Feasibility/Collaboration Proposal:

Model Assisted Design of Granular Products

Model calibration as a Tool for Material Characterisation

Annual Meeting 2023

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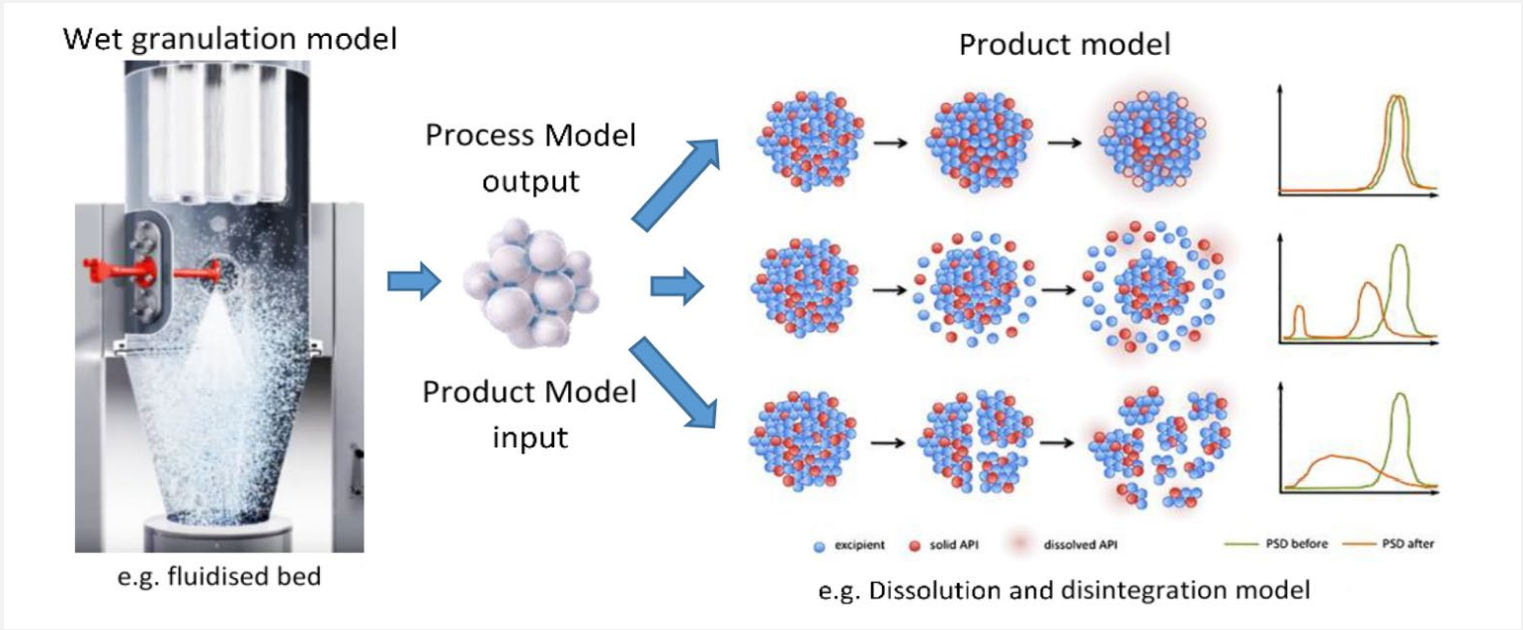
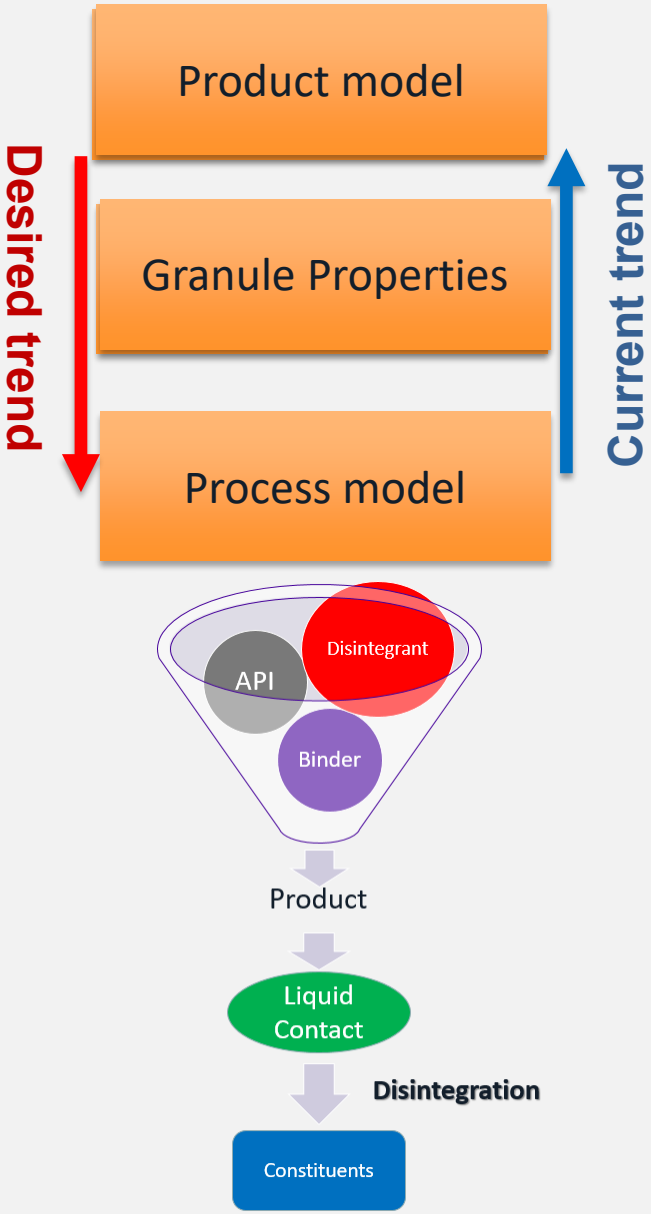
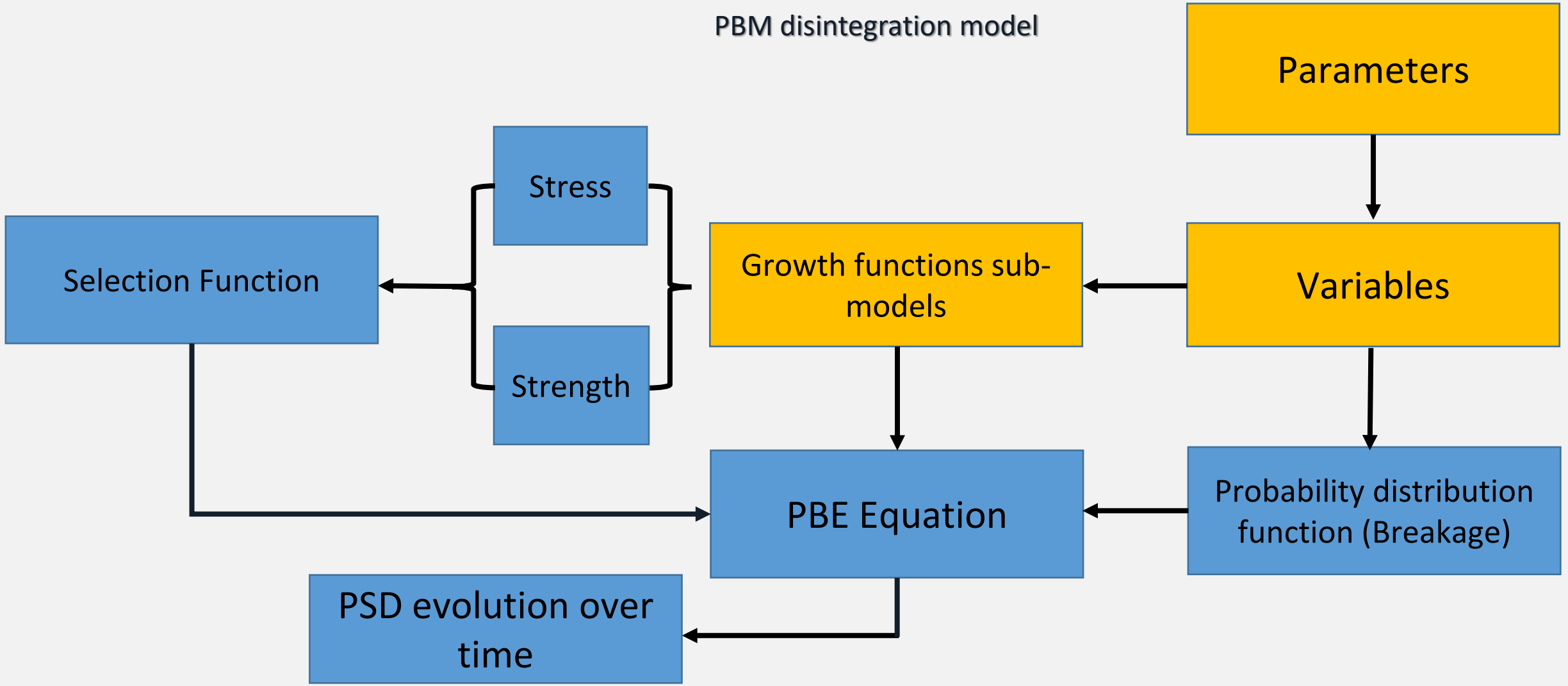
Product Performance: Disintegration





