Development of a population balance model for continuous twin-screw granulation in pharmaceutical manufacturing

Ashish Kumar, Krist V. Gernaey, Thomas De Beer, Ingmar Nopens

AIChE Annual Meeting 2014

Session: Agglomeration and Granulation Processes

Laboratory of Pharmaceutical Process Analytical Technology

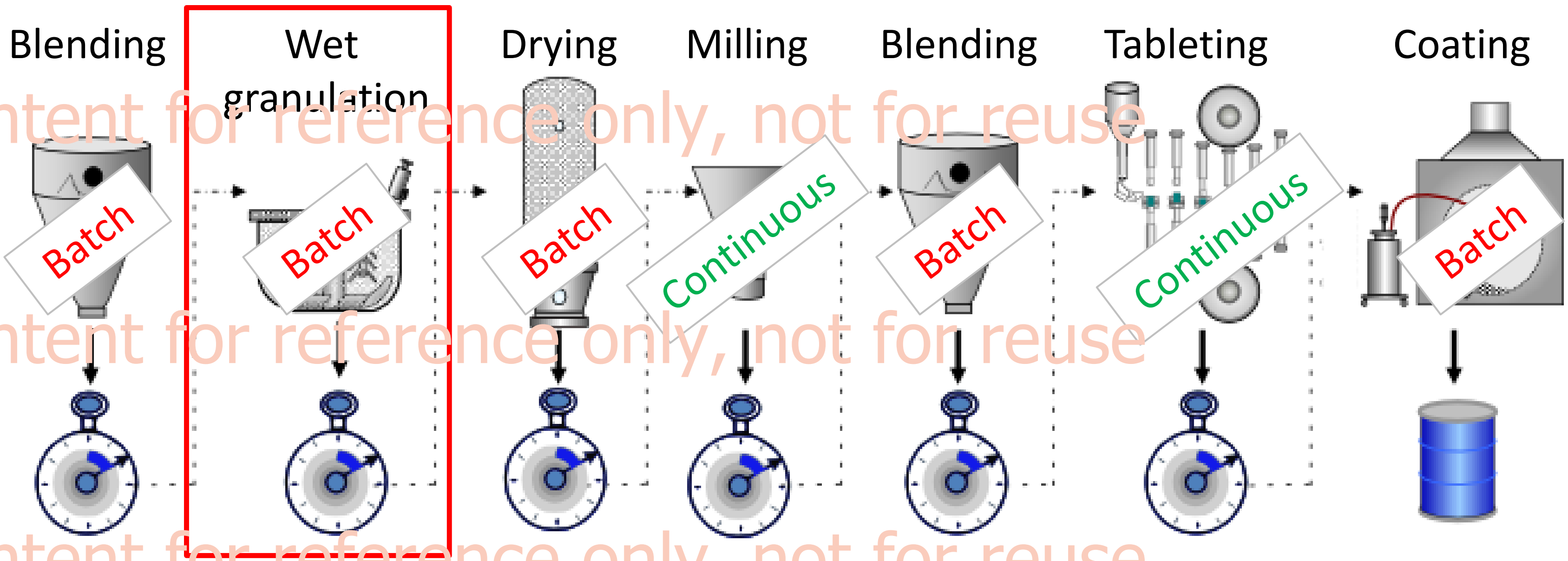
Faculty of Pharmaceutical Sciences

BIOMATH, Department of Mathematical Modelling, Statistics and Bioinformatics

Faculty of Bioscience Engineering

Universiteit Gent

Current solid-dosage manufacturing is slow and expensive

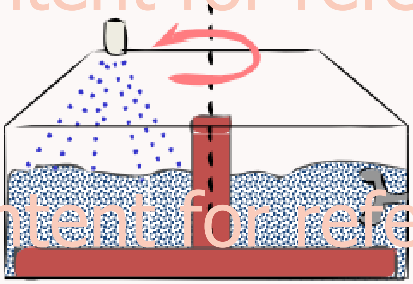


Product collected after each unit operation

Actual processing time = days to weeks

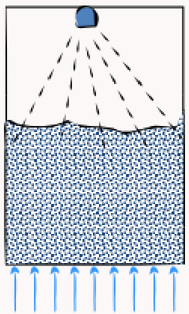
