Needle crystal shape modification through combined additive, T-cycling and wet-milling: experimental validation and modelling approach

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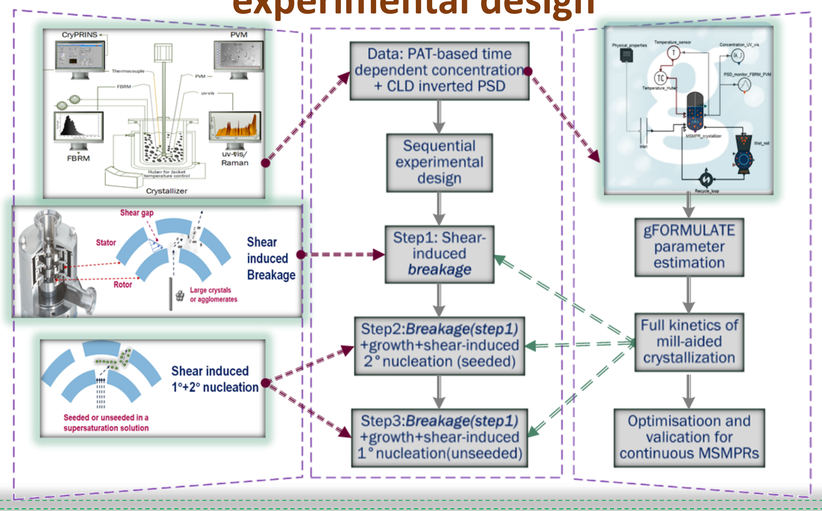
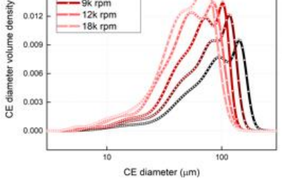
1. Model development through information rich experimental design



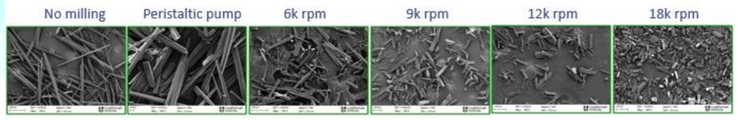
2. Experiment & Model – mill breakage

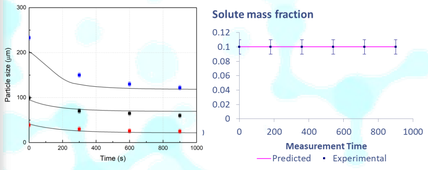


Particle size inverted from FBRM CLD

Experiment	D10 (μm)	D50 (μm)	D90 (μm)	Aspect Ratio
Seeded crystal	56	115	158	0.2?
6k rpm	48	94	135	0.2?
9k rpm	39	77	110	0.2
12k rpm	35	68	102	0.3
18k rpm	31	61	98	0.4

Commercial lovastatin product with agglomerates and wide CSD.





$$B(x,y) = \phi\left(\frac{x}{y}\right)^{\gamma} + (1-\phi)\left(\frac{x}{y}\right)^{\beta} \quad (0 \le \phi \le 1)$$

$$S(y) = Sc\left(\frac{y}{y_{crystal}}\right)^{\alpha} \quad (y_{critical} \le y)$$

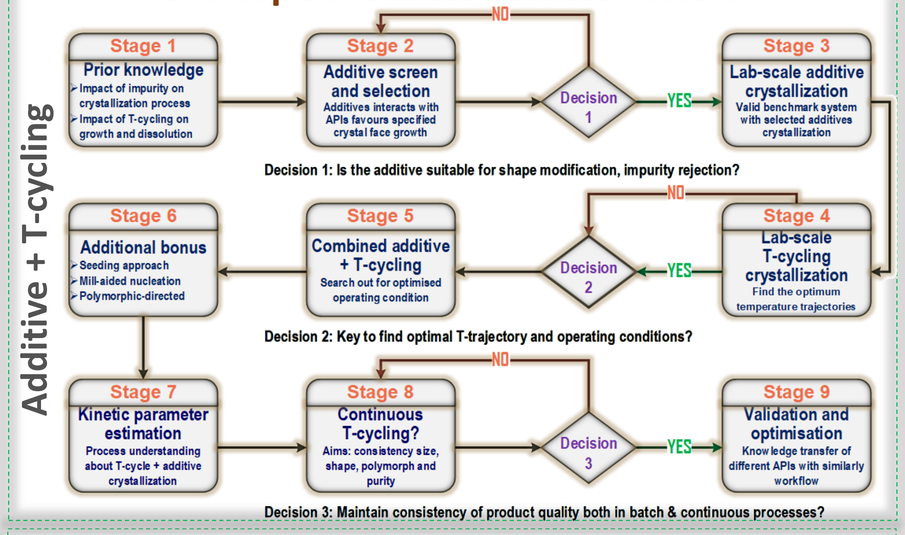
x: size of product; y: breaking particle size;