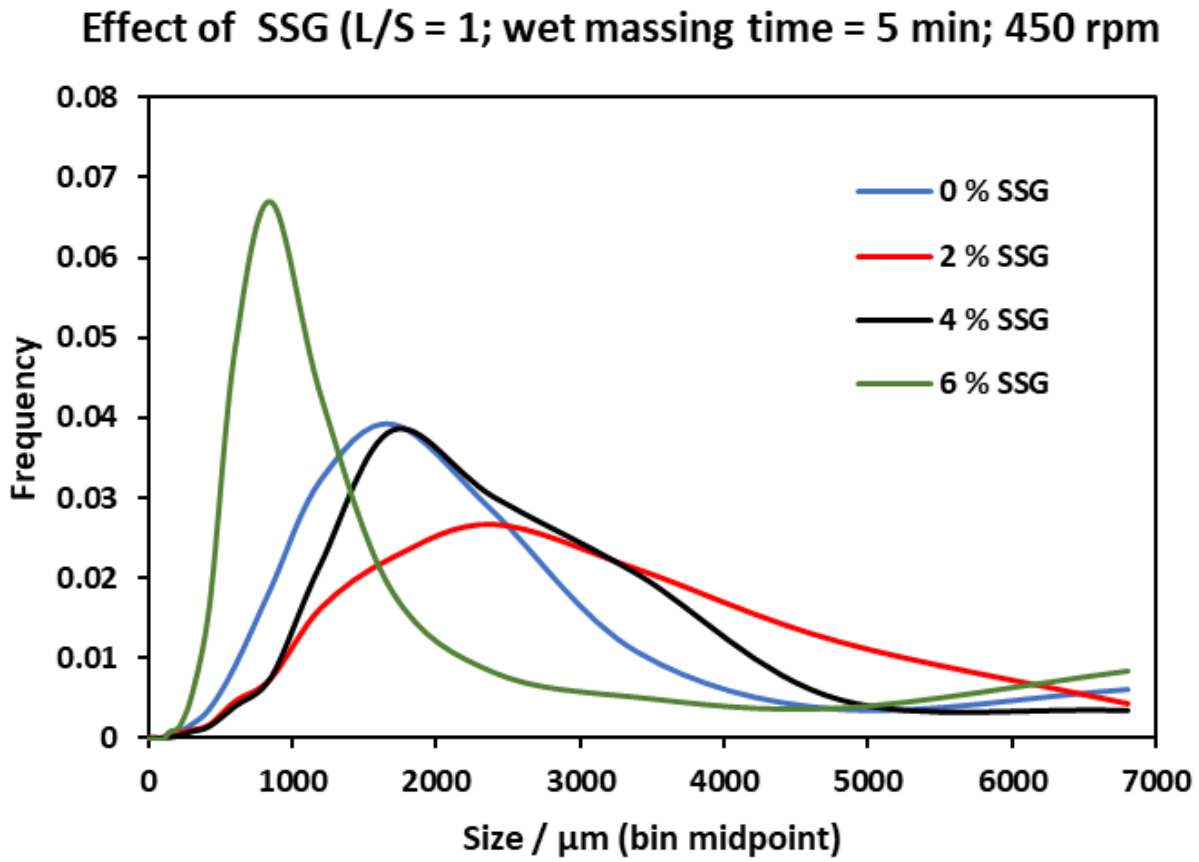
GlattGroup, Glatt Top-Spray granulation process by fluidized bed. (2013)
D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