Traditional to new granulation method

High-shear mixer



Drum

Fluidised-bed

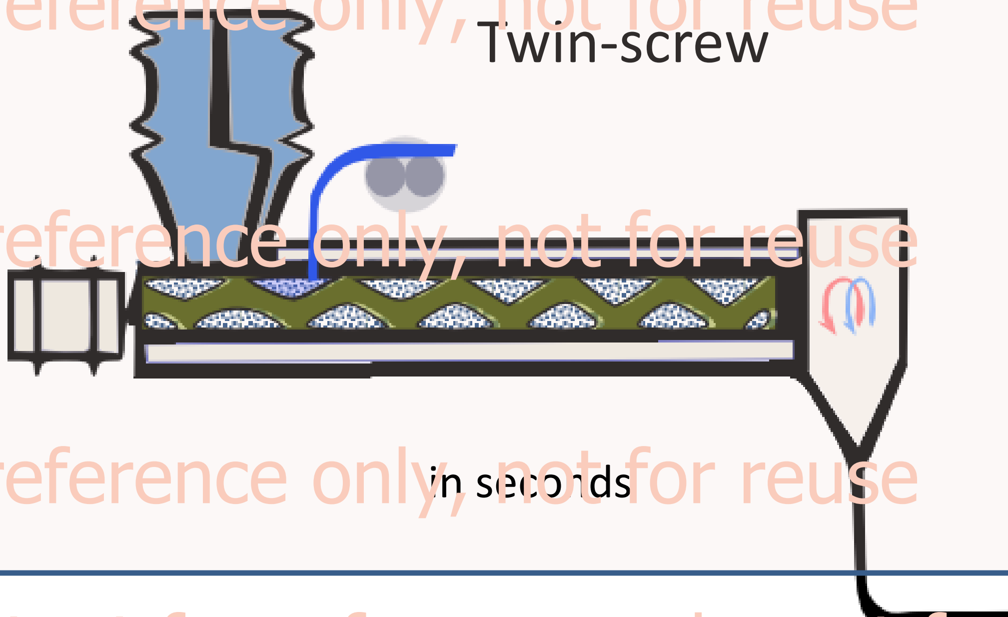


From minutes to hours

Batch

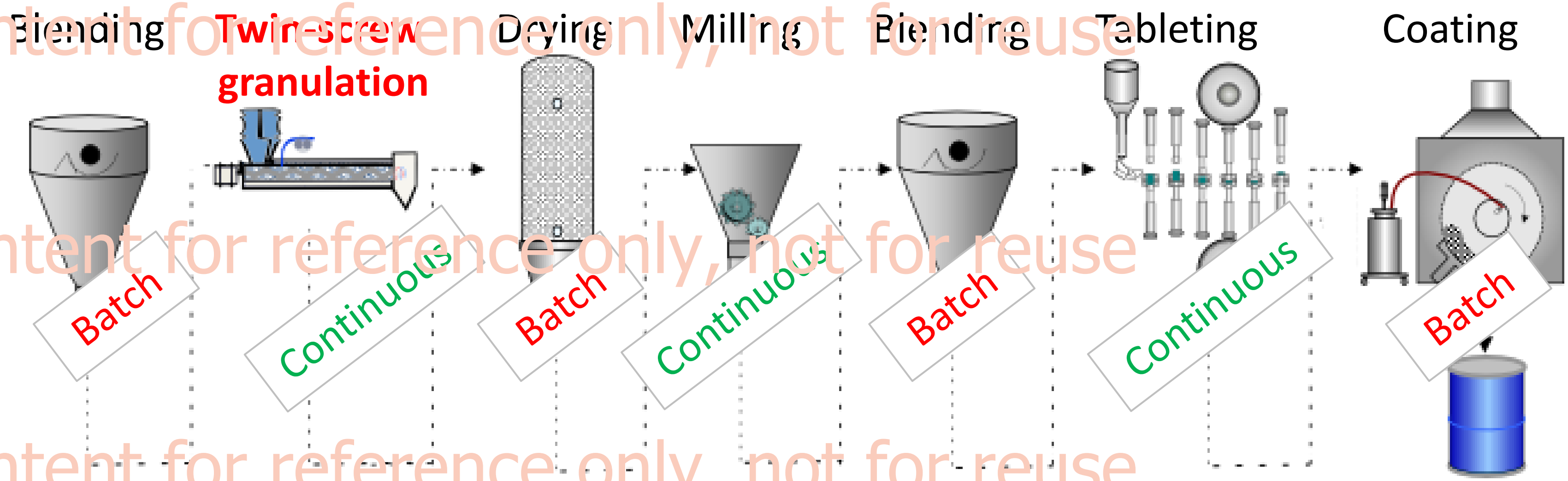
Continuous

Twin-screw



in seconds

Easy to integrate with other unit operations of pharmaceutical manufacturing



Continuous manufacturing line

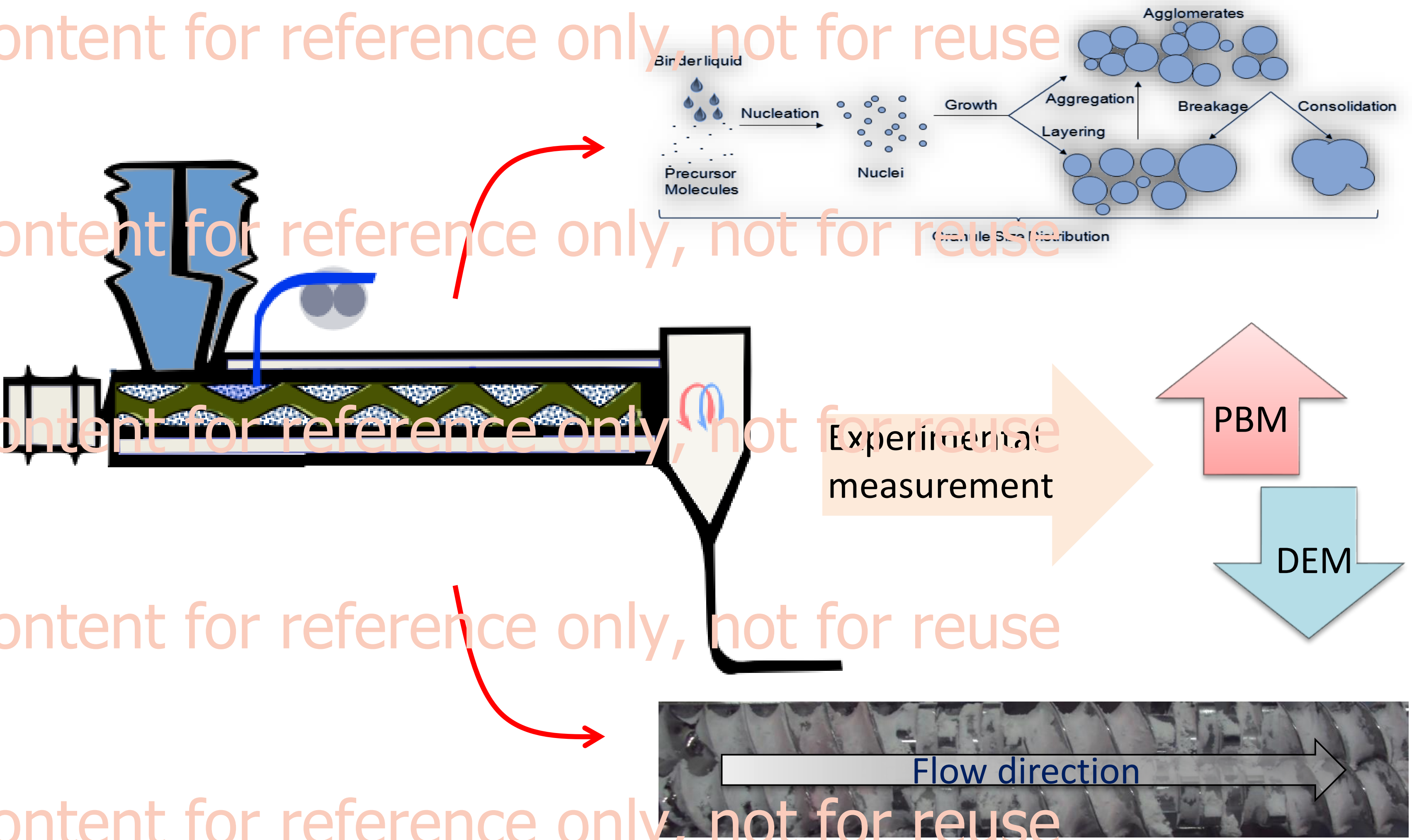
Consigma™-25 system

Continuous twin-screw granulator

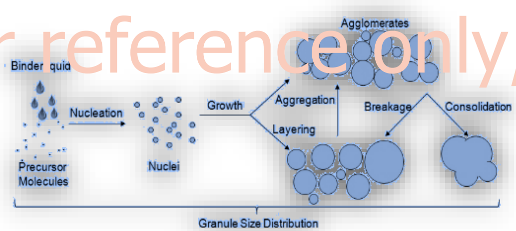
Segmented Fluid bed dryer

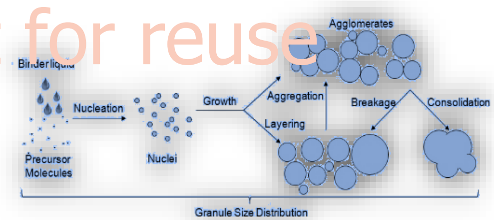
Granule conditioning module

Both geometry and process conditions drive constitutive mechanisms



Understanding the role of screw design

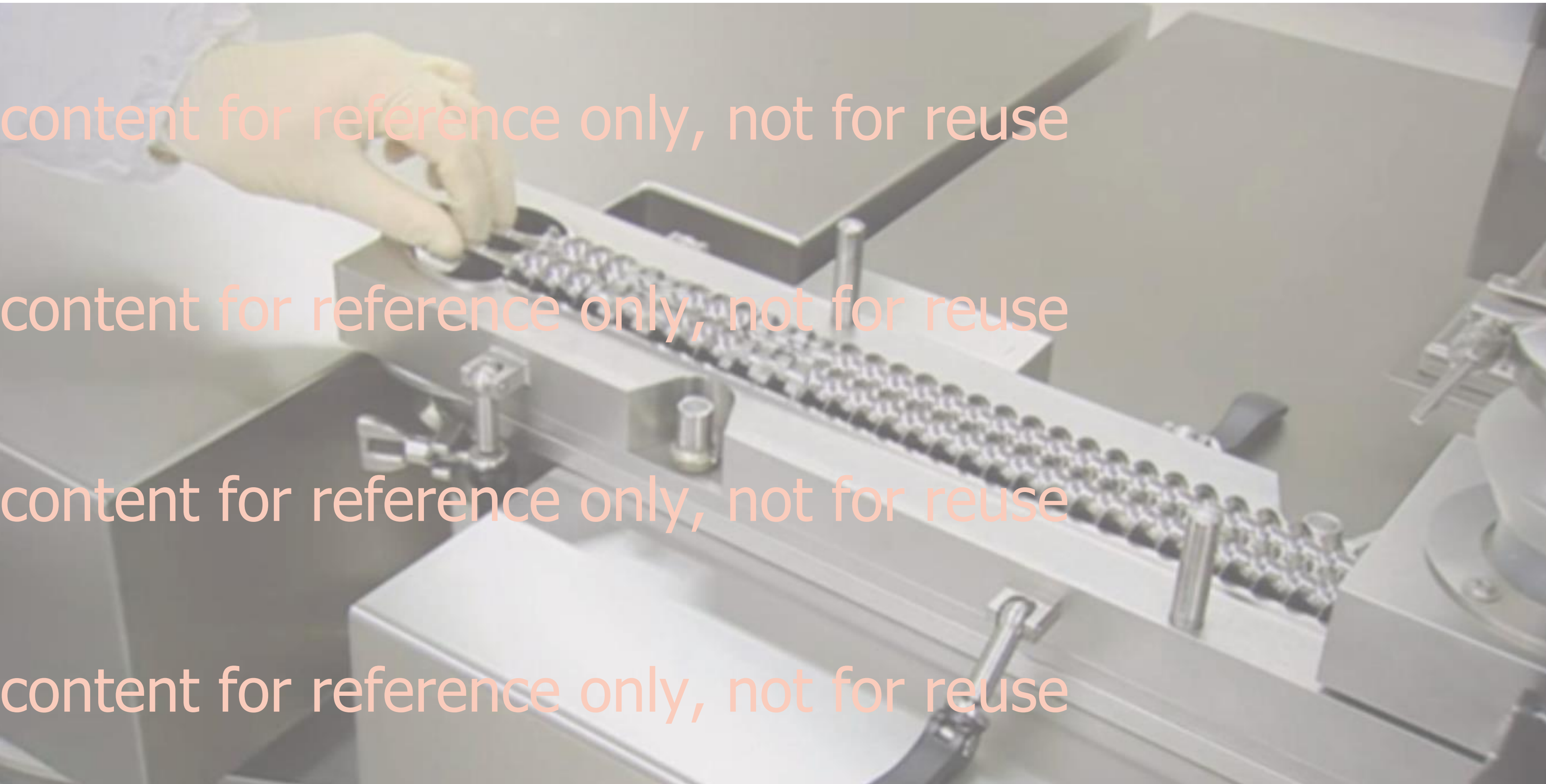




Consigma™-1 system

(GEA pharma systems, Collette)

