Applying Crystallization Modelling to Improve the Understanding of a Batch Cooling Process of an Agrochemical Active Ingredient

Rhea Brent, Manish Parmar, Pauline Sillers, Michael Bryce, Gillian Clelland and Neil George **(SYNGENTA)**

Hassan Mumtaz and Niall Mitchell **(PSE)**

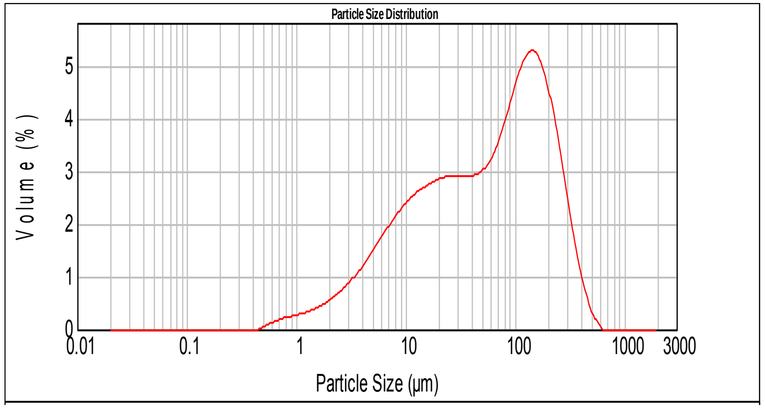
Active Ingredient Crystallisation: Experimental Study

Introduction

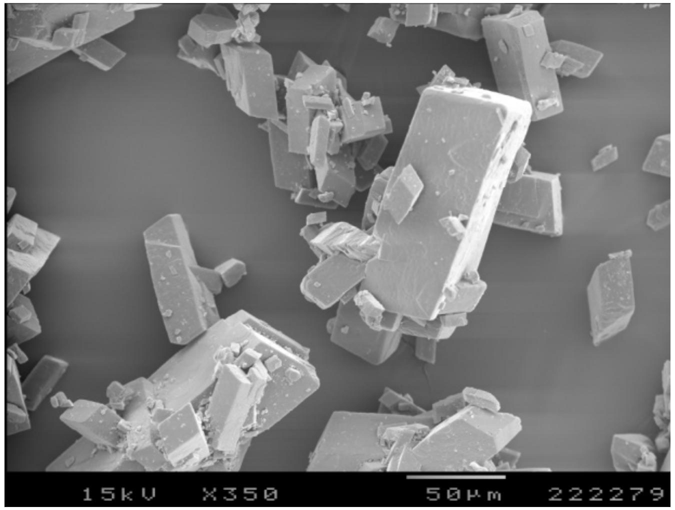
- A large part of Syngenta's business is the sale of crop protection products for agricultural use.
- Manufacture of the agrochemical active ingredients (AIs) can vary between 10 to 10000s of tonnes per annum (depending on the product).
- A large proportion of Syngenta AIs are isolated by a final crystallisation step
- The isolation of the final product should yield particles with a consistent, narrow particle size distribution (PSD) and polymorphism
- Importance for isolation and drying time and for subsequent formulation (discharge and milling).

Syngenta AI-X Current Process

- AI-X currently manufactured and isolated by a cooling crystallisation process
- Currently isolation has batch to batch variability– in extreme cases rate decreases four-fold.
- Occasionally, subsequent batches must be held in a slurry hold vessel until the centrifuge is freed up.
- The AI is not likely to be polymorphic
- Poor filtration has been attributed to the width of the particle size distribution.