Structure of Models in gPROMS



Experimental setup and Formulations

High-shear mixer granulator set up

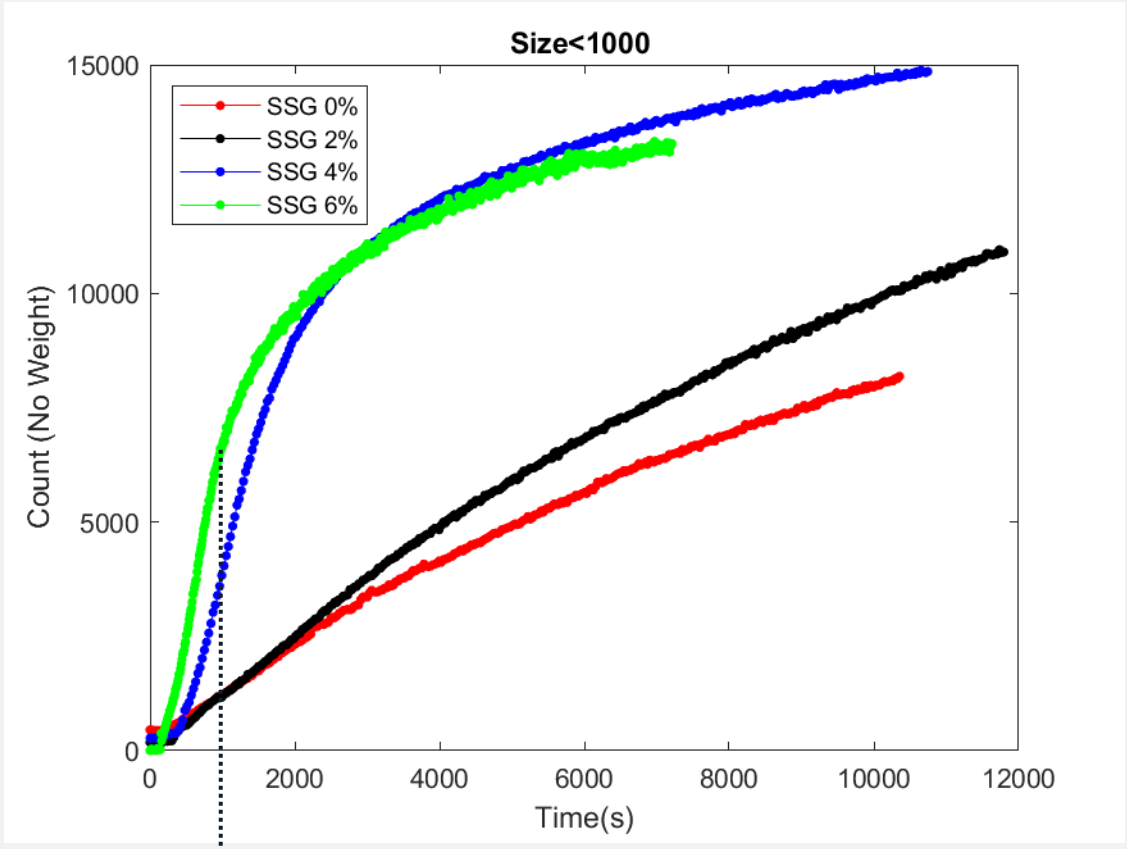


- Solid mass for the granulation = 500g
- Impeller speed = 450 rpm
- Binder addition time = 3 minutes
- The binder was injected to the mixer using a Peristaltic pump

Granule Characterisation - G400 FBRM Probe

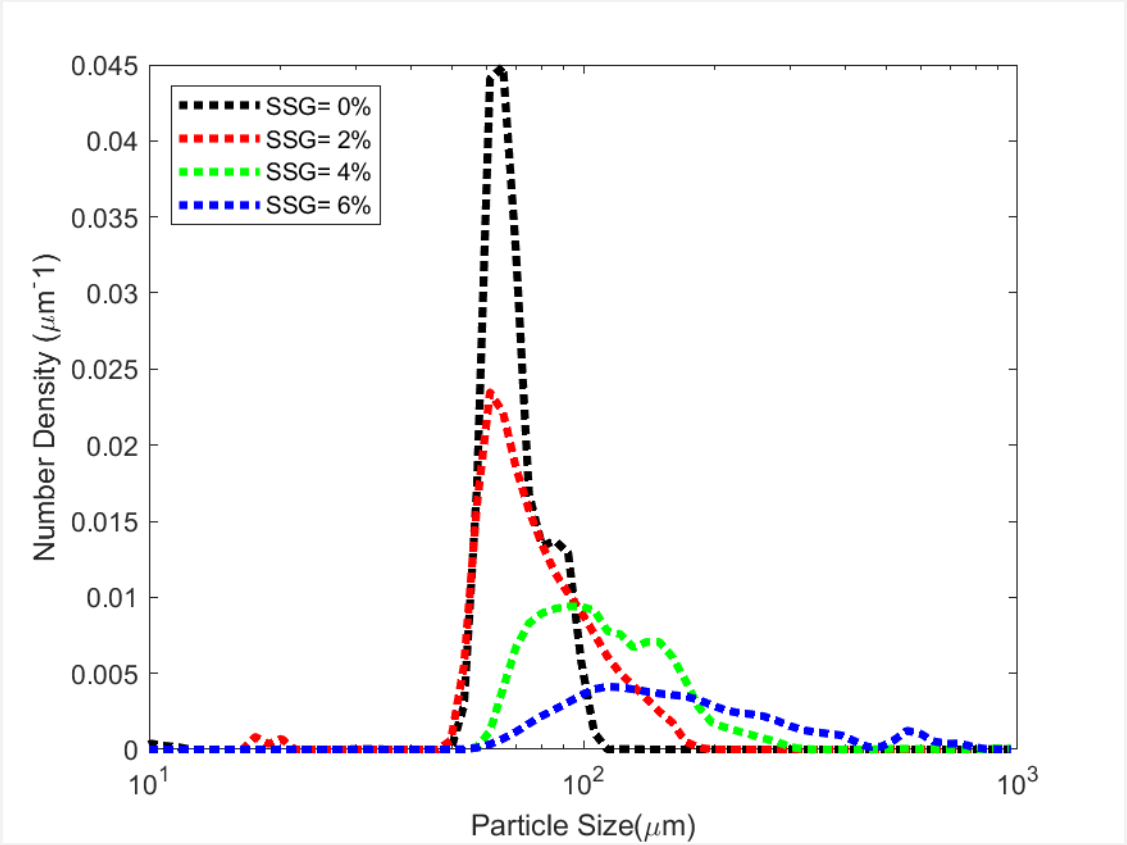
Effect of SSG Concentration (L/S = 1)

