Enabling model-predictive design: Rapid development of a PBM for an anti-solvent and cooling crystallisation in two different reactor geometries

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PURPOSE

- The study aimed to develop a rapid model using gProms FormulatedProducts for a proprietary single polymorph active pharmaceutical ingredient (API) crystallisation at small scale for **early process understanding.**
- The model outcomes are then later used to **inform the experimental design of continuous crystallisation** for multi-addition antisolvent and cooling crystallization in both continuous oscillatory baffled reactor (COBC) and mixed-suspension and mixed- product removal (MSMPR) crystalliser.

OBJECTIVE(S)

To achieve the model development for a proprietary molecule with one polymorphic form, the model development process was separated into 3 stages:

- Rapid development of models for batch stirred tank reactor (STR) process using gProms FormulatedProducts modelling platform.
- Extension of models to batch moving fluid oscillatory baffled crystalliser (MFOBC) with reduced number of experiments.
- Benchmarking process understanding from the parameter estimation model followed by process evaluation in continuous platforms.

METHOD(S)

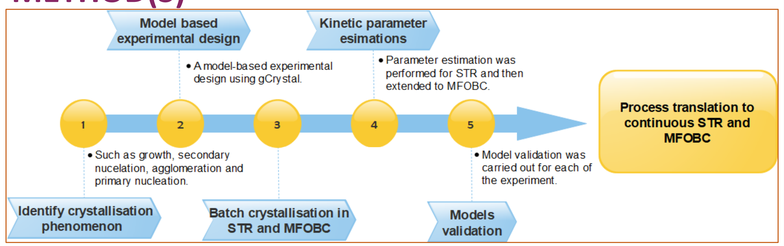

Fig. 1: Summarised infographics describing process implementation for parameter estimation

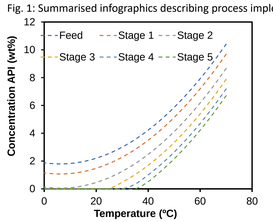

Fig. 2: Solubility profile for 5-stage combined cooling-antisolvent crystallisation

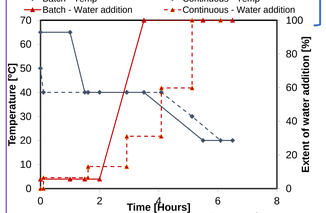

Fig. 3: Temperature and antisolvent addition profiles

- Model development for the batch STR process (phase 1 – totalling 12 experiments), and extended to MFOBC (phase 2 – totalling 6 experiments) to include the effect of hydrodynamics.

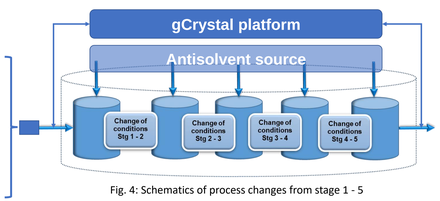

Fig. 4: Schematics of process changes from stage 1 - 5

- The model validation requires a series of batch small-scale experiments. Antisolvent addition strategy was varied to control supersaturation spikes based on model predictions.
- For each experimental design, calibration of PAT, model development and model validation was carried out.
- **Caveat** – due to fouling and encrustation, parameter estimation was only carried out for stages 1 – 3 of the process design.
- However, evaluation in continuous systems were carried out for all the five stages.

RESULT(S)

Parameter estimations in batch systems

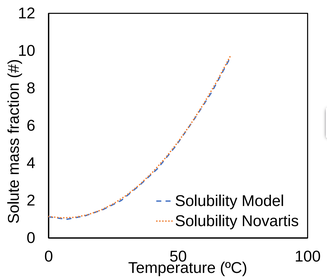

Fig. 5: Solubility modelling on the model platform.

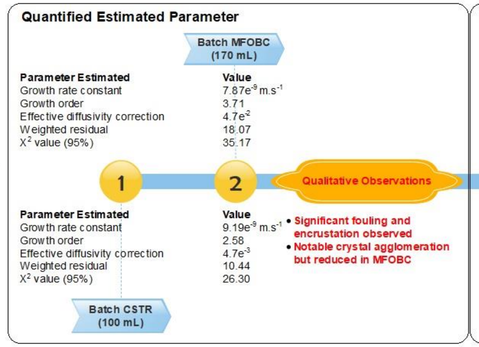

Fig. 6: Quantified estimated parameters in the batch STR and MFOBC

Process evaluation in continuous systems

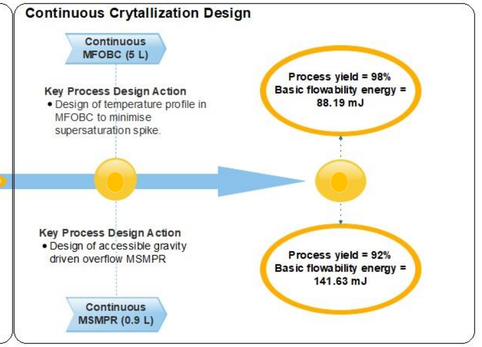

Fig. 9: Process evaluation in continuous platforms – MSMPR and COBC. The process yield was obtained from concentration prolife of mother liquor and the flowability energy of the final product determined.