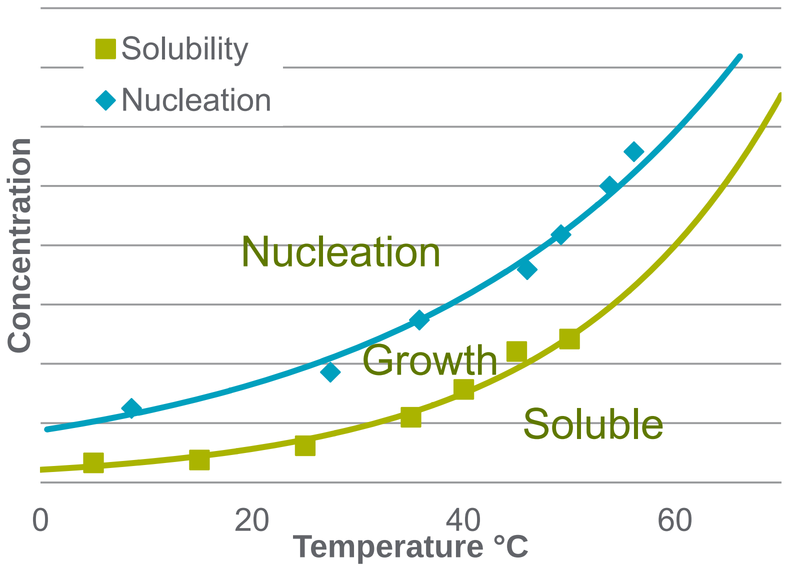


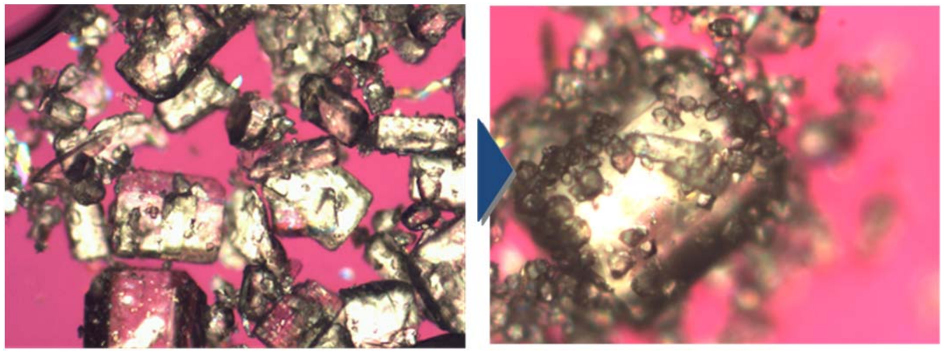
Typical particles from plant batches



AI-X Poor Isolation Properties

- Possible sources of poor filtration characteristics:
- Impurities (habit modification)
- Breakage of crystals
- Poorly controlled nucleation (primary and secondary)





Secondary nucleation of particles

AI-X Poor Isolation Properties

Proposed methodologies to narrow particle size distribution:

- Seed the batch
- Modify the cooling profile

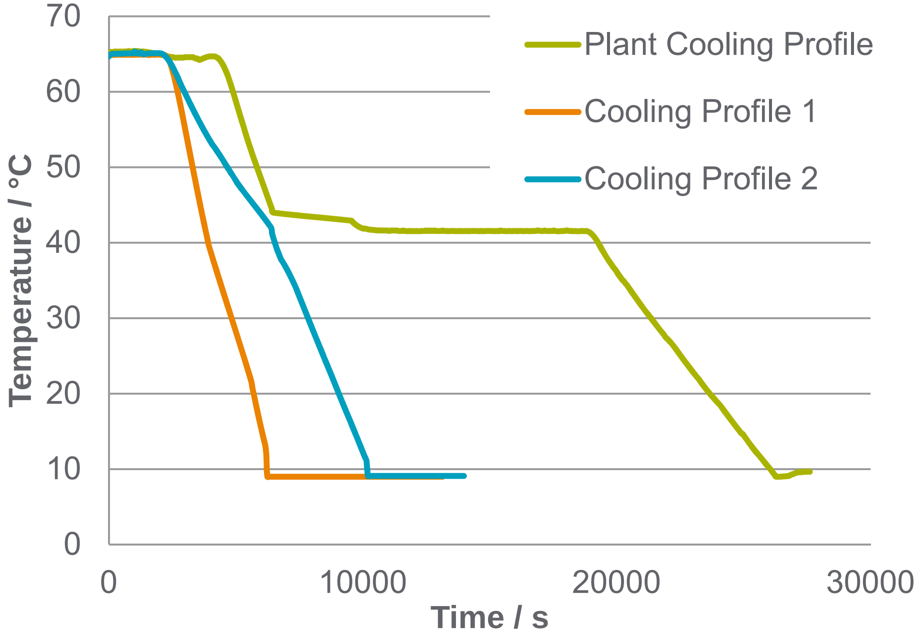
Criteria:

- No additional batch time
- Impurity profile must remain within specification
- No additional complexity to process

Crystallisation Scale-down of AI-X

- Experiments performed at 10 L based on a scaled-down version of the plant crystalliser.