a) Particle count vs time



Time = 1000 sec

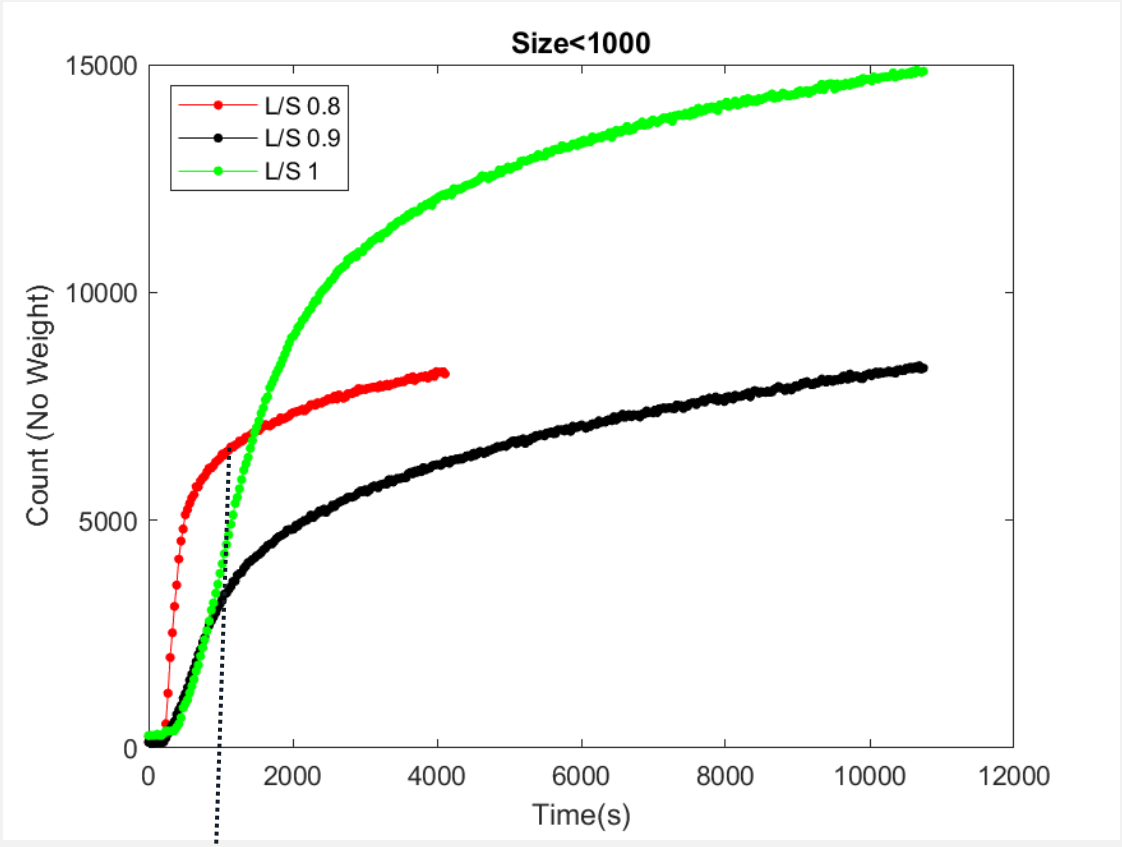
b) Number density vs PSD



Granule Characterisation - G400 FBRM Probe

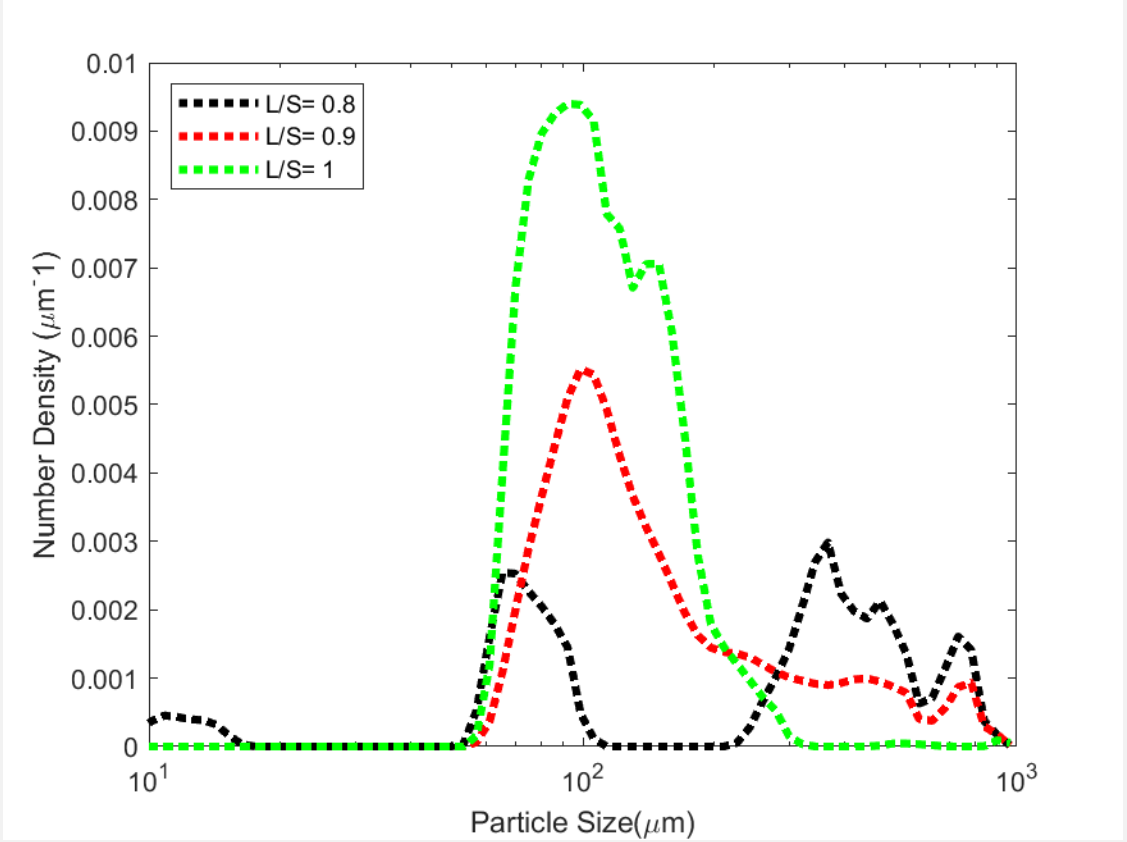
Effect of L/S (SSG Concentration = 4%)