Open barrel of a twin screw granulator

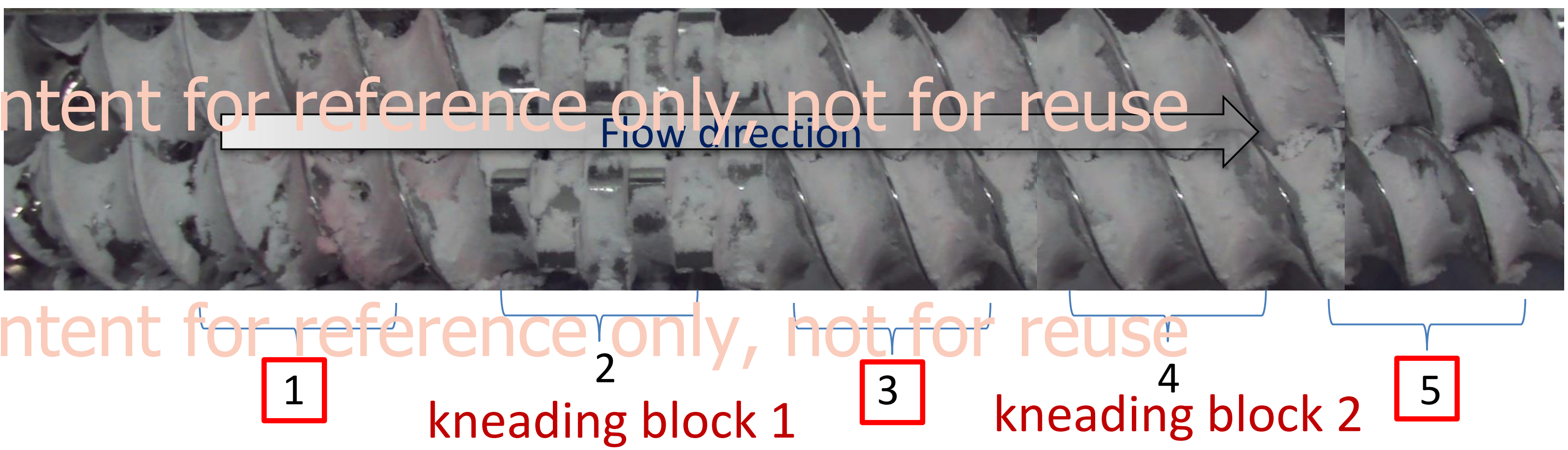


Consigma™- 1 experiments

Granulated Lactose monohydrate with distilled water

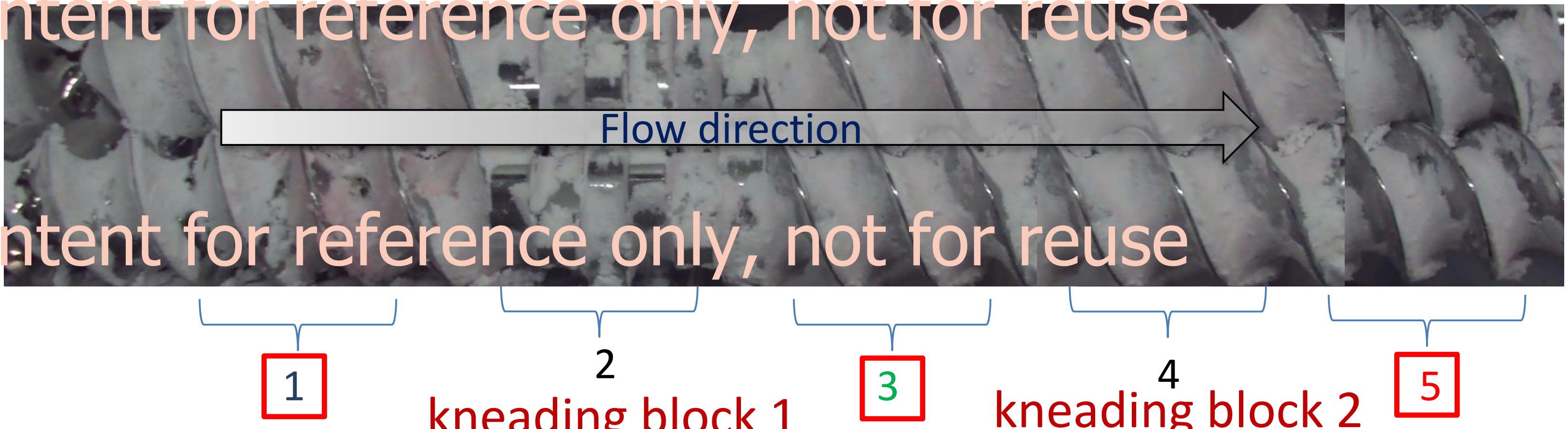
Factors:

Parameters	Low	High
Throughput	10 Kg/h	25 Kg/h
Liquid-solid ratio	4.58 %	6.52%
Screw speed	500 RPM	900 RPM

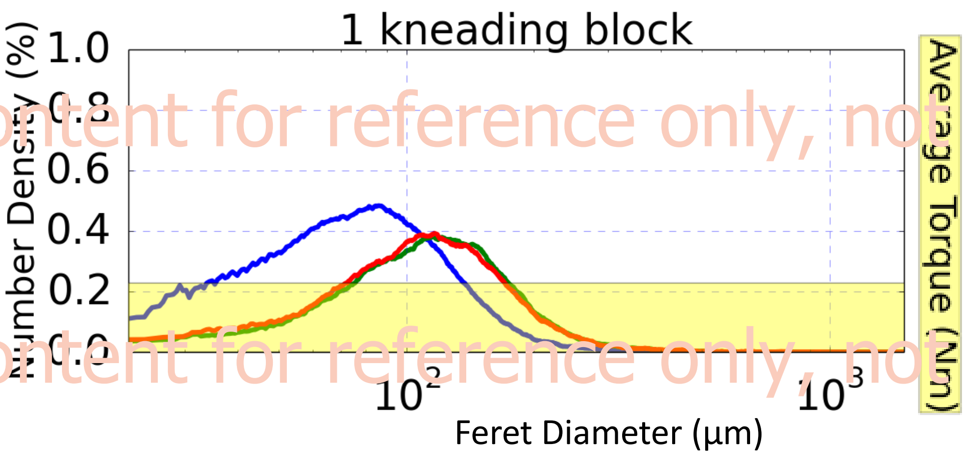


Responses: Particle characterization by Dynamic Image Analysis (Location 1, 3, 5)

Consigma™- 1 experiments

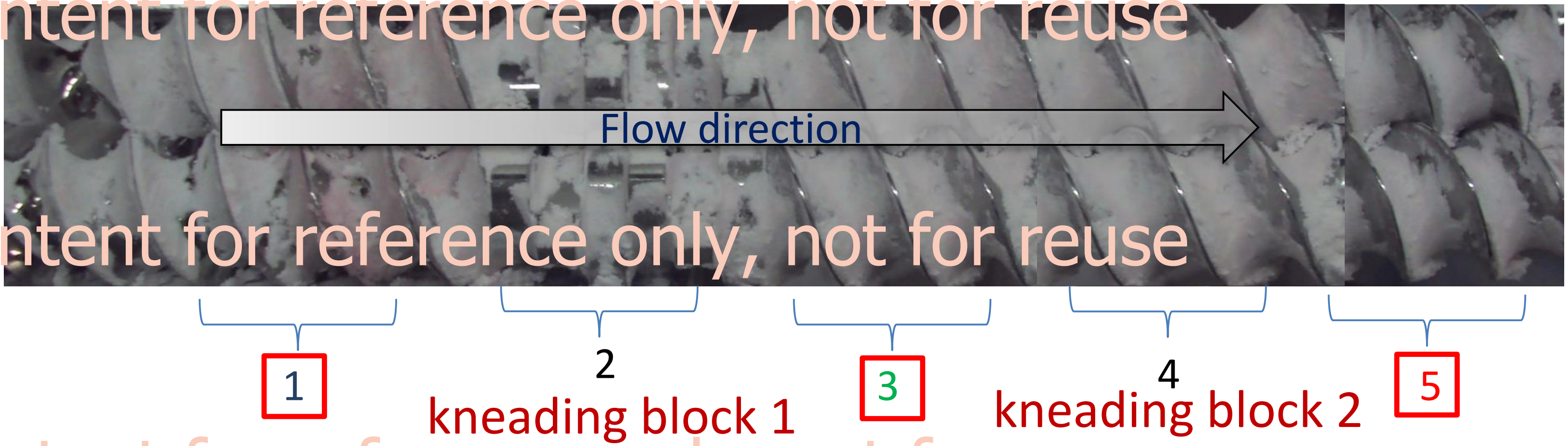


Throughput High	Liquid-solid ratio High	Screw speed Low

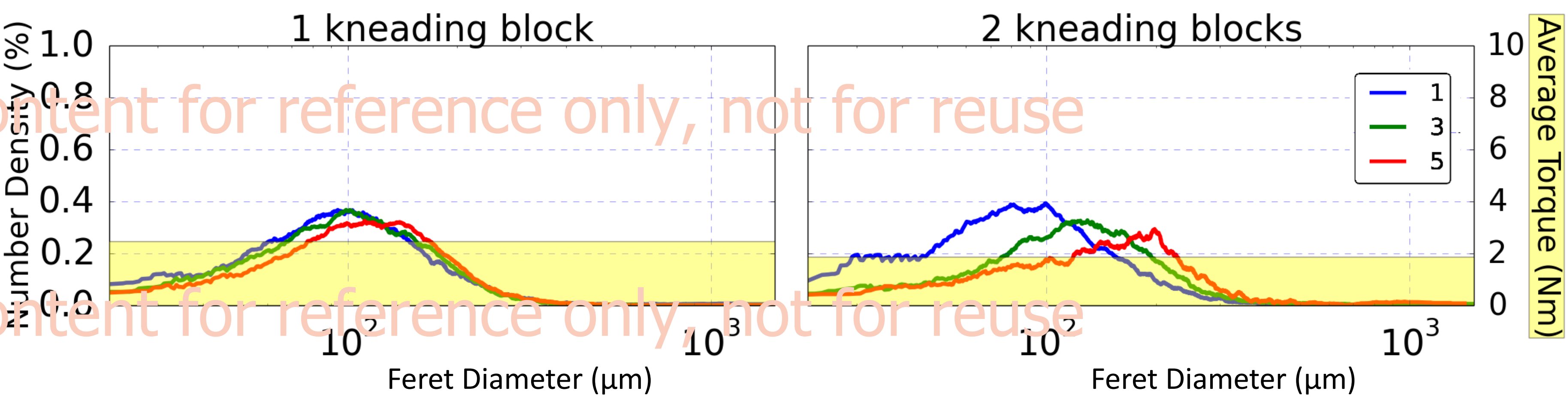


For details see: Kumar, et al. "Experimental investigation of granule size and shape dynamics in twin-screw granulation." *I J Pharma* 475.1 (2014): 485-495.

