Model-based characterisation of twin-screw granulation for continuous solid dosage manufacturing

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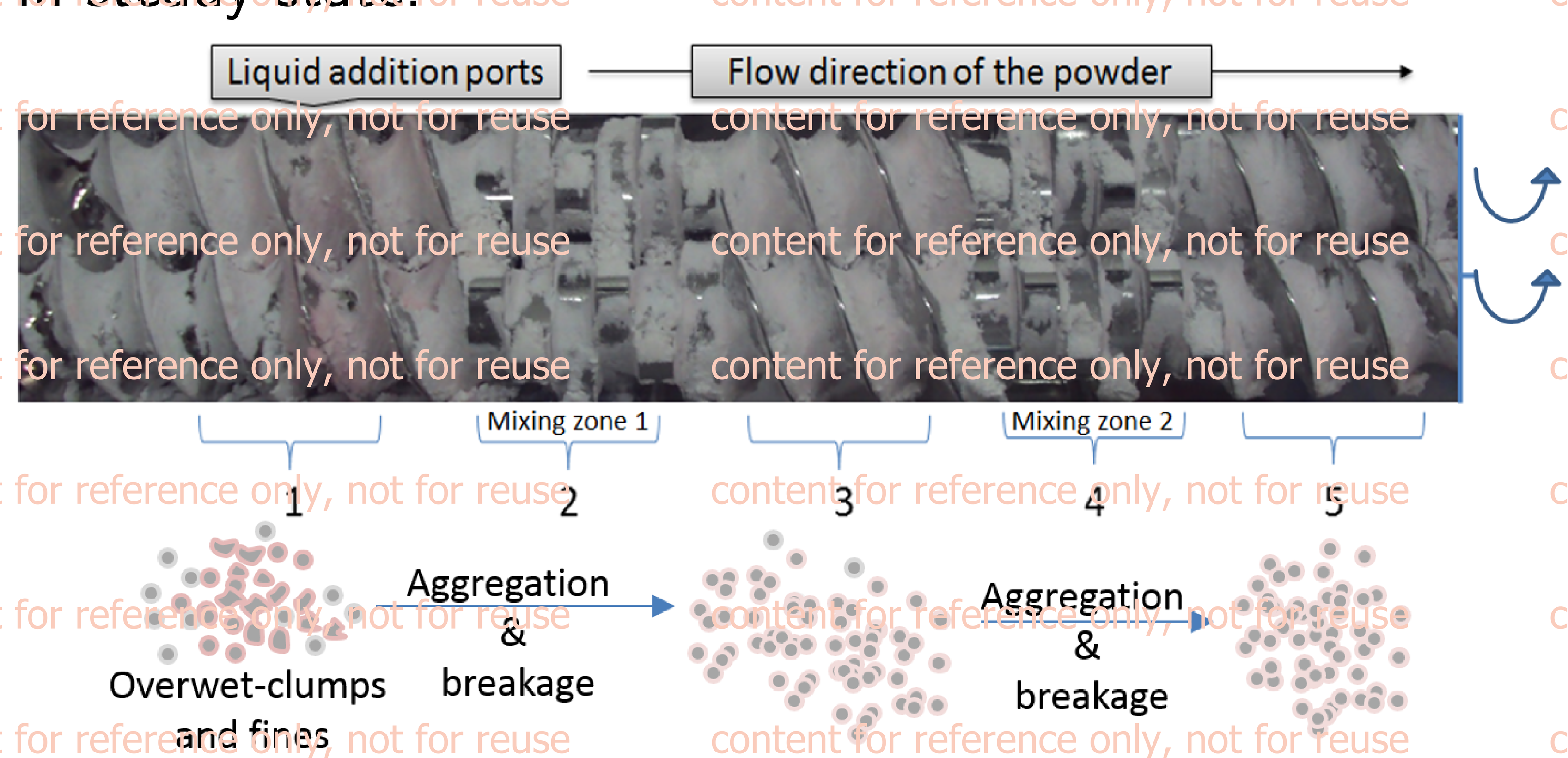
Introduction

- The twin-screw granulator (TSG) is a potential tool for wet granulation in future continuous solid dosage manufacturing.
- However, little is known about how process and equipment settings affect the evolution and kinetics of granule formation.
- Available experimental characterisation studies have primarily focused on the effect of these settings on granule properties at the TSG outlet due to the barrel opacity.
- Aim: A model-based characterisation in combination with experimental calibration has been applied to **track the particle size evolution within the TSG**.

Twin-screw wet granulation

- Granulation time is short (in the order of seconds).
- At appropriate time scales and conditions, granulation is in steady state.



Tracking particle size dynamics in mixing zones

- Two mixing zones in the TSG were assumed as well-mixed compartments.
- Population balance model was used to track particle size evolution in mixing zones.

$$\frac{\partial n(t,x)}{\partial t} = \frac{Q_{in}}{\tilde{V}} n_{in}(x) - \frac{Q_{out}}{\tilde{V}} n_{out}(x) \quad \text{GSD balance}$$

Aggregation term:

$$+\frac{1}{2}\int_0^x \underbrace{\beta(t, x-\varepsilon, \varepsilon)}_{\text{aggregation rate}} n(t, x-\varepsilon) n(t,\varepsilon)\, d\varepsilon - n(t,x)\int_0^\infty \underbrace{\beta(t,x,\varepsilon)}_{\text{aggregation rate}} n(t,\varepsilon)\, d\varepsilon$$

Breakage term:

$$+\int_0^\infty \underbrace{b(x,\varepsilon)}_{\text{breakage fun.}} \underbrace{S(\varepsilon)}_{\text{selection rate}} n(t,\varepsilon)\, d\varepsilon - \underbrace{S(x)}_{\text{selection rate}} n(t,x)$$