a) Particle count vs time

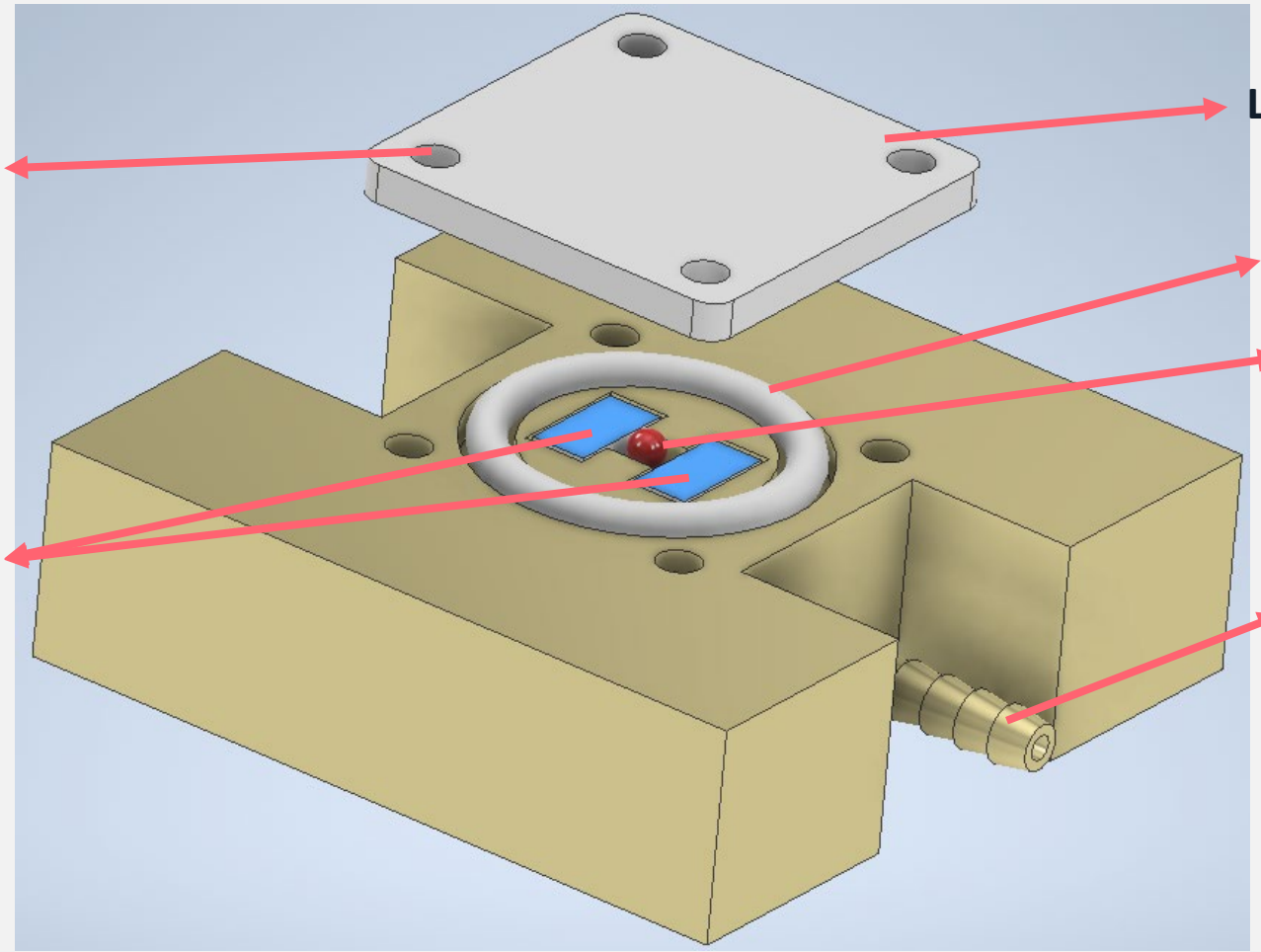


Time = 1000 sec

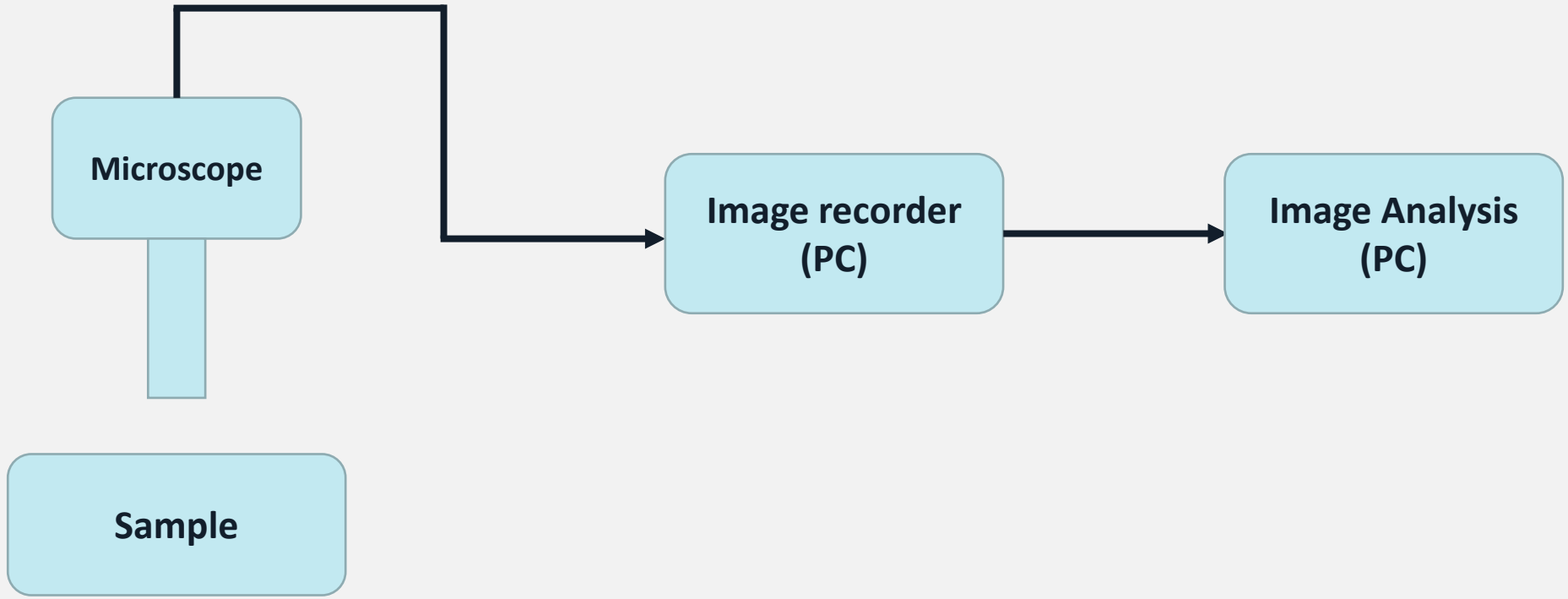
b) Number density vs PSD



Granule Swelling Characterisation – Flow Cell



Granule Swelling Characterisation – Flow Cell