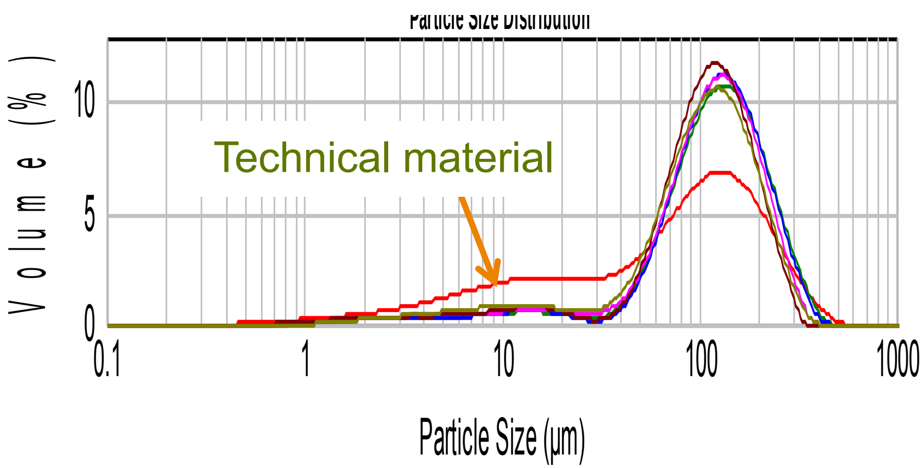
- Replicate plant cooling profile
- Two different cooling profiles:



- Seeding with 2 different seeding quantities (1 and 2 % w/w of small PSD)- slightly modified cooling profile and agitation

Experimental Results: Unseeded Cooling Profile Modification

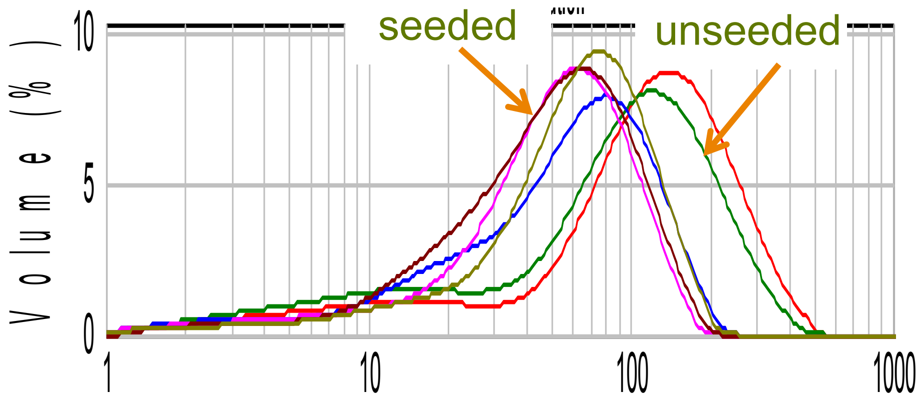
Conditions	Mean Volume D4,3	Span (D90-D10)/D50
Plant profile	116.0	1.7
Cooling profile 2 (faster)	126.0	1.5
Cooling profile 1 (fastest)	129.2	1.5



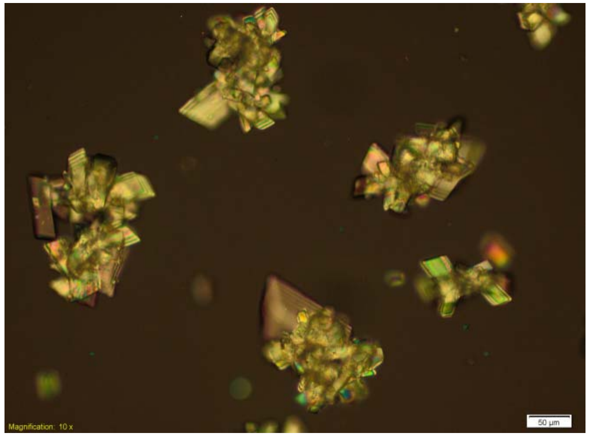
- Small change in particle size distribution of crystals from faster cooling.
- Beneficial to decrease crystallisation time on plant.
- Cooling profile 1 (fastest) would be difficult to achieve with current equipment – also impurity profile unacceptable

Experimental Results: Seeded Crystallisations

Conditions	Mean volume D4,3	Span (D90-D10)/D50
unseeded	118.5	2.1
Seeded with 1 % w/w	61.2	1.8
Seeded with 2 % w/w	63.6	1.7



