Micro-scale process development and optimization for crystallization processes

Cameron J. Brown [a]*, Niall Mitchell [b]

[a] CMAC Future Manufacturing Research Hub, [b] Process Systems Enterprise Ltd., *cameron.brown.100@strath.ac.uk

ISIC 20 September 3–6, 2017, Dublin, Ireland

Introduction and motivation

Initial experimental phases of crystallization process development are commonly carried out at very small scales, typically using 1-5mL vessels, with the aim of selecting a:

- solvent based on solubility
- crystal solid state

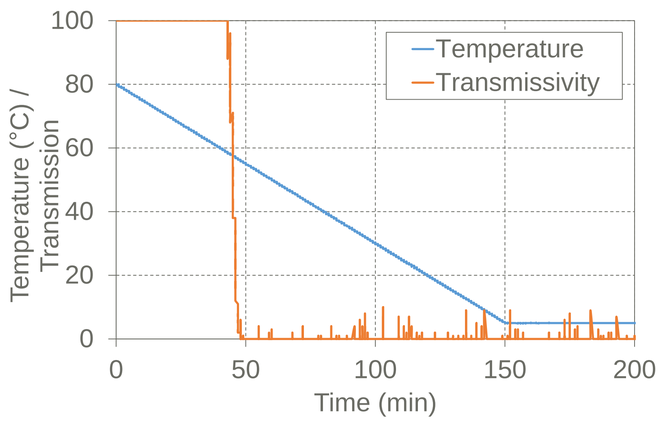
These activities are commonly conducted in high throughput reactor systems, such as the Crystalline (Technobis Crystallization Systems).

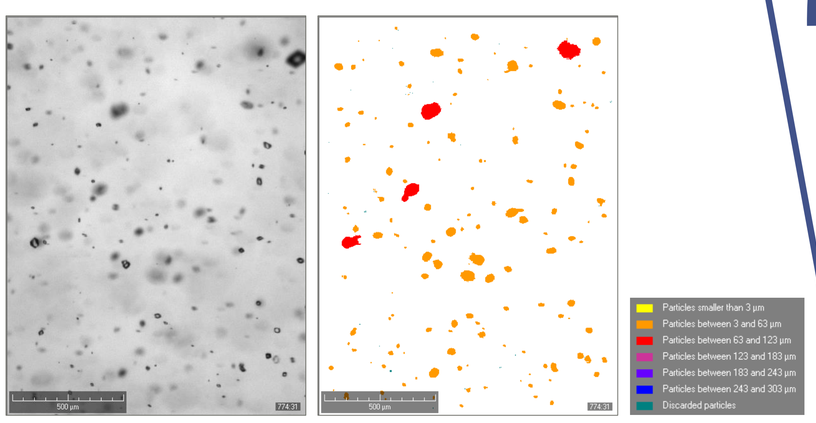
For the development, validation and optimization of crystallization process models this data is typically not utilized and the selected solution system is probed experimentally and more quantitatively at much larger scales, typically between 100 – 1000 mL.

A more quantitative usage of the data generated at small scale for the development of process models which may significantly reduce the number of larger scale experiments required, would aid in addressing the increasing constraints on time and materials in pharmaceutical development.

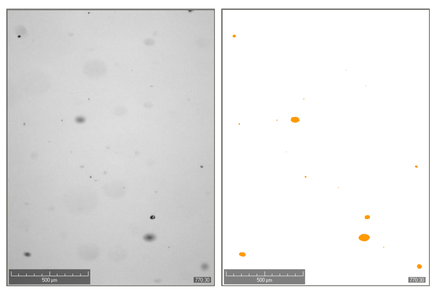
Typical raw Crystalline data

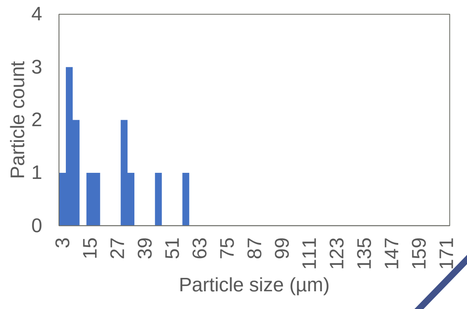
Sample turbidity and block temperature are recorded throughout. Addition of *in situ* camera module allows for the imaging of suspended particles and the determination of particle size distribution (PSD) through image analysis