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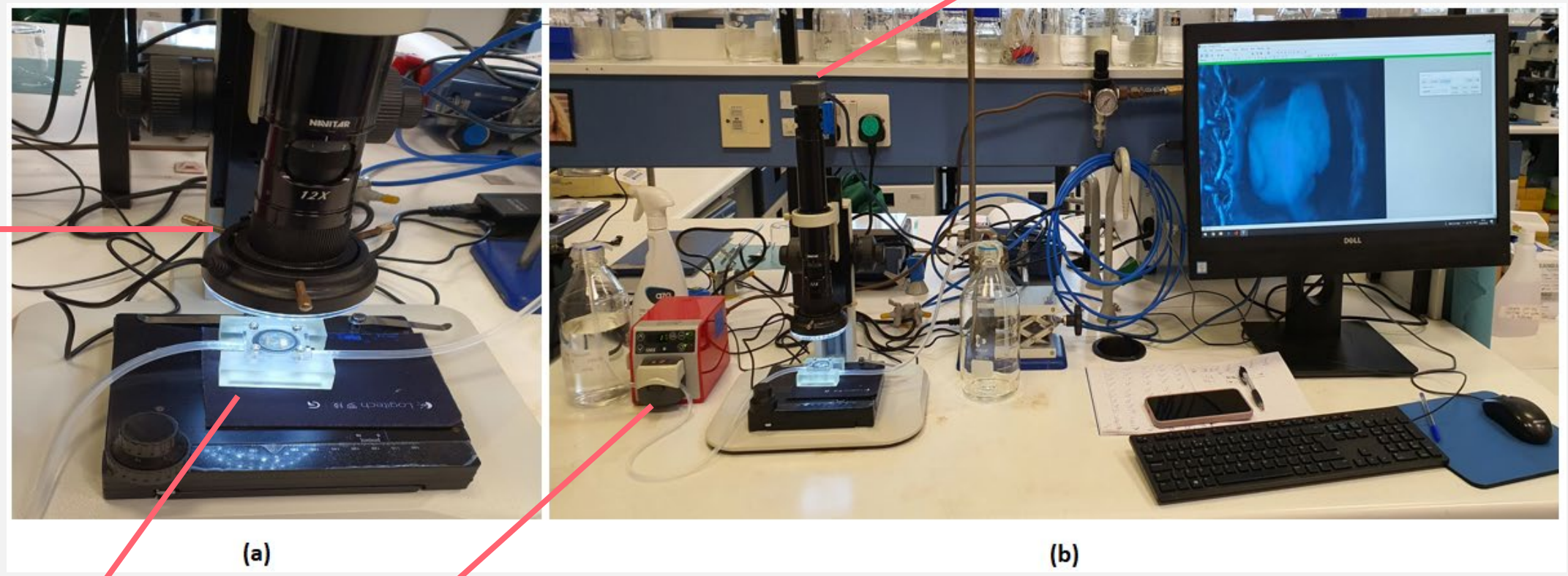
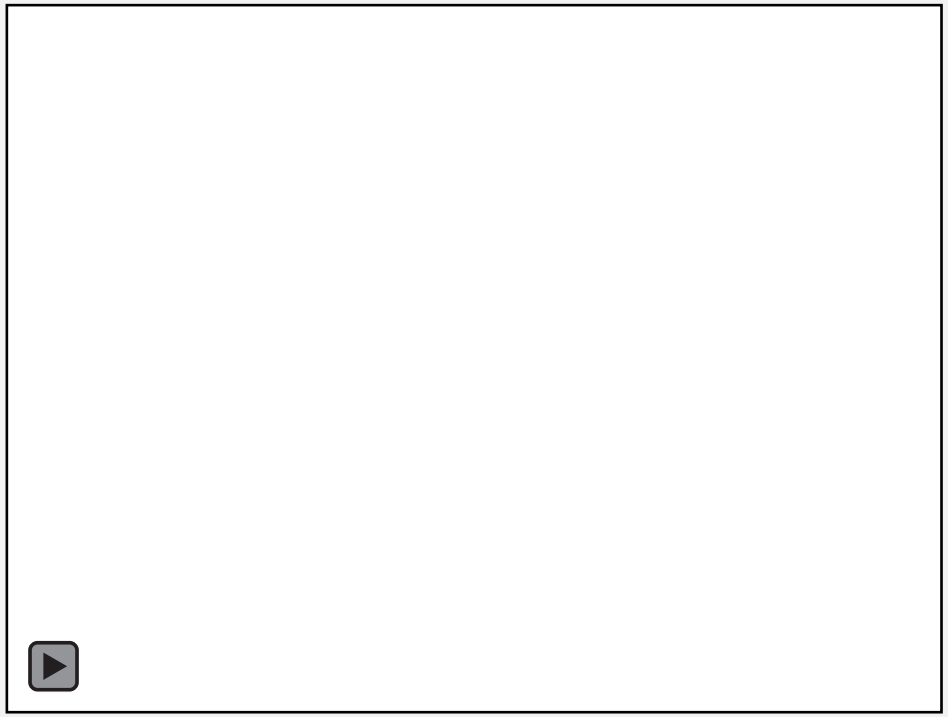
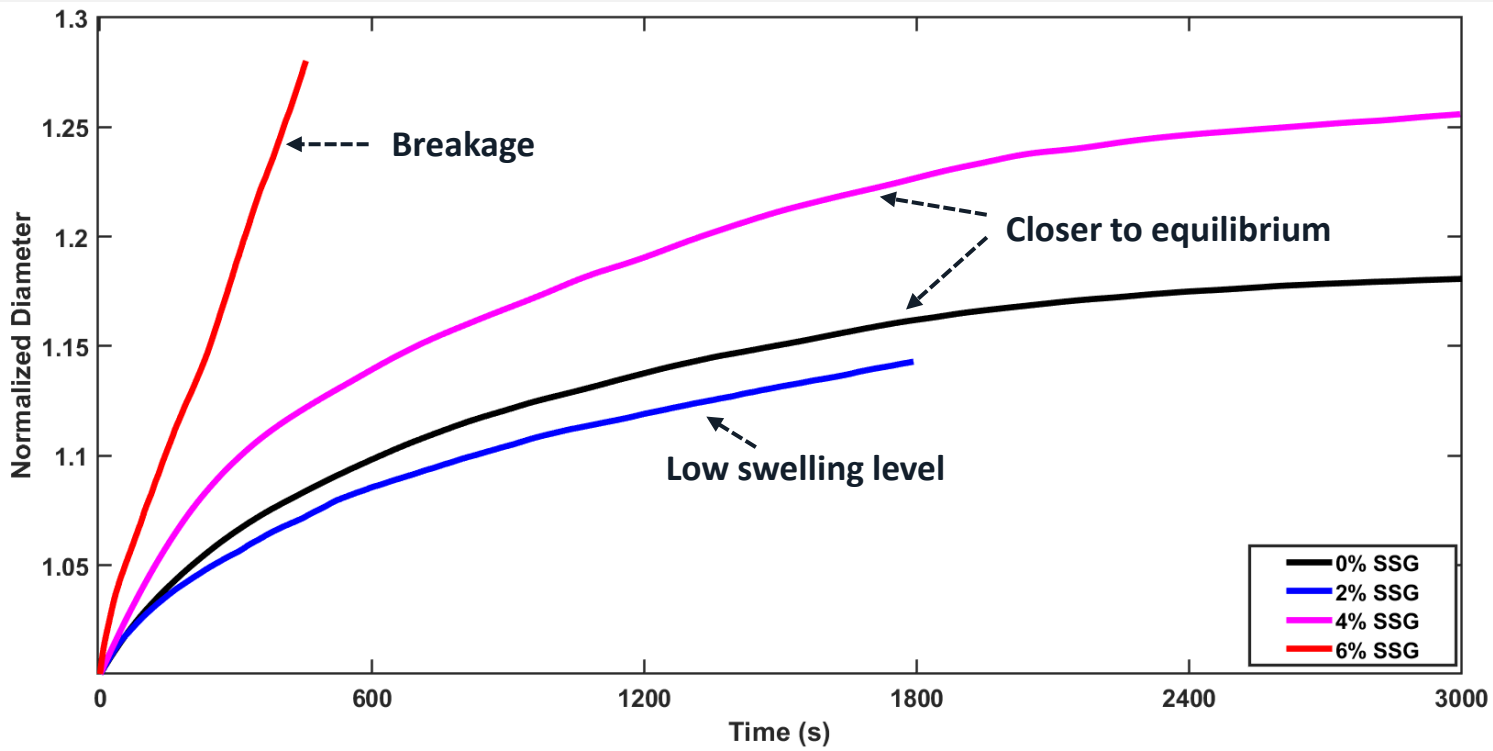
Granule Swelling Characterisation – Flow Cell



Granule Swelling Characterisation – Flow Cell

- With decrease in the SSG content (< 6%), level of swelling reduces, possibly due to plasticization impact of HPMC (12.5%)
- Decrease in absorption and swelling efficiency due to absorption of water in the high shear granulation process
- Significant difference in the swelling behavior between granules of SSG content of 4% and 6% is observed