Consigma™- 1 experiments

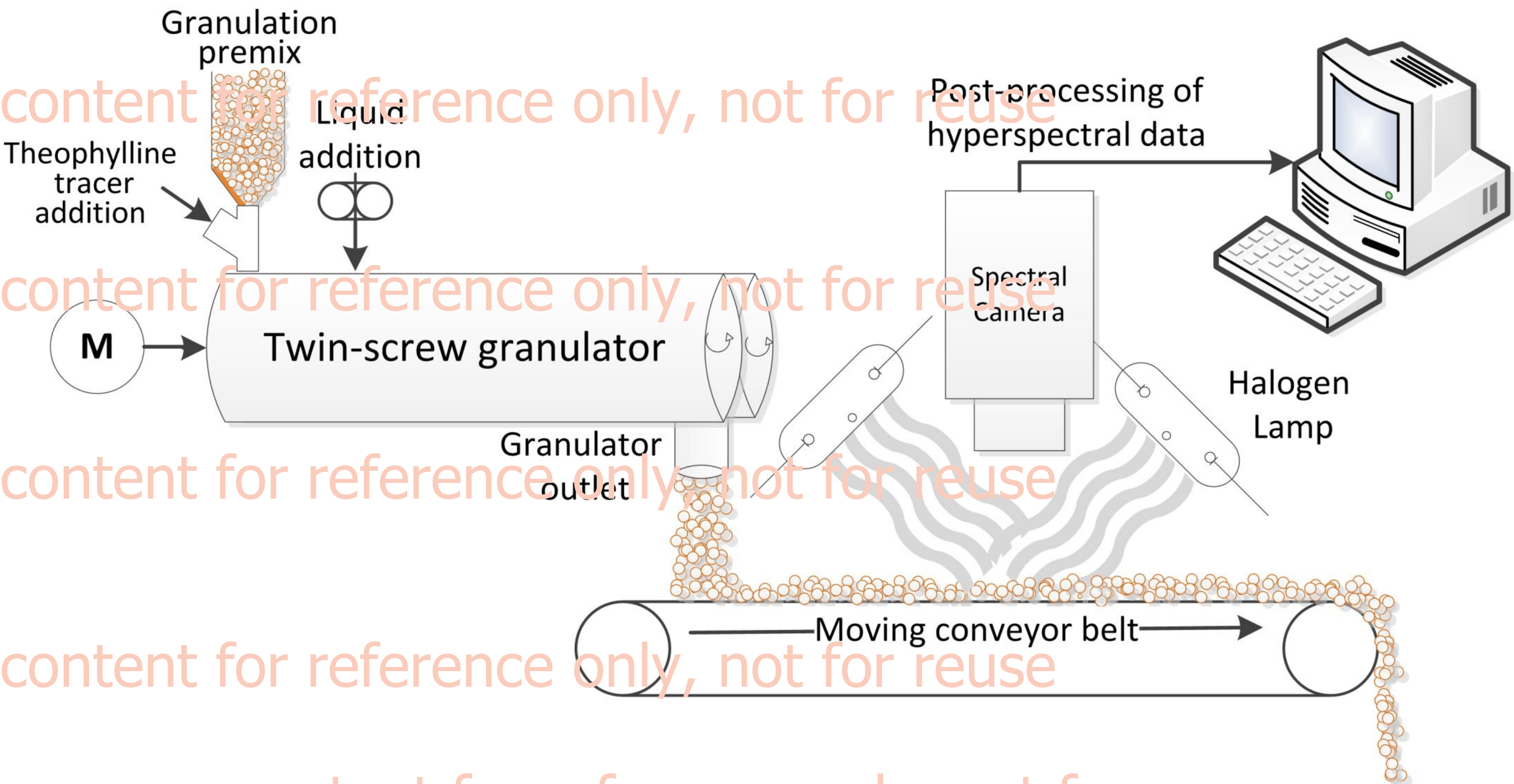


Throughput High	Liquid-solid ratio High	Screw speed High

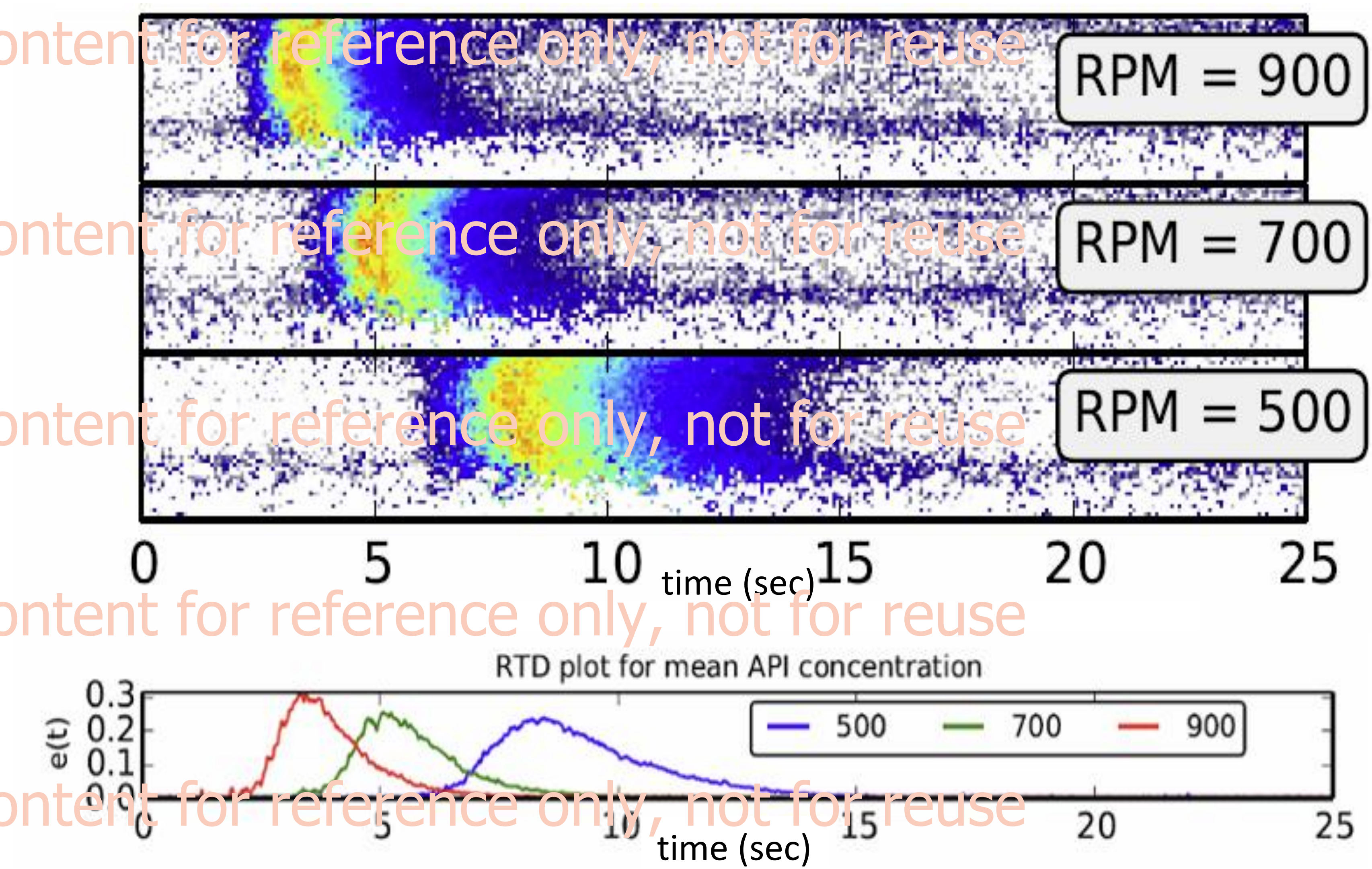


For details see: Kumar, et al. "Experimental investigation of granule size and shape dynamics in twin-screw granulation." *I J Pharma* 475.1 (2014): 485-495.

Tracer concentration in granules produced was measured using NIR chemical imaging

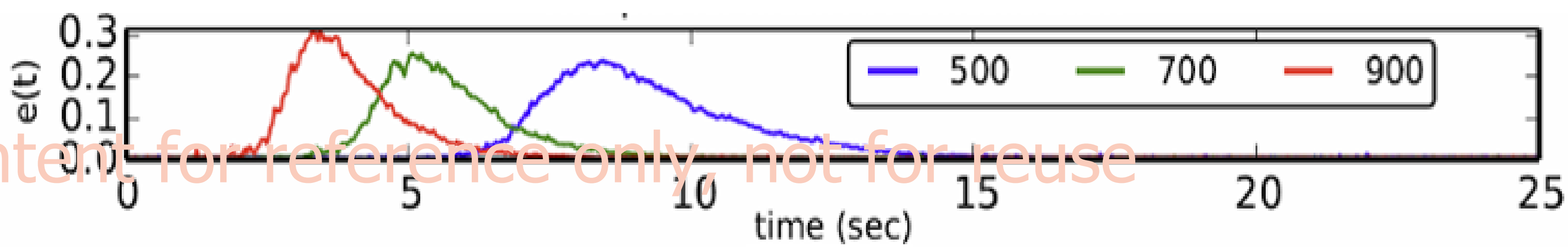


API Map was used to measure RTD



For details see: Kumar, et al. "Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging." *E J Pharma. Biopharma.* 87.2 (2014): 279-289.

Measure of the mean of the distribution



$$\tau = \frac{\int_0^\infty t \cdot e(t)dt}{\int_0^\infty e(t)dt}$$

Mean residence time, τ

For details see: Kumar, et al. "Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging." *EJ Pharma. Biopharma.* 87.2 (2014): 279-289.