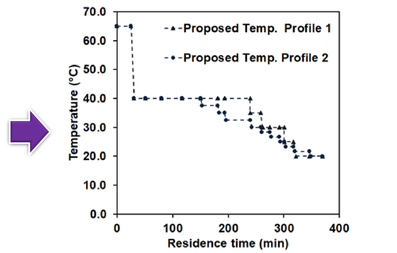

Fig. 10: Temperature profiles implemented for the COBC (temp. profile 2)and MSMPR.(temp. profile 1)

Dimension	Instrument used	COBC	MSMPR
PSD span	Mastersizer	2.05 ± 0.020	2.33 ± 0.120
BET surface area at SS (m^2g^{-1})	BET	0.601 ± 0.095	0.647 ± 0.019
Basic flowability energy (mJ)	FT4 powder rheometer	88.168 ± 13.511	141.633 ± 3.061
Yield (%)	HPLC	98%	92%
Particle shape	Morphologi, SEM and optical microscope	Less agglomerated needle-like crystals	agglomerated needle like crystals

Table 1: Solid and liquid state analyses of the final products from the COBC and MSMPR.

Key notes

- The growth and secondary nucleation kinetic parameters were estimated for the API in both crystallisers for stages 1 – 3.
- API crystallisation was found to be surface controlled, with secondary nucleation as a dominant crystallisation phenomenon.
- The standard deviation of each parameter is large and would require further experimentation to minimise.
- Similar particle size distribution (PSD) was obtained from the surface integration experiments in both platforms.
- Encrustation and fouling at higher supersaturation were found to limit the supersaturation driving force in the STR.

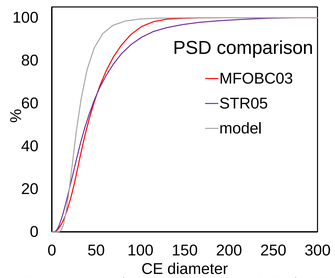

Fig. 7: Comparison of modelled and experimented PSDs for the surface integration experiment in the batch systems.

- Temperature profiles and antisolvent addition rates/port position were determined to minimise fouling and encrustation based on the supersaturation understanding obtained from the parameter estimation studies.
- The supersaturation spikes informs the design of continuous process.

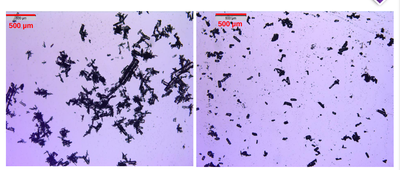

Image obtained from batch-STR product Image obtained from batch-MFOBC product

Fig. 8: Microscopic images of final crystals obtained from the batch systems.

Key notes

- The experimental and model data obtained from this initial study informed the experimental design and operation of the continuous platform.
- 5-stage multi-addition antisolvent-cooling crystallization in both COBC and MSMPR platforms
- The final COBC and MSMPR products resulted in approximately 98 and 92% yield respectively.
- Reduced agglomeration observed in the COBC and the powder has better flow properties compared to MSMPR.
- Products with higher yield and enhanced crystal attributes were obtained in the continuous COBC compared to MSMPR system.

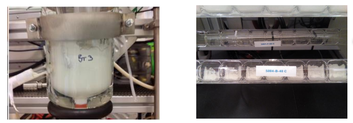

Fig. 12: Images showing extent of encrustation in COBC and MSMPR reactor vessel.

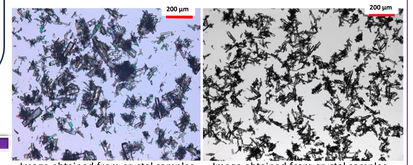

Image obtained from crystal samples obtained from stage 5 of the COBC. Image obtained from crystal samples obtained from stage 5 of the MSMPR.

Fig. 11: Microscopic images of final crystals obtained from the batch system.

CONCLUSION(S)

- A rapid parameter estimation models were developed in gProms FormulatedProducts for batch STR and MFOBC multi-stage crystallisation to enable process understanding.
- Enhanced growth was observed in the batch MFOBC compared to STR with growth rate constant of $9.19e^{-9}m.s^{-1}$ and $7.87e^{-9}m.s^{-1}$, and growth order of 2.96 and 3.71 obtained respectively.
- The established model showed that the crystallisation of the proprietary API is surface integration controlled and differences observed in the crystal size distribution in comparison with model distribution were due to fouling and encrustation. Future work to focus on incorporation encrustation and fouling into the model.
- Based on the combined models and experiments at small-scale, the antisolvent addition strategies were evaluated to minimise supersaturation spike which may result in fouling and encrustation in the continuous crystallisation process.

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