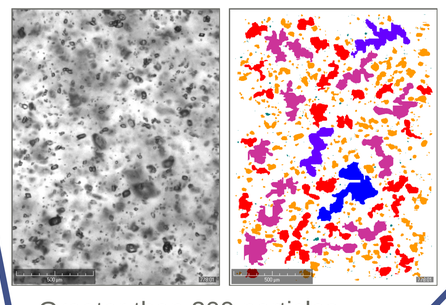


Particle count threshold



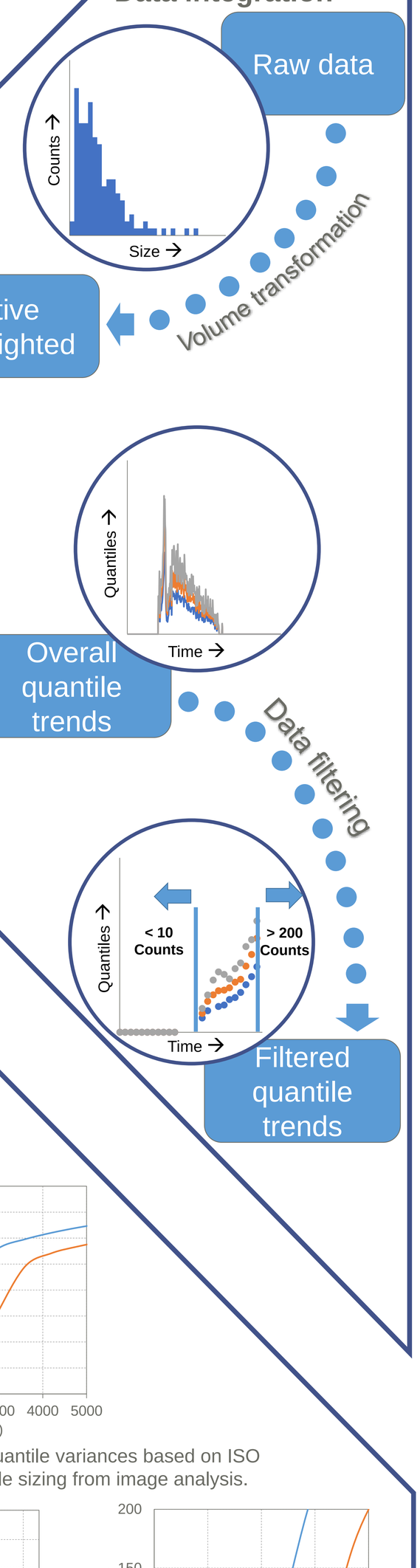


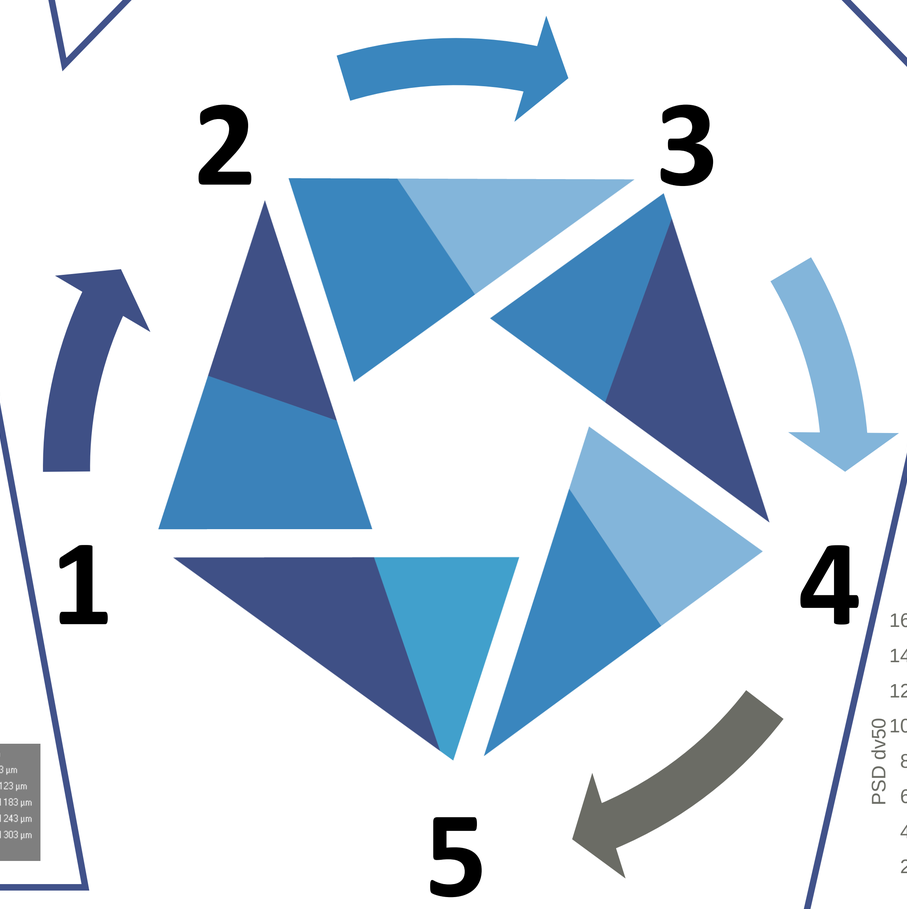
Less than 10 particles. Clear segregation of particles. Insufficient particles for statistical PSD



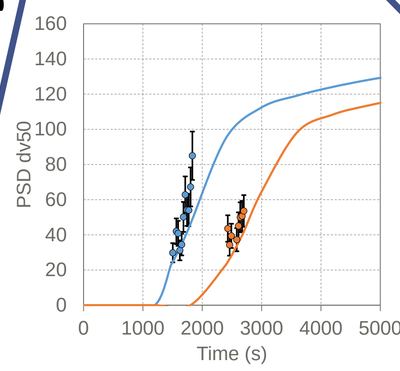
Greater than 200 particles. Significant probability of particle overlap. Sufficient particles for statistical PSD.