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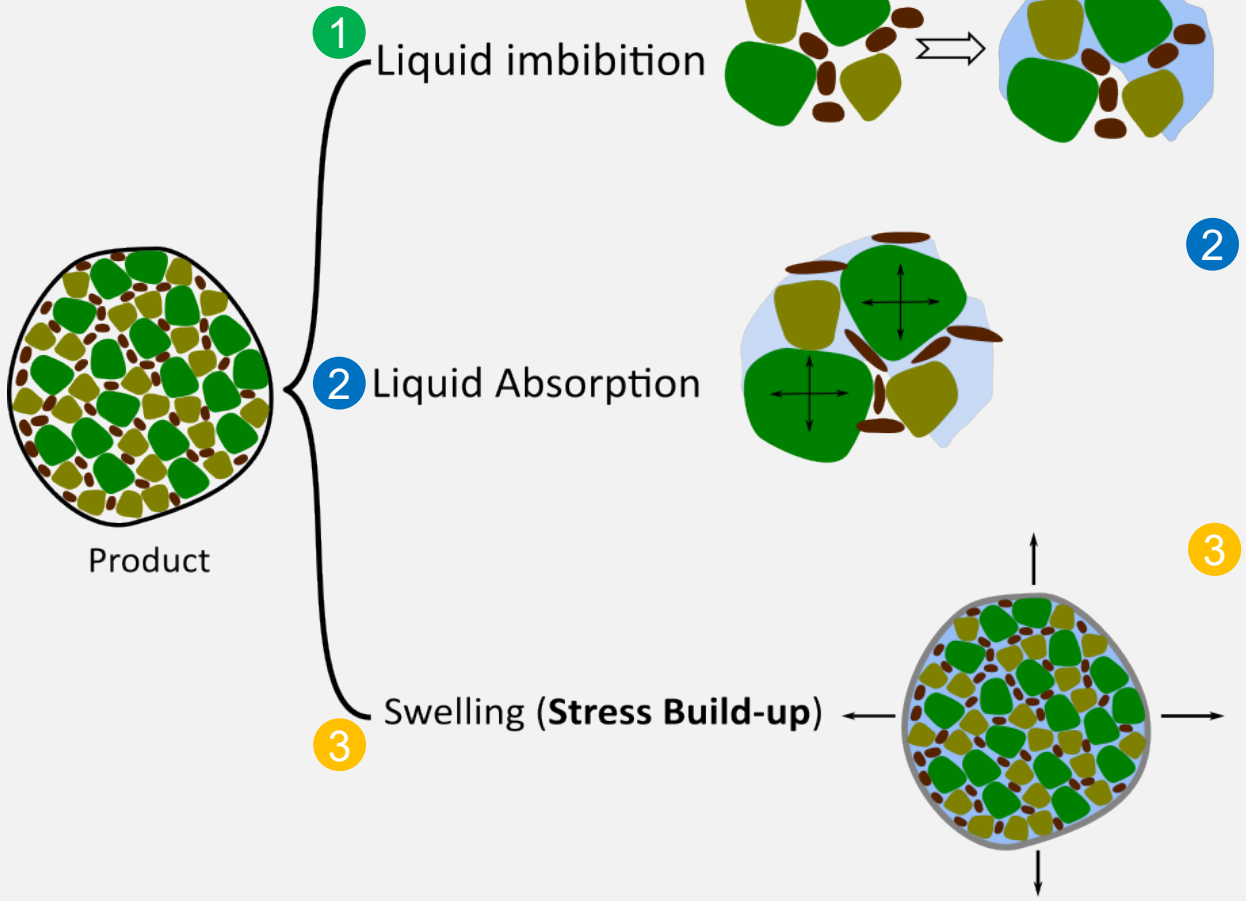
Mechanisms



1 Liquid penetration rate at granule's surface based on Darcy's law

$$\left(\frac{dV_l}{dt}\right)_{sin} = \overbrace{4\pi R^2 \frac{k_{per}}{\eta} \lim_{r\to R} \frac{\partial P_c}{\partial r}} - \underbrace{\sum n_{p,i} \frac{dV_{p,i}}{dt}}$$

$$V_l = \varepsilon S V$$

Total liquid absorbance by the solid phase

2

$$\left(\frac{dV_{s,i}}{dt}\right)_{sin} = n_{p,i} \frac{dV_{p,i}}{dt} \rightarrow$$ liquid absorbance by ith component in the solid phase

$$\sum V_{s,i} = (1-\varepsilon)V = \sum n_{p,i} V_{p,i} + V_{binder}$$

3

$$\left(\frac{d\varepsilon}{dt}\right)_{sin} = \sum x_{v,i} f_i(\varepsilon, Q_i) \frac{dQ_i}{dt}$$

Dependency of porosity on mass absorption ratios of solid phase

$$f_i(\varepsilon, Q_i) = \Gamma_i \frac{(\varepsilon_{max}-\varepsilon)(\varepsilon-\varepsilon_{min})}{Q_i}$$

$$Q_i = \frac{\rho_l}{\rho_{s,i}} \frac{V_{p,i}}{V_{p.i}(0)} - \frac{\rho_l}{\rho_{s,i}} + 1$$

t: time, R: granule radius, ε: porosity, S: saturation, V: volume, V_l: volume of liquid in granule, k_{per}: permeability, P_c: capillary pressure, $n_{p,i}$: number of ith component in the solid
$V_{p,i}$: volume of a single ith component particle, $V_{s,i}$: volume of ith component in the granule, V_{binder}: volume of the binder in the granule, $x_{v,i}$: volume fraction of ith component in the solid
Q_i: mass absorption of ith component, Γ_i: porosity factor of ith component, ε_{max}&ε_{min}: minimum and maximum porosity, $\rho_{s,i}$: density of ith component
ρ_l: fluid density ,$V_{p.i}(0)$: initial volume of a single ith component particle

Model Parameters

Measured parameters:

Process parameters:

Estimated parameters:

Model	Variable	Method to Quantify	Method	Value
Single Granule	Initial porosity	Characterised	GeoPyc/Mercury Prosimetry	Changing
	Initial radius(mm)	Characterised	Flow cell measurement	Changing
	SSG mass component	Process	-	Changing
	Binder to Solid ratio	Process	-	0.125
	Initial radius of SSG particles(μm)	Characterised	Malvern mastersizer	50 μm
	Initial radius of MCC particles(μm)	Characterised	Malvern mastersizer	85 μm
	Porosity factor (Γ)	Estimated	Least square	Changing
	Diffusivity	Estimated	Least square	Changing
	Maximum absorption ratio	Estimated	Least square	Changing
Population Balance Model	Shape related factor	Estimate	FBRM	-
	Number of particles produced	Estimate	FBRM	-
	Neck strength of the binder	Estimate	FBRM	-
	Bulk modulus at zero porosity	Estimate	FBRM	-

GSA for single granule swelling model

Process Parameters

Parameter \ Response	Porosity		Normalized diameter	
	First Effect	Total Effect	First Effect	Total Effect
Initial porosity (ε_0)	0.30	0.48	0.15	0.31
Initial diameter of superdisintegrant in μm ($D_{sup,0}$)	0.27	0.57	0.36	0.73
Initial diameter of excipient in μm ($D_{exp,0}$)	0.07	0.26	0.09	0.32
SSG mass percentage ($x_{m,sup}$)	0.02	0.1	0.05	0.12
Liquid to solid ratio	0	0	0	0

Porosity Related Parameters