- Effect of seeding: mean size and overall distribution of the particles was reduced
- Apparently no difference between the effects of using different amounts of seed
- The viscosity of the resulting crystal slurry was high – stirring was difficult



Experimental Results: How Particle Size Relates to Batch Filtration Time

Cooling profile modification

Experiment	Cake Resistance ($x10^8$ m/Kg)
Plant cooling profile	8.8
Cooling profile 1	7.4
Cooling profile 2	10.3

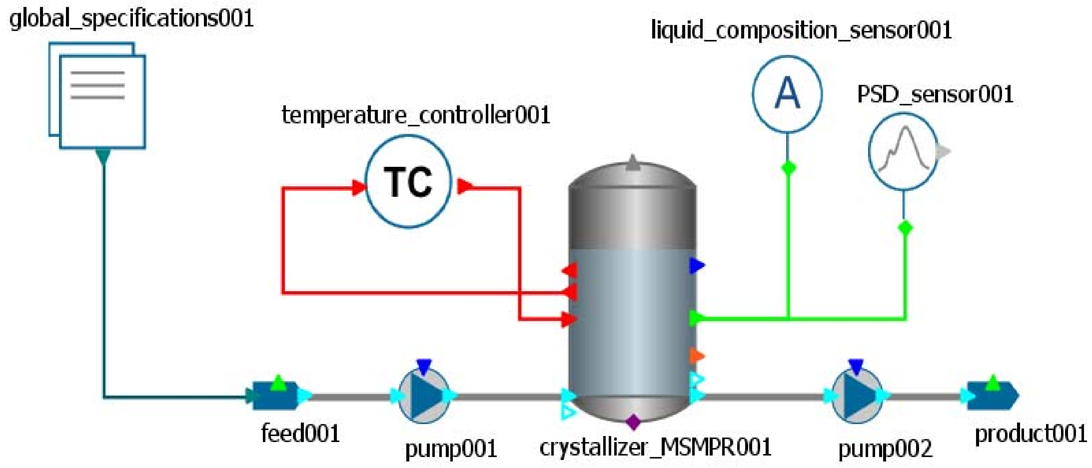
Seeding modification

Experiment	Cake Resistance ($x10^8$ m/Kg)
Unseeded cooling profile	9.6
Seeded 1 % w/w	0.5
Seeded 2 % w/w	1.2

Active Ingredient Crystallisation: Modelling Study

Building the 10 L Scale Model in gCRYSTAL

- Set up a model of the crystalliser (pump in seeds at time x, set temperature control etc..)
- Physical properties of AI-X: solubility, density etc..
- Crystalliser details: vessel dimensions, agitation, slurry volume etc..
- Experimental data: concentration and particle size vs. time (include variance of data)



Flowsheet model in gCRYSTAL

Parameter Estimation

- Combined seeded and unseeded experiments into one model. Included experimental data on PSD and concentration vs. time

Based on experience of the system and experimental data, the following aspects considered:

- Mechanisms and Models
- Dominance of secondary nucleation, attrition, agglomeration etc..
- Which models best fit the dominant phenomena
- Experimental Data
- Data quality / repeatability
- Quantity / experimental space coverage

- For AI-X, suspected that secondary nucleation and attrition would be important phenomena to model.

Parameter Estimation: Equations Used

- Primary Nucleation (Mullin)

$$J_{prim} = \ln A_0 \exp\left(\frac{-16\pi(\alpha\sigma)^3 v_0^2}{3k^3T^3 \ln S^2}\right)$$

$\ln A_o$ = pre-exponential factor

α = surface energy correction factor

Parameter Estimation: Equations Used

- Secondary Nucleation (Evans)

$$J_{sec} = \ln k_n \sigma^n \frac{N_Q}{N_P} k_v \rho_c \varepsilon \int_{L_{min}}^{\infty} n \ L^3 \, dL$$

$\ln k_n$ = secondary nucleation rate constant

n = order of supersaturation dependency on secondary nucleation

L_{min} = Particle size at which crystals are prone to attrition

Parameter Estimation: Equations Used

- Growth (Mersmann)

Mass transfer

$$D_{AB} = \alpha \frac{kT}{6\pi\eta \frac{d_m}{2}}$$

Surface integration

$$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_{int}(L) - C_{sat}}{\rho_{crys}}\right]^g \qquad \text{if } C_{bulk} - C_{sat} > 0$$