Kernels, solution method & parameter estimation

Aggregation kernel (constant kernel)	Breakage kernel (Austin, 2002)
$\beta(x,y) = \beta_0$	$S(y) = S_0(y)^{\mu}$, $b(x,y) = \dfrac{\frac{\phi\gamma x^{\gamma-1}}{y^{\gamma}} + \frac{(1-\phi)\alpha x^{\alpha-1}}{y^{\alpha}}}{\frac{\phi\gamma}{\gamma+1} + \frac{(1-\phi)\alpha}{\alpha+1}}$

- Sectional method known as the Cell Average Technique was applied to solve the PBM.
- Parameter sets were derived by minimizing the root mean square error (RMSE) between experimental and simulated data via Monte Carlo simulations.

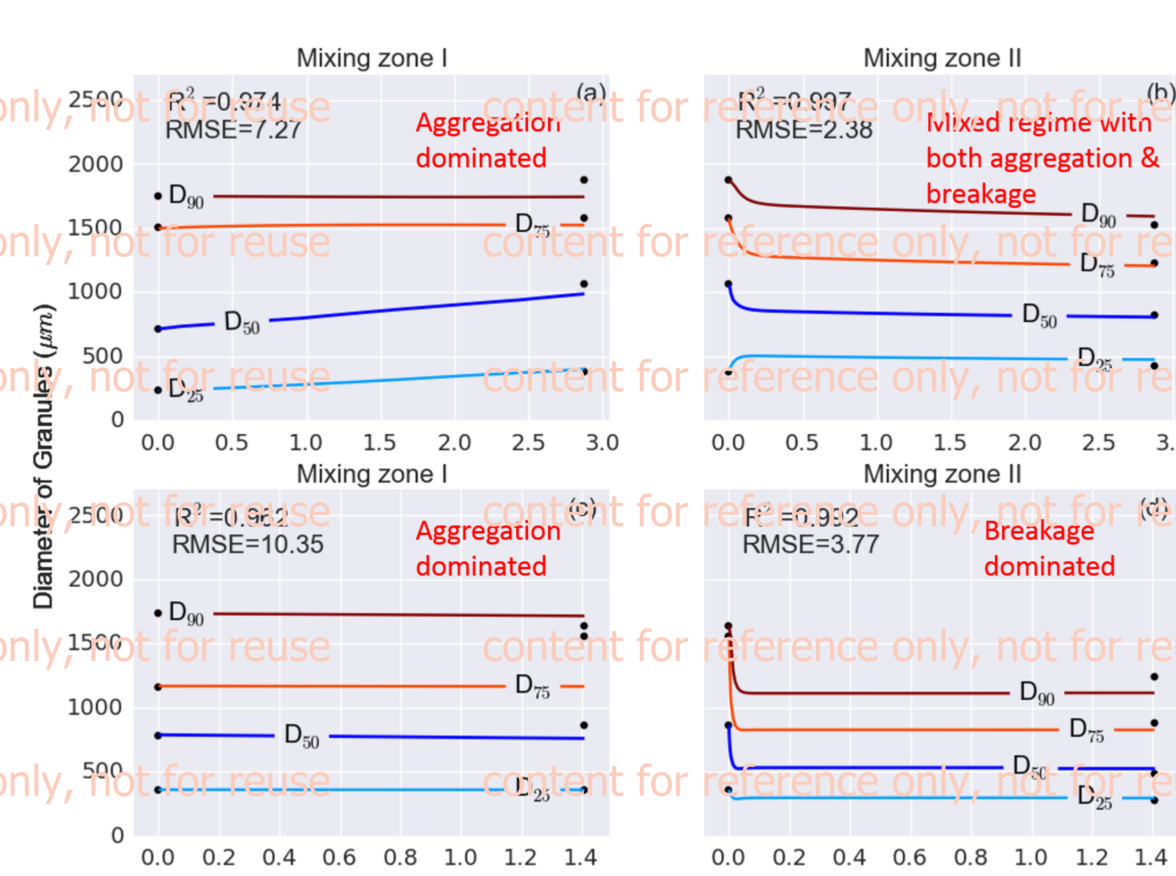
$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}(y_{sim.} - y_{exp.})^2}{n}}$$

- The confidence interval of the fitted parameter was determined using the bootstrap estimation method.

Table: Estimated model parameters with corresponding confidence intervals (95 %) for two mixing zones at different screw speeds

Screw speed	Low (500 rpm)		High (900 rpm)	
Mixing zone	I	II	I	II
β_0	3.02E-03 ± 1.47E-04	1.95E-01 ± 4.56E-02	9.18E-02 ± 4.07E-03	4.99E-02 ± 1.80E-02
S_0	2.53E-02 ± 5.91E-03	7.99E-01 ± 4.35E-02	3.11E-02 ± 2.25E-03	5.72E-01 ± 3.55E-02
α	1.13E-05 ± 8.83E-06	6.11E-01 ± 3.19E-02	1.26E-03 ± 3.29E-04	4.38E-01 ± 9.30E-02
γ	4.05E+00 ± 7.60E-01	3.81E-03 ± 2.18E-04	2.63E-01 ± 9.02E-03	4.49E-02 ± 3.78E-03
ϕ	1.03E+00 ± 2.31E-01	5.43E-02 ± 2.24E-03	1.18E+00 ± 3.89E-01	1.50E-02 ± 2.13E-03

Particle size evolution in mixing zones



Take home message

By choosing appropriate process conditions, regime separation can be achieved in TSG, allowing improved design and operation of the continuous granulation process.

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