Population balance models can track granule attributes

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

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

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

$$-\underbrace{S(x)}_{\text{selection rate}} n(t,x)$$

Semi-empirical kernels

Aggregation Kernel

$$\beta(x, y) = \beta_0$$

(Constant kernel)

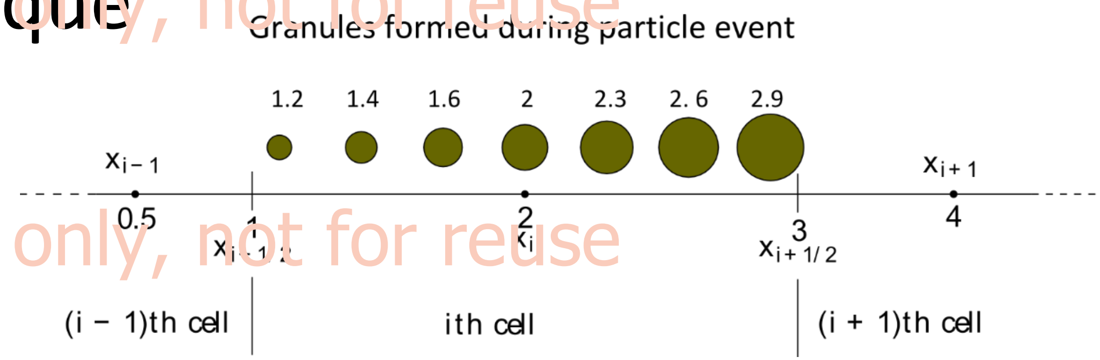
Breakage Kernel

$$S(y) = S_0 (y)^{\mu}$$

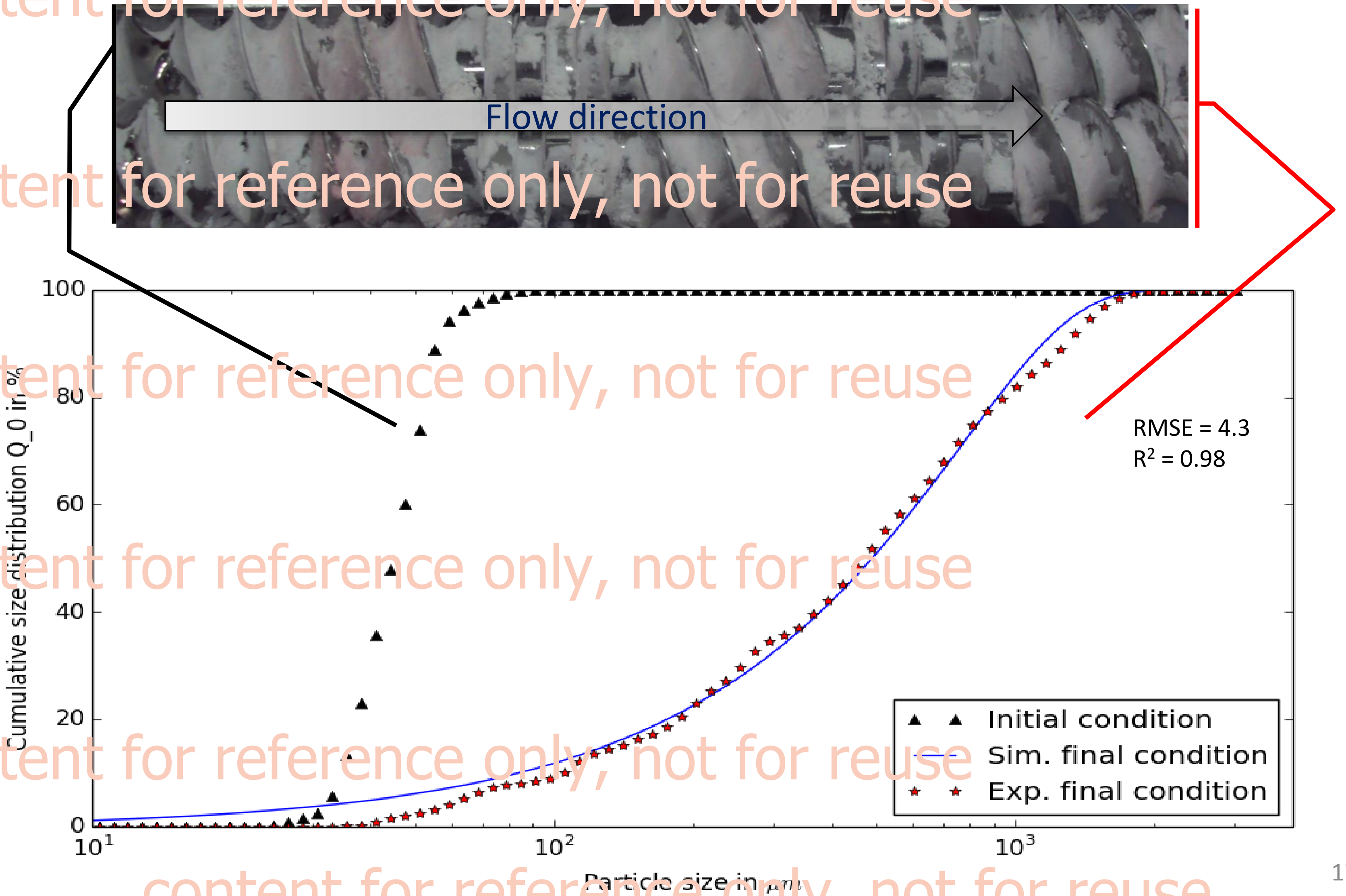
$$b(x, y) = \frac{\frac{\phi \gamma x^{\gamma-1}}{y^{\gamma}} + \frac{(1-\phi)\alpha x^{\alpha-1}}{y^{\alpha}}}{\frac{\phi\gamma}{\gamma+1} + \frac{(1-\phi)\alpha}{\alpha+1}}$$

(Austin, 2002)