α = correction factor (diffusion co-efficient)

k_g = surface integration

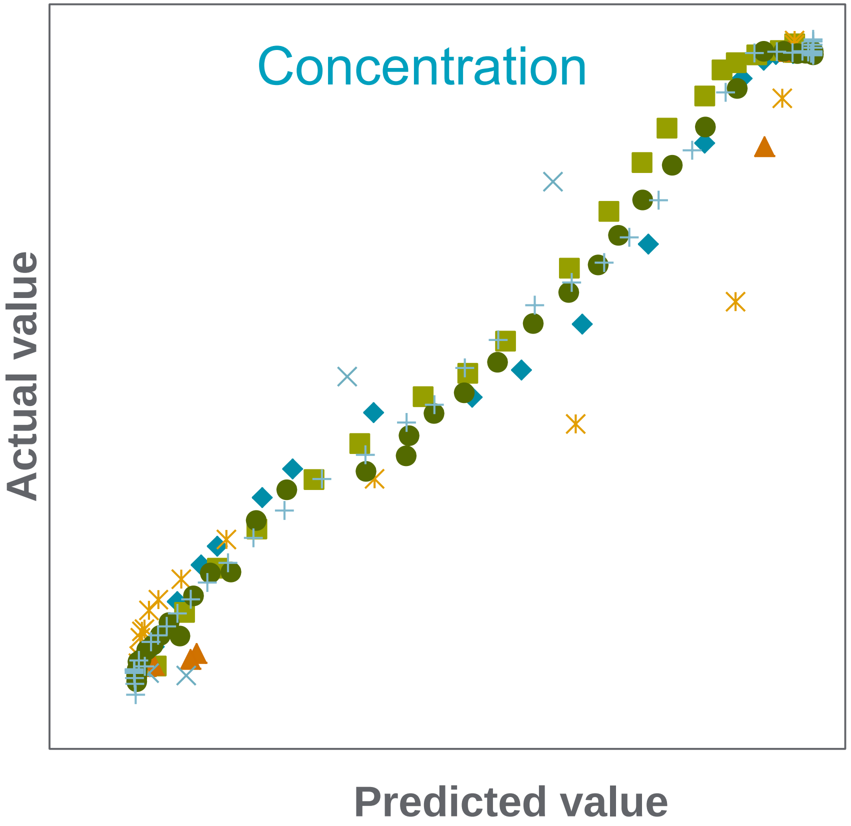
$E_{A,g}$ = Activation energy surface integration

g = supersaturation dependency on surface integration

Results from the Model: Experiments at 10 L Scale

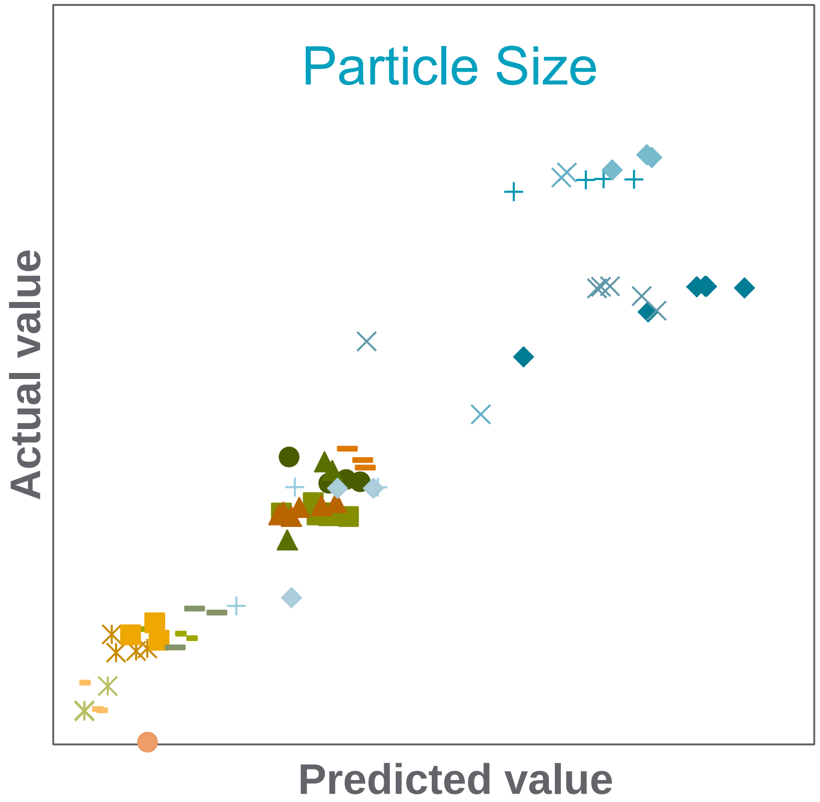
Phenomena	Estimated Parameter	Value Obtained
Secondary Nucleation	Rate constant ($\ln k_n$)	17.8
	Order (dependence on supersaturation) (σ^n)	0
	Particle size at which crystals undergo attrition (L_{min})	73.2 µm
Growth	Order (surface integration dependence on supersaturation) (g)	1.4

