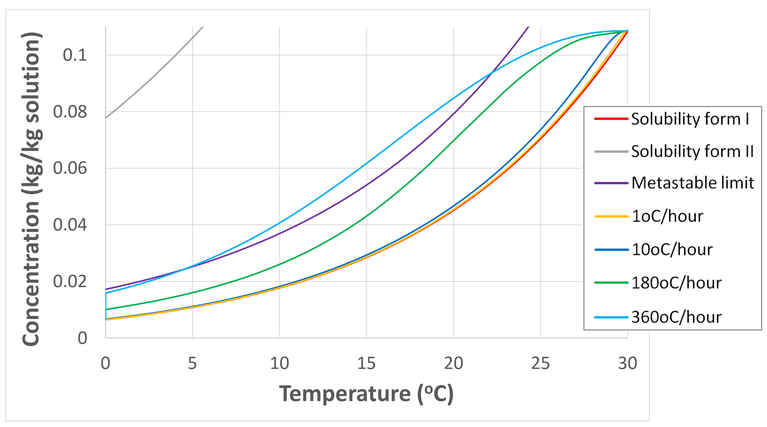
1. Process design: Perform simulations and target the effect of a specific property. Give directions in order to obtain a desired PSD.



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

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 (360°C/hour) would be required for primary nucleation to occur.



Model prediction of solute concentration profiles for different cooling rates (after seeding). The solubility curve of form I (stable) and form II (unstable), as well as the metastable limit, are drawn for comparison.

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

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