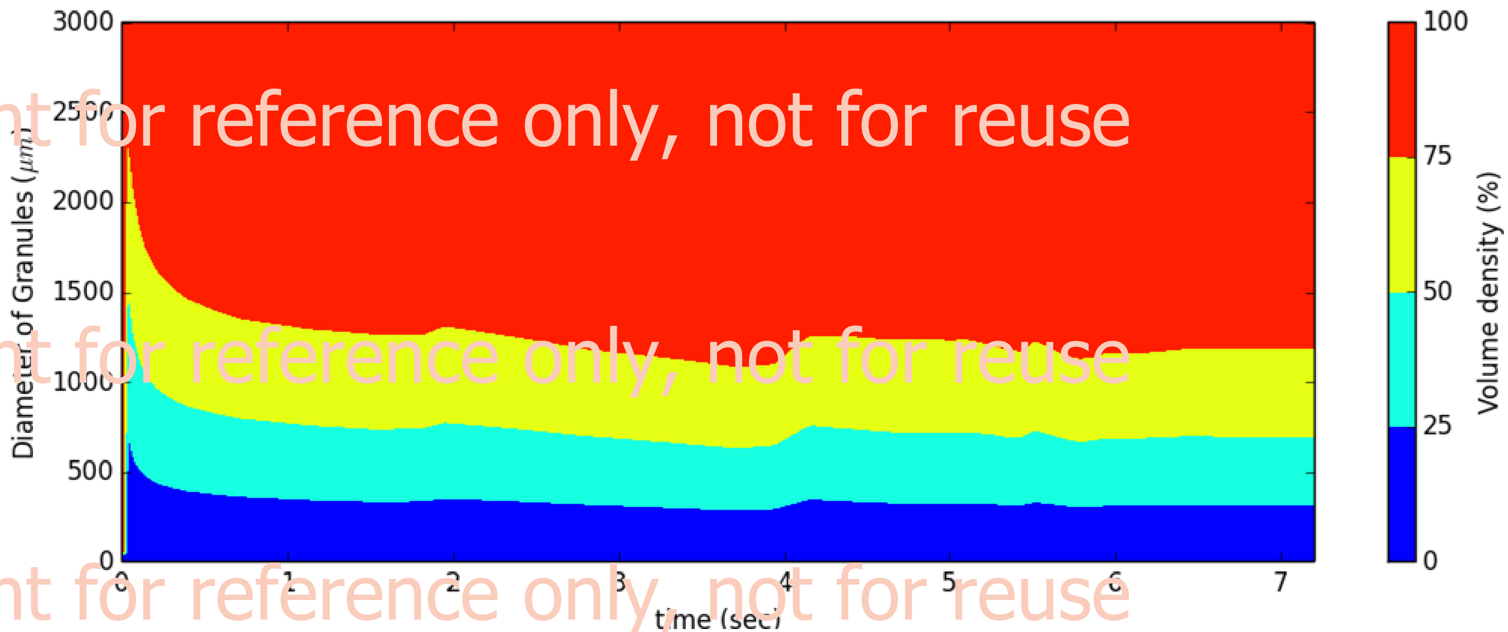
Cell-average technique



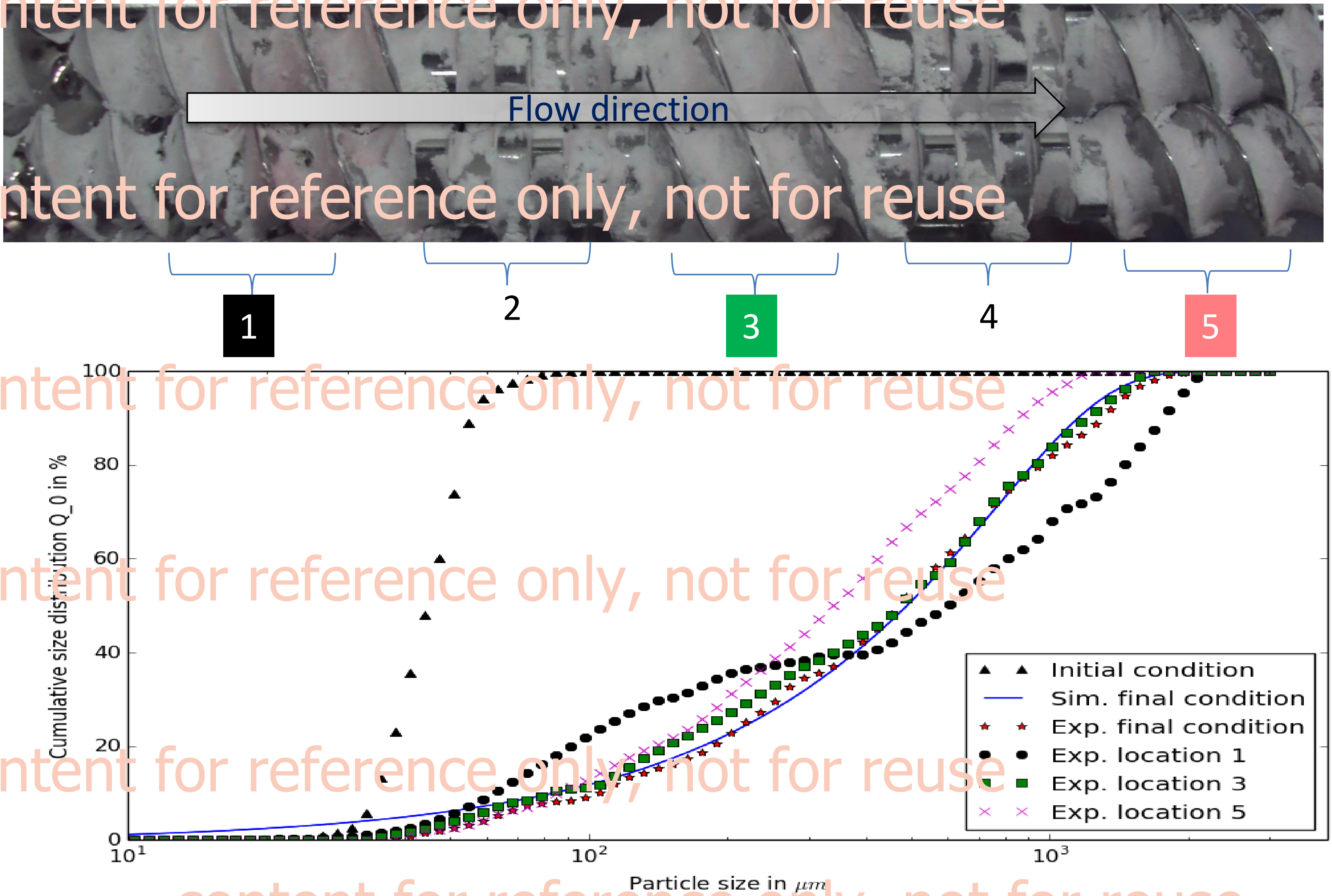
Experimental and simulated data have a good agreement

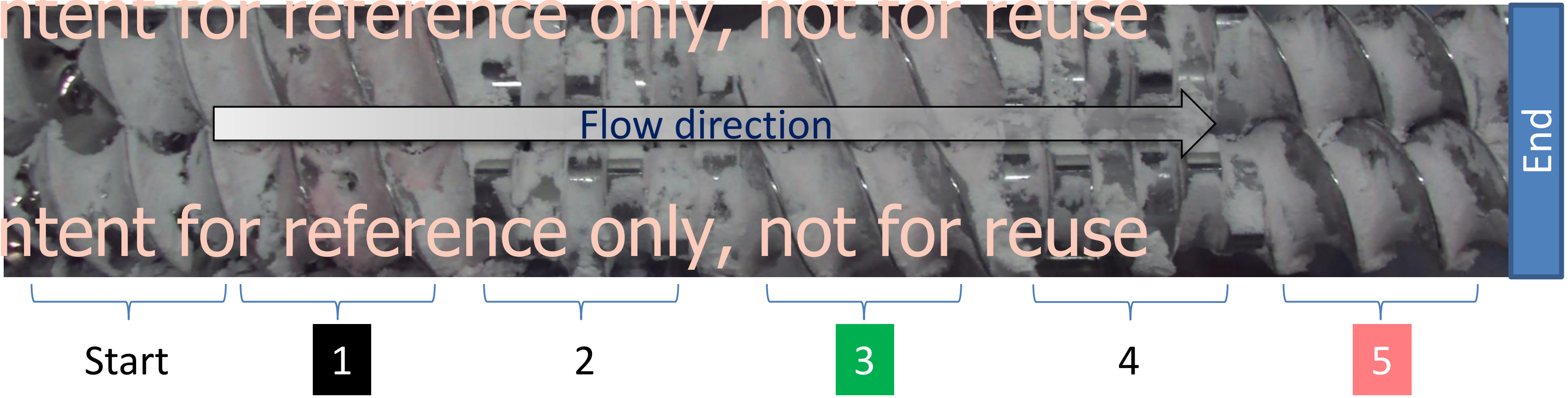


Particle population dynamics during granulation



including effect of granulator design on granule size distribution





	Parameter	Significance	Location 1	Location 3	Location 5	End
	RMSE		16.25	2.72	2.14	4.3
Aggregation	β_0	Collision frequency (sec^{-1})	1052.53	1632.92	820.79	5055.40
Breakage	S_0	Selection function constant for breakage	0.07	0.99	2.40	3.31
	α	Width of fragment distributions	0.17	0.31	0.39	0.35
	γ	width of fragment distributions	22.21	28.89	2.64	200.30
	ϕ	mass content of first breakage distributions	0.02	0.00	0.02	0.01

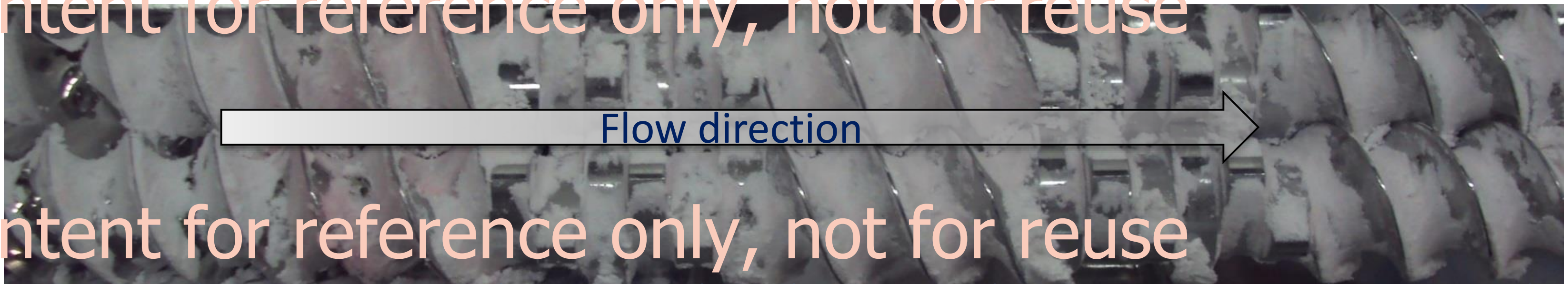
γ, ϕ and α are dimensionless material constants.

ϕ is the weight parameter to quantify the mass content of first breakage distributions.

γ and α are width of the fragment distributions ϕ and $1-\phi$, respectively.

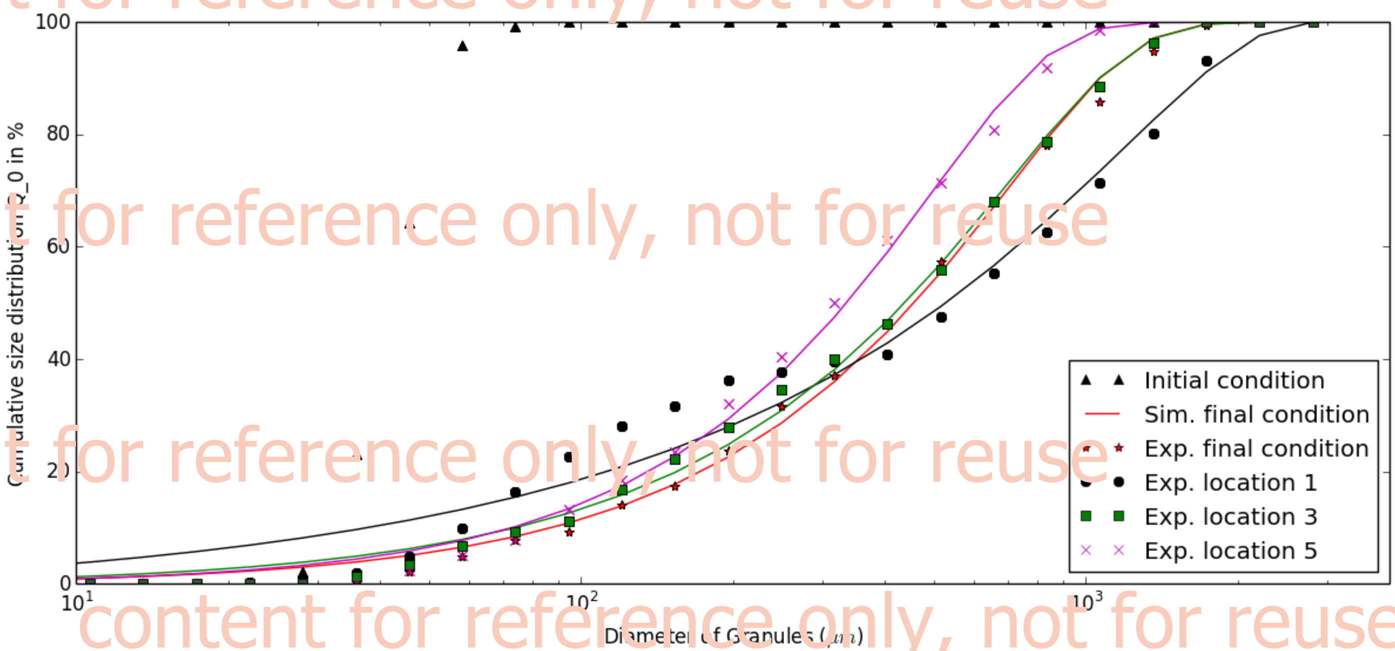
Quadratic selection function, $S(y) = S_0 (y)^{\mu}$ where μ was 1/3.