- Secondary nucleation and growth good statistical fit by model.
- Dominant phenomena in process are the favourable crystal growth kinetics and attrition of crystals growing larger than 73 µm.
- Primary nucleation poorer statistical fit by model: likely to be due to dominance of secondary nucleation in the system



× cooling profile 1 (fastest)

⚹ cooling profile 2 (faster)



◆ D50 plant profile 1

× D90 plant profile 2

+ D90 plant profile 3

◆ D90 cooling profile 1 (fastest)

Model Fit to Experimental Data

Building the Plant Scale Model and Optimisation

- Scale up to plant vessel, modified agitation and added experimental data on end concentration and particle size
- Used estimated growth parameters from 10 L and estimated:
- Primary nucleation rate constant
- Secondary nucleation rate constant
- Minimum size for attrition

Phenomena	Estimated Parameter	Value Obtained (10 L model)	Value Obtained (plant model)
Secondary Nucleation	Rate constant (ln k_n)	17.8	15.5
	Particle size at which crystals undergo attrition (L_{min})	73.2 µm	76.8 µm

syngenta

Modelling Results: Effect of Modifying Seed Quantity

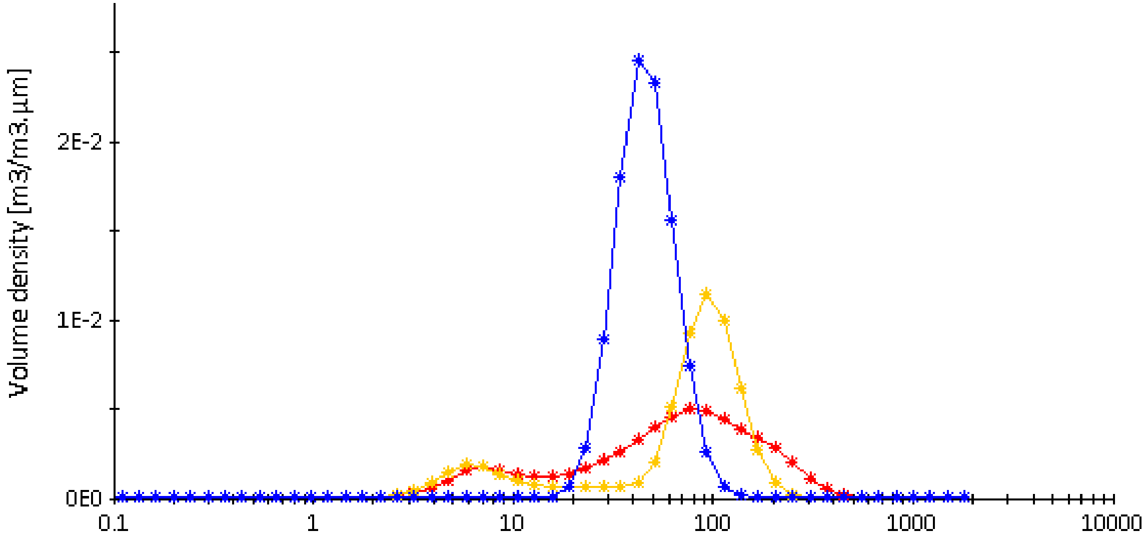
Same seed PSD used as lab scale work

Final PSD

Unseeded crystalliser

Seeded high loading

Seeded low loading



Unseeded:

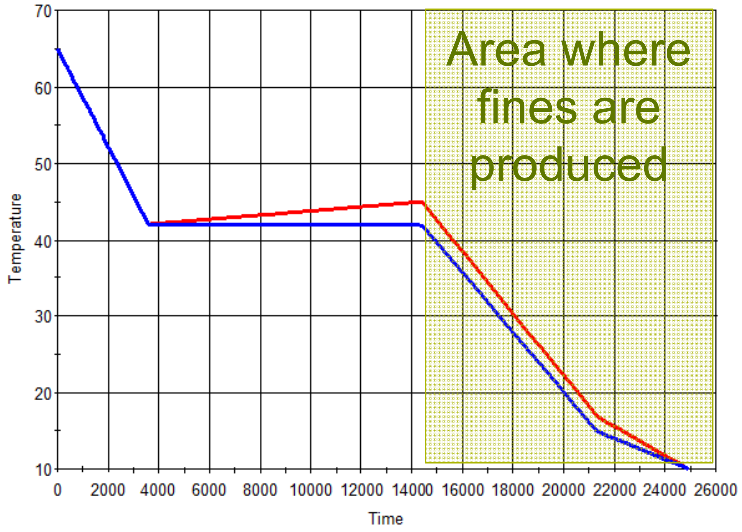
Plant model reasonably replicates the observed PSD from experiment

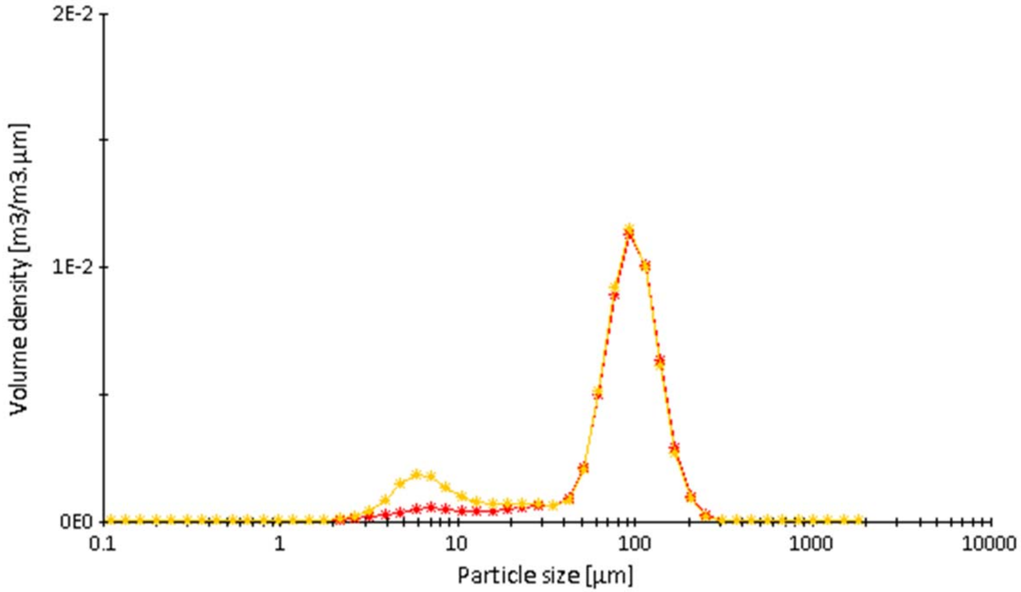
Seeds:

High loading of seeds suggests a narrow mono-modal size distribution of particles can be achieved- viscosity?

Low loading span is narrower- may be a good compromise between filtration and viscosity