Data integration

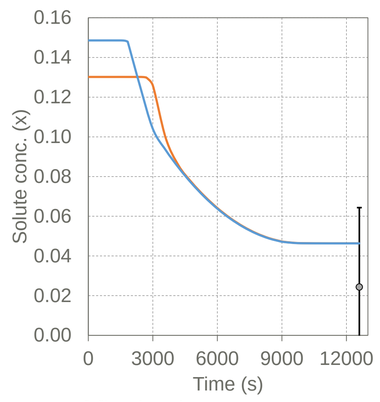


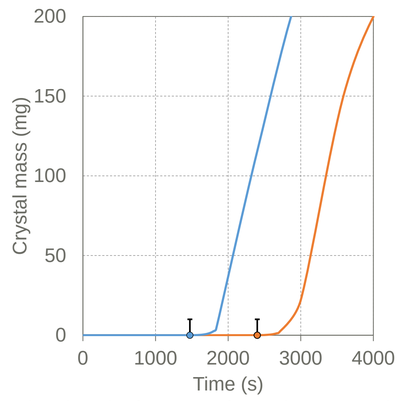


Parameter estimation



Particle size distribution quantile variances based on ISO standard errors for particle sizing from image analysis.



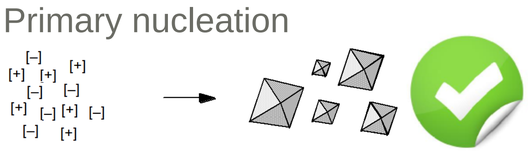


An estimate of final solute concentration is required to help complete the material balance. However, a large variance is placed on this as it is unknown if the solution reached equilibrium.

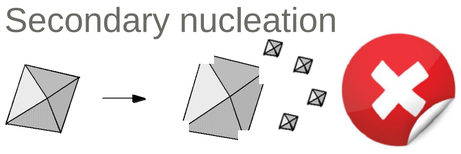
Mechanism discrimination

Enabling mechanism discrimination through sensitivity analysis at an earlier stage of process development

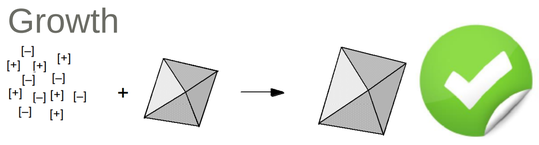
Primary nucleation



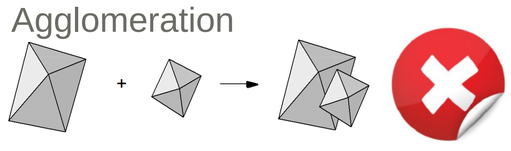
Secondary nucleation



Growth



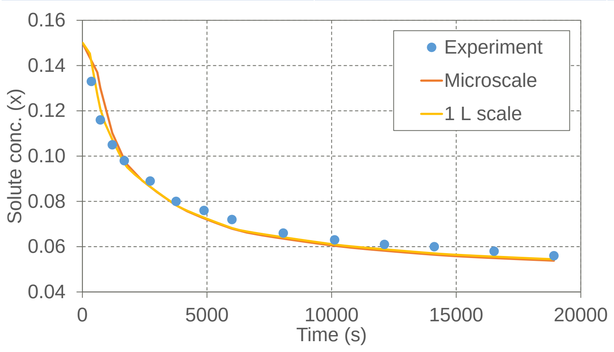
Agglomeration

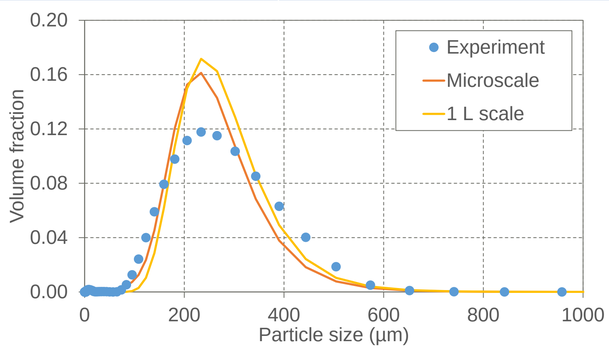


Comparison to at scale parameter estimation

Experimental scales & systems

	Estimation at microscale	Estimation at 1 L scale	Estimation at microscale with refinement at 1 L scale
Microscale experiments (5 mL each)	8 (as part of solubility measurement)	-	8 (as part of solubility measurement)
1 L scale experiments	-	7	3
Total API usage	**4 g**	**1200 g**	**520 g**





Summary

- Initial **estimates of crystallisation kinetics parameters** can be obtained at the microscale as part of typical solubility measurement experiments.
- Through sensitivity analysis, **mechanism discrimination** can be performed to identify the most dominant crystallisation phenomena.
- Using these initial estimates a **57 % reduction in API usage** can be achieved when compared with estimating parameters solely at lab scale (1 L).