POSTER 48

A crystallisation development workflow for the manufacturability improvement of active pharmaceutical ingredients

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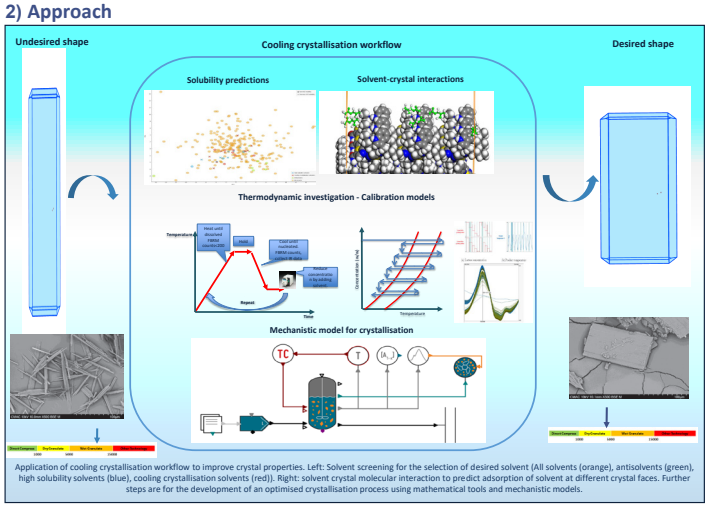
1) Introduction

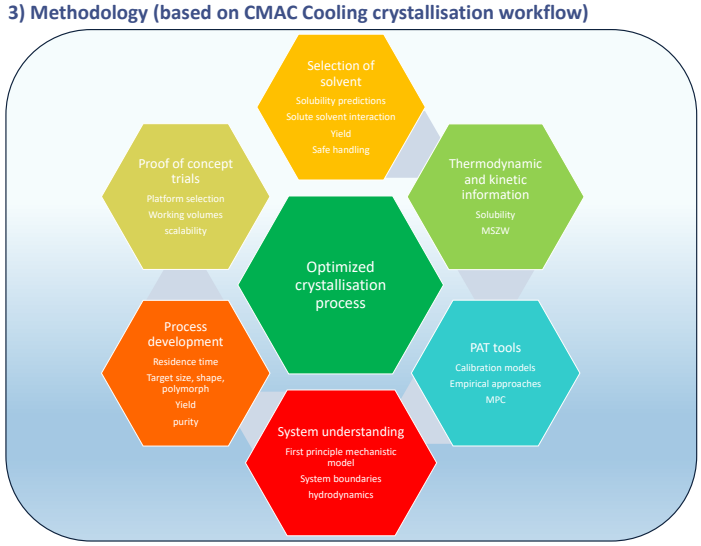
- More than 70% active pharmaceutical ingredients (APIs), in the development pipeline, exhibit poor manufacturability (e.g., Isolation, flowability, tabletability) posing major challenges in the production of consistent product with desired performance[1]. Crystallisation is a key operation in the isolation of the majority of pharmaceuticals and has been demonstrated as a critical process to improve manufacturability of the drug.
- Whilst basic design principles for crystallisation are known, as well as the fundamental mechanisms of crystal nucleation and growth, applying these in the context of pharmaceutical development with the associated constraints on time and materials is challenging. As a result, decisions made on the one aspect of the process, may involve development stages both on the DS (drug substance) and the DP (drug product) side.
- Brown et al[2] has established a systematic workflow methodology that enables rapid development of crystallisation process based on process understanding. At the central toof this methodology, is among other things the deployment of in-silico assisted solvent selection (for the selection of solvents optimising yield and productivity) and miniaturisation platforms (Crystal16/Crystalline). In this work, the aforementioned workflow is reinforces with the use of Molecular Dynamics simulations to support the selection of solvents favouring the growth of crystals with desired functional properties.
- It is demonstrated that quantitative understanding of the facet-specific interactions of solvent molecules with the growing crystals, offers a reliable tool for the selection of solvents favouring the growth of specific crystal facets. This exercise enabled the drastic shift in the crystal habit of the API. It also demonstrated the role, not only of the functional groups, but of steric interactions as well, on solvent-solid interactions. This improved workflow has been successfully applied of the workflow to improve the morphology of a UCB API . The combined use of in silico tools and miniaturisation platforms enabled the rational selection of solvent and process conditions, at the different stages of the development. The development of optimised crystallisation process with desired product attributes was achieved through the adherence on the fundamentals of crystallisation, without relying on empirical models. Therefore, this work highlights the need for persistence in first principles in order to successfully implement robust process development workflows.

2) Approach



Application of cooling crystallisation workflow to improve crystal properties. Left: Solvent screening for the selection of desired solvent (All solvents (orange), antisolvents (green), high solubility solvents (blue), cooling crystallisation solvents (red)). Right: solvent crystal molecular interaction to predict adsorption of solvent at different crystal faces. Further steps are for the development of an optimised crystallisation process using mathematical tools and mechanistic models.