Modelling Results: Effect of Modifying Cooling Profile with Low Loading of Seeds





Original plant cooling profile

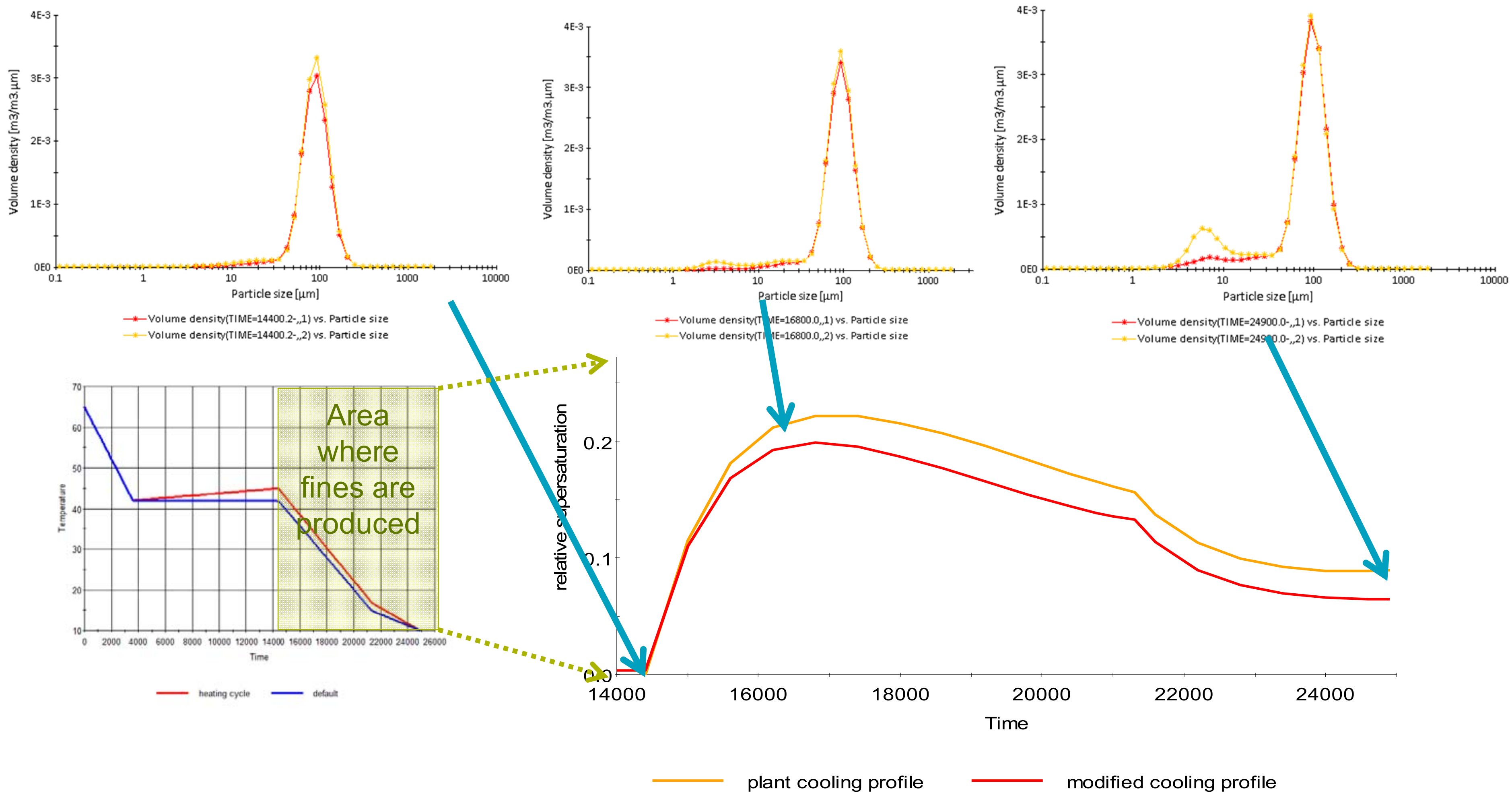
Modified cooling profile

Seeded low loading plant cooling profile

Seeded low loading modified cooling profile

- Reduction of fines apparent when a temperature ramp is implemented during the hold period

Modelling Results: Effect of Modifying Cooling Profile with Low Loading of Seeds



syngenta

Conclusions

- Lab to commercial scale batch cooling crystallisation has been successfully modelled.
- Modelling indicates that attrition is dominant in this crystallisation.
- To reduce the span of the particle size distribution the amount of attrition needs to be reduced, only apparent way is to reduce the size at which particles can grow.
- It is possible that by varying the seed amount, the PSD could be optimised.
- It is also possible that the temperature profile could be modified using temperature cycling to improve the PSD.

Future Work

- Collect additional plant data to observe scalability of kinetics from 10 L model
- Validate findings with further experiments at 10 L scale
- Run a full optimisation of the plant model
- Implement the effect of slurry viscosity and impurity uptake

Reflections on use of Modelling

Useful as a tool:

- To study the key phenomena in the crystallisation and their kinetics
- Screen inconsistent data
- Explore the effect of recipe changes on particle size distribution

- Would be beneficial to be able to model the affect of pumping out into the slurry hold vessel, where further breakage/attrition is expected

Acknowledgements

- Manish Parmar – 10 L experimental work/model building
- Pauline Sillers and Gillian Clelland – small scale seeding work and plant data/model building
- Michael Bryce – plant data/model building
- Neil George – technical input

- Hassan Mumtaz and Niall Mitchell – support and consultancy on model building and interpretation