α, ϕ, γ, β estimated parameters

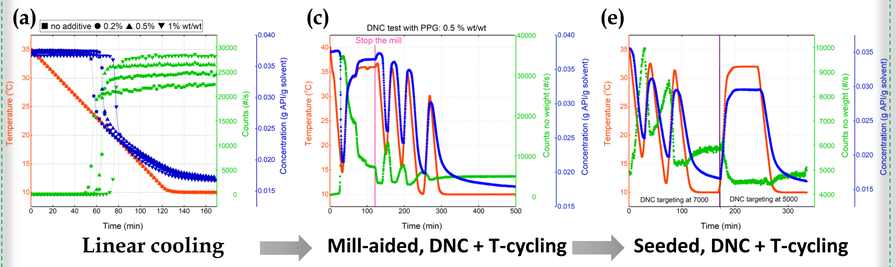
$y_{critical}$: maximum stable size; Sc: constant breaking rate at $y_{critical}$

Kinetic parameters	α	β	φ	γ	S	S_0	y_{stable} 6k rpm	y_{stable} 9k rpm	y_{stable} 12k rpm	y_{stable} 18k rpm
Unit	[−]	[−]	[−]	[−]	[−]	$[s^{-1}]$	$[\mu m]$	$[\mu m]$	$[\mu m]$	$[\mu m]$
Milling-aided	0.28	930	0.02	0.654	1.5E-4	0.008	175	160	150	130

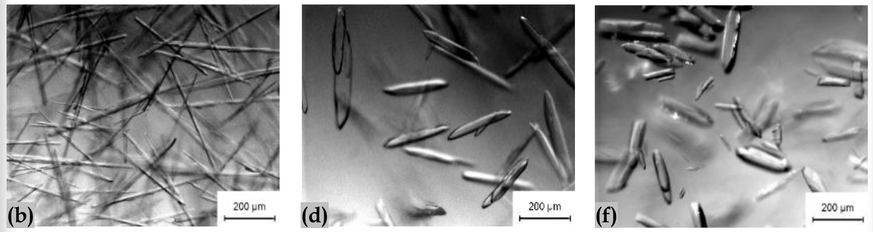
3. Shape modification work flow



4. Additive + T-cycles of dissolution and growth



Linear cooling → **Mill-aided, DNC + T-cycling** → **Seeded, DNC + T-cycling**



FBRM counts #/s ➡, **Temperature** ➡ and **concentration** ➡ profile and in situ PVM images showing the crystals at the end for:

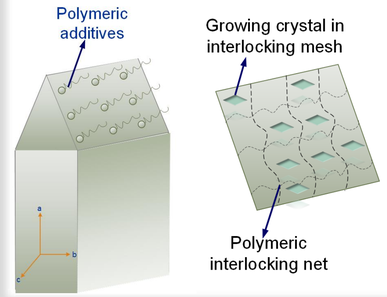
(a) and (b) Linear cooling crystallization of lovastatin/ethyl acetate

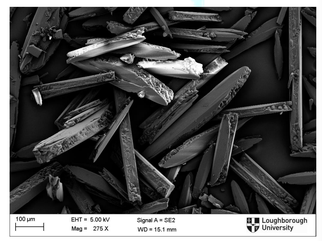
(c) and (d) Lovastatin/ethyl acetate/PPG-4000 with mill-aided, DNC + T-cycling crystallization

(e) and (f) Lovastatin/ethyl acetate/PPG-4000 with seeded, DNC + T-cycling crystallization

5. Additive T-cycling crystallization

- The aspect ratio of needle-shaped crystals is modified by polypropylene glycol (PPG), which acts as growth blocking agent on selected crystal faces.
- The fastest growth path along the [100] direction is suppressed while the [010] direction indicating distinctively growth gives spindle body shape.
- The images show that growth from solution is disrupted on some surfaces resulting in an uneven microstructure, whilst growth on other planes remain relatively flat.





6. Conclusions and future work

Conclusions on needle shape modification:

- Shape modification is achieved by using additives + temperature cycling resulting in decorrelating growth and dissolution, which overall inhibit growth along the a-axis at [100]
- Sequential parameter estimation conducted to isolate different size change mechanisms

Future work will focus on:

- Additive effects on wet mill crystallization and impact of wet-mill on impurity rejection
- 2D PBE gFORMULATE model will be used to enhance the prediction capabilities for needle crystallization process
- Optimal experimental design: Model-based design of experiment (work with Zhuang Sun)

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