3) Methodology (based on CMAC Cooling crystallisation workflow)



Conclusions

- Digital solvent screen and solvent crystal interaction prediction were close to experimental outputs and solvent selection was fast and easy with the help of these tools in order to attain required morphology.
- A robust concentration calibration model was established with a maximum error of ± 0.4%. This model was helpful in establishing mechanistic model for crystallization.
- Sequential parameter estimation approach was used to design experiments for kinetic parameter estimation using population balance model.
- Model predictions were within measurement error.
- Required morphology was achieved with the help of crystallisation workflow and digital tools.
- Proof of concept large scale process was established using process optimization tool in G-formulated product for the developed model. Required targets were achieved in the POC batches

Referrences

1: Co-processed particles: An approach to transform poor tableting properties, Roopwani, R.; Buckner, I. S. . J. Pharm. Sci. 2019, 108, 3209-3217.

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3: A Practical Approach for Using Solubility to Design Cooling Crystallisations, Frans L. Muller, Mark Fielding and Simon Black, Organic Process Research & Development 2009 13(6), 1315-1321 DI: https://doi.org/10.1021/op9001438

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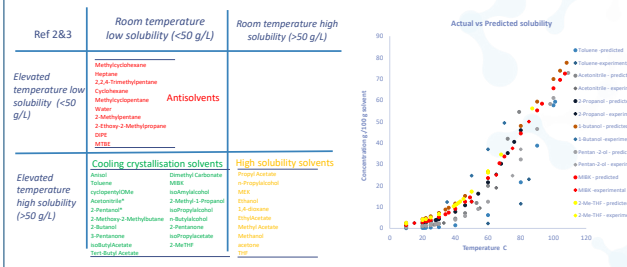
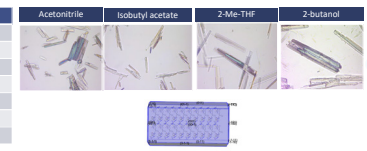
4) Results

Solubility predictions

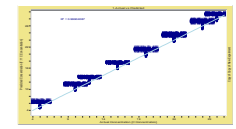


Solvent crystal interaction

Solvent	Absorption energy kCal/mol)		
Crystal face	001	100	011
Acetonitrile	-8.87	-13.76	-14.20
2-Me-THF	-366.37	-115.05	-213.65
Isopropyl acetate	-398.59	-123.90	-231.28
3-pentanone	-648.30	-196.22	-369.10
MIBK	-648.93	-198.52	-370.64
Isobutanol	-450.77	-139.10	-259.92

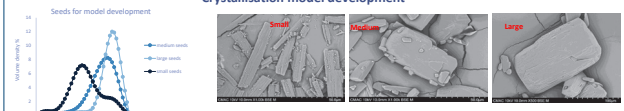


PAT- Calibration Models



Grams PLS calibration model with GAP 2 derivative and 4 factors
Prediction error 0.2 – 0.5 g/100g solvent

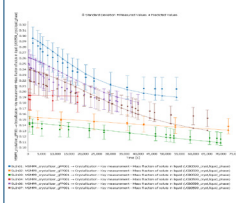
Crystallisation model development

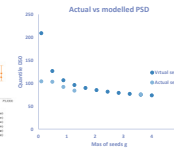


Seeds were generated using magic lab and dissolution cycles

Model development

Sequential parameter approach to estimate kinetics

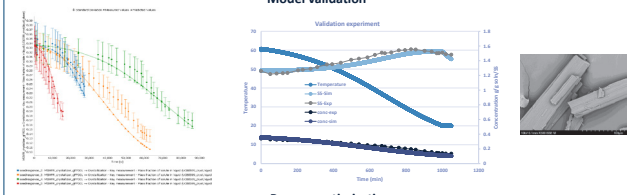




Parameter	Value	Unit
Growth rate constant	4.85	m/s
Activation energy	54663	J/mol
Supersaturation order	1.51	

Experiment	Growth rate µm/s	Actual D50	Predicted D50
SuInt01	0.0085	67.1	77
SuInt02	0.00162	62.5	65.90
SuInt03	0.0026	67.3	70.45
SuInt04	0.00032	57.7	57.67
SuInt06	0.0067	72.9	74.53
SuInt07	0.0078	85.26	88.47

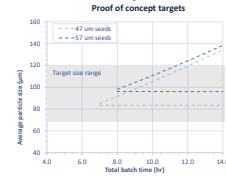
Model validation



Process optimization

Proof of concept targets

Conditions for optimisation	
Parameters	ranges
Objective function (D50)	50-150
Batch time	7-14 hr
Temperature (constraint)	20-50C
Yield (constraint)	0.9-1.0
End temp (constraint)	19.50 – 20.5
Seed load	1-10%
Temp profile	4 point - set point



Batch	D50 Attained	Particle Span	Target D50
seeds	47	1.22	
POCB1	87.79	1.5	90
POCB2	118	1.22	120

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