Including effect of granulator design on granule size distribution

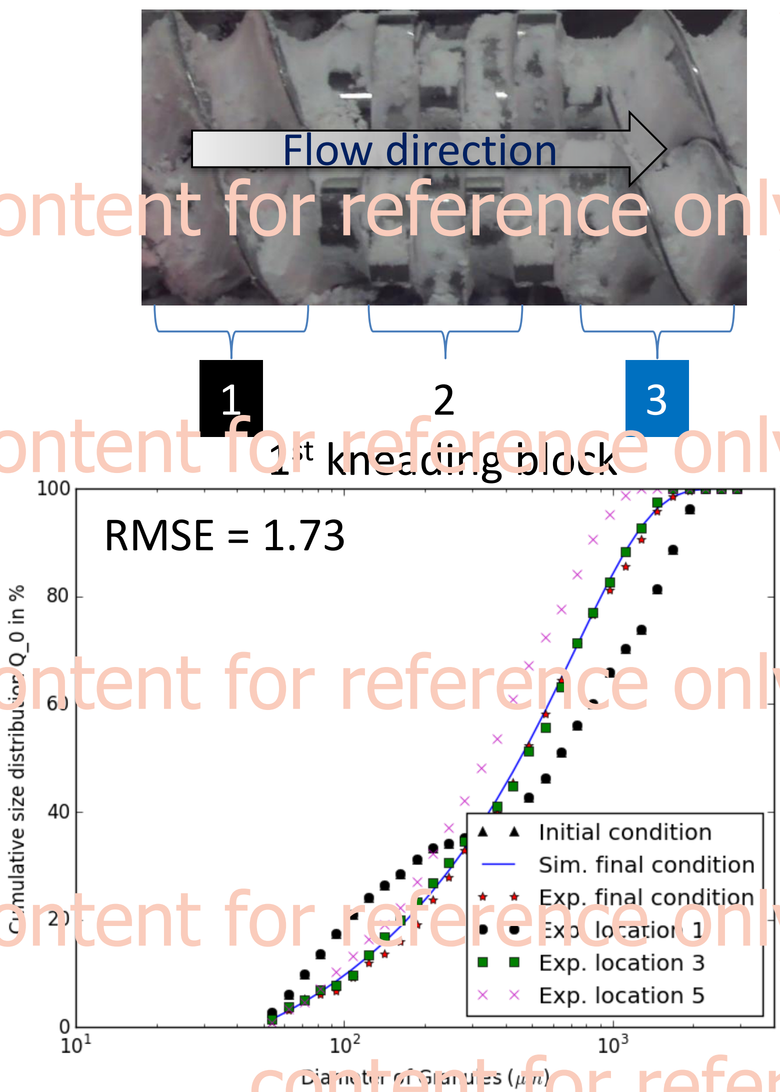


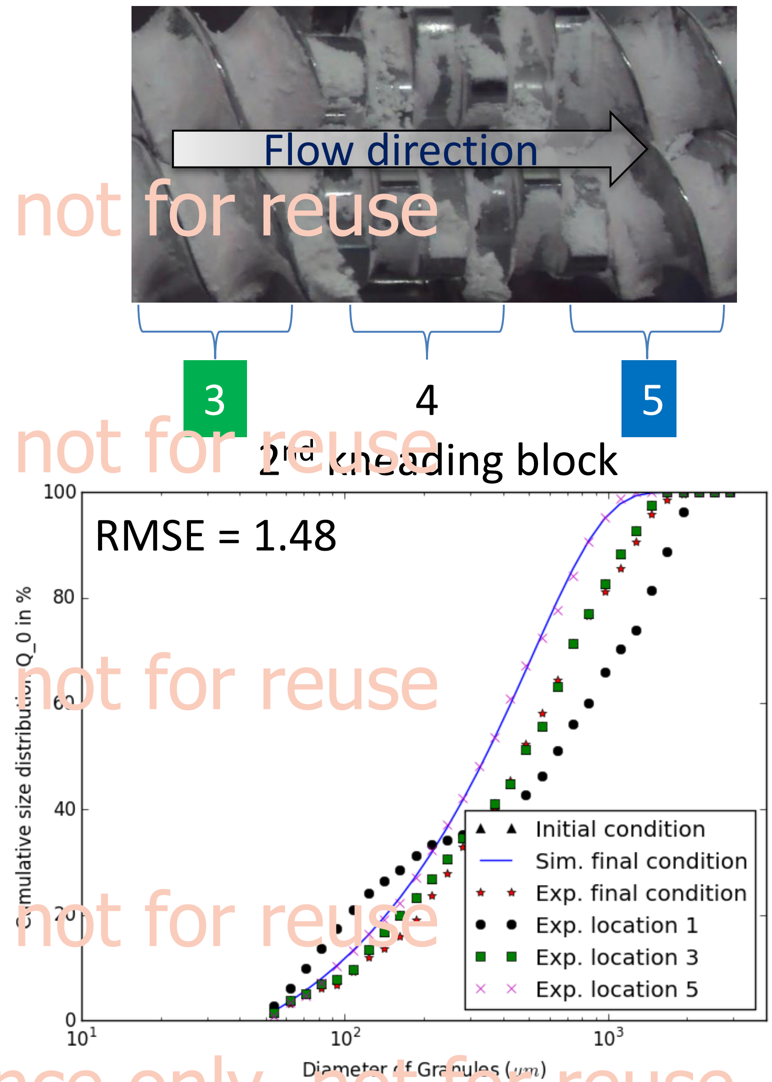
Start	1	2	3	4	5

PMSE	16.25	2.72	2.14



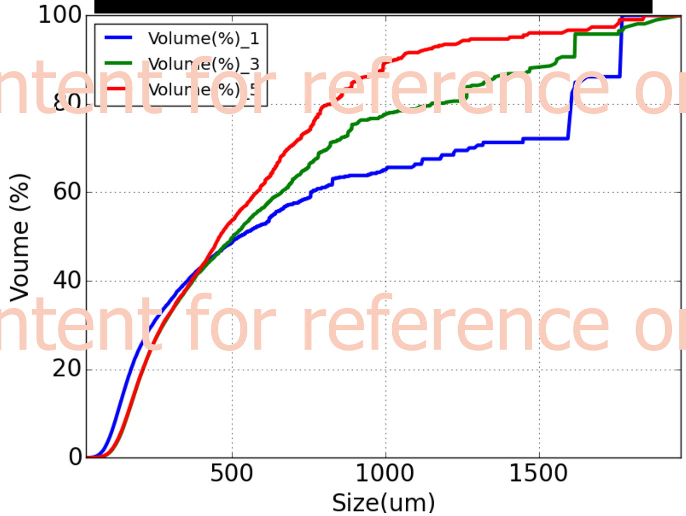
Including effect of granulator design on granule size distribution



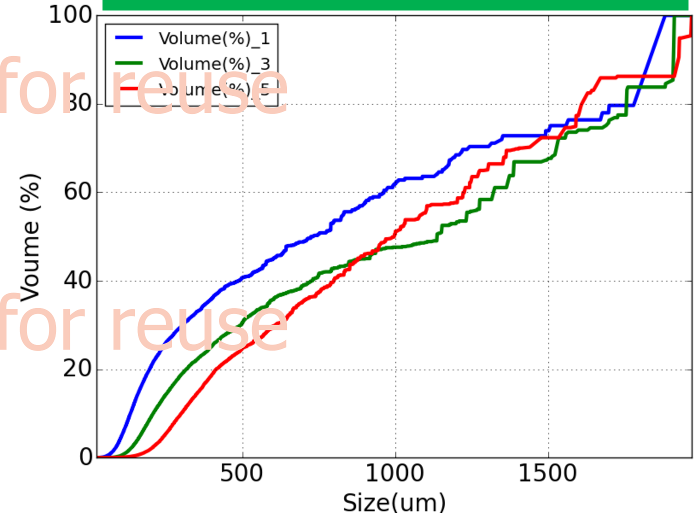


Throughput High | Liquid-solid ratio High | Screw speed Low

1 mixing zone

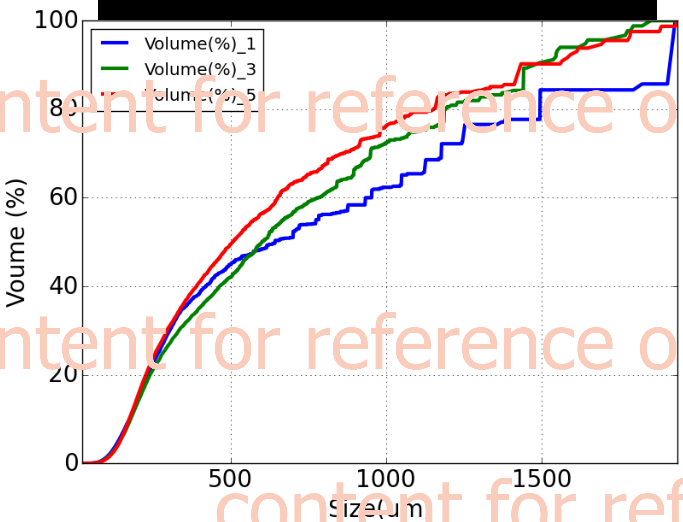


2 mixing zones

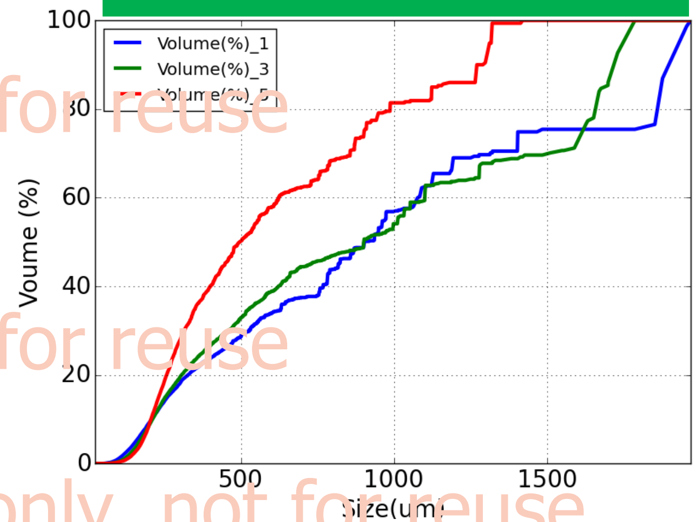


Throughput High | Liquid-solid ratio High | Screw speed High

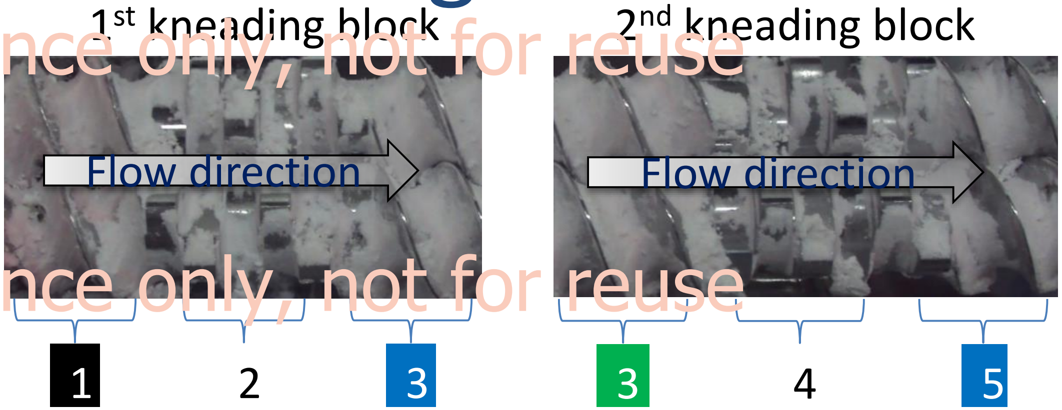
1 mixing zone



2 mixing zones



Investigating effect of screw speed and screw configuration



High throughput, high L/S

	Low Screw Speed				High Screw Speed			
	1 mixing zone		2 mixing zones		1 mixing zone		2 mixing zones	
Zone	1-3	3-5	1-3	3-5	1-3	3-5	1-3	3-5
RMSE	2.424	2.317	2.716	3.929	1.153	3.366	8.176	3.772
R^2	0.989	0.987	0.984	0.983	0.989	0.983	0.97	0.982

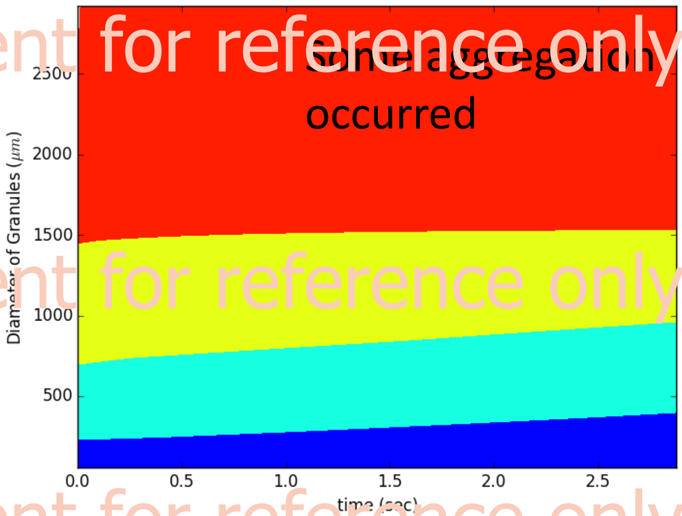
Throughput High
Liquid-solid ratio High
Screw speed Low
Location 1-3
Location 3-5
1 mixing zones
Overwetted lumps breaking
Almost nothing happened
Screw speed High
Overwetted lumps breaking
Shear supported further breakage
Diameter of Granules (μm)
time (sec)
Volume density (%)
0
25
50
75
100

Throughput **High** | Liquid-solid ratio **High**

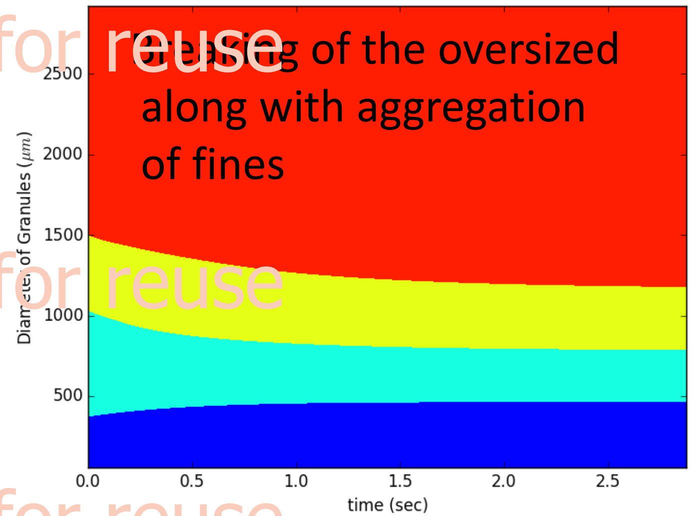
mixing zones

Screw speed **Low**

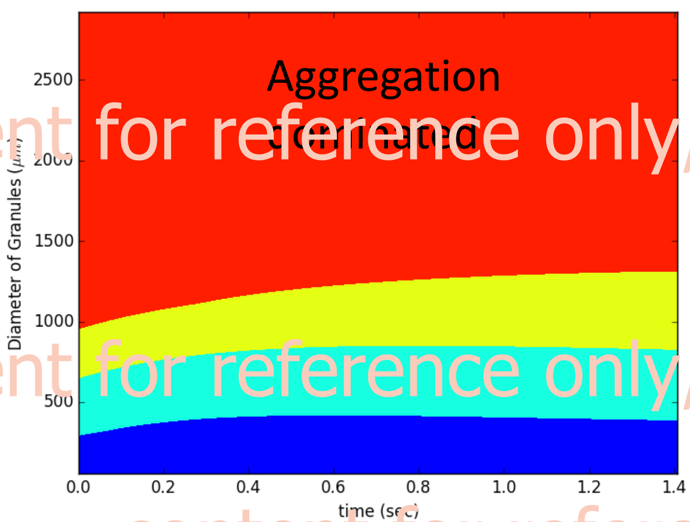
Location 1-3

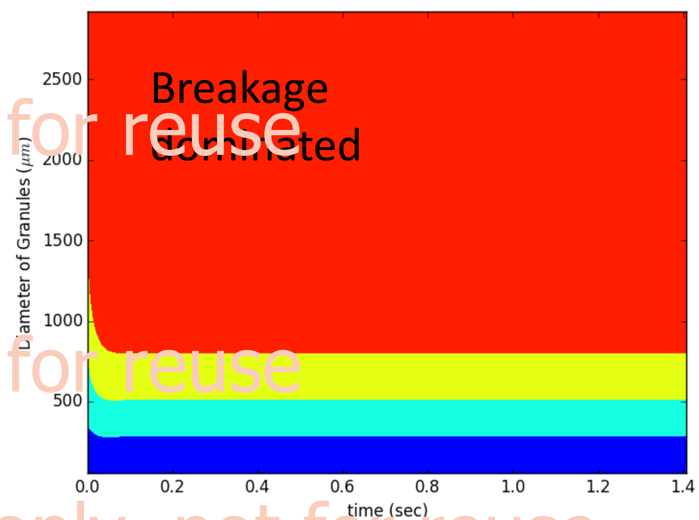


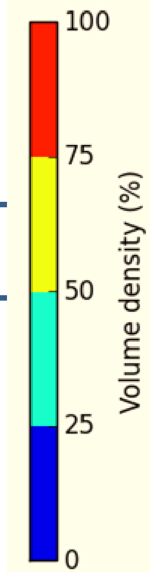
Location 3-5



Screw speed **High**







Conclusions

- Along with experimental study, an improved insight can be obtained by model-based analysis.
- Wetting kinetics requires a separate explanation in the twin-screw granulation modelling.
- Aggregation and breakage are most dominant phenomena in the twin-screw granulation.
- Particle population dynamics and screw geometry effect can be better understood by compartmental PBM, and can ultimately be used for predictive modelling of twin-screw granulation.

Acknowledgements

Ashish.Kumar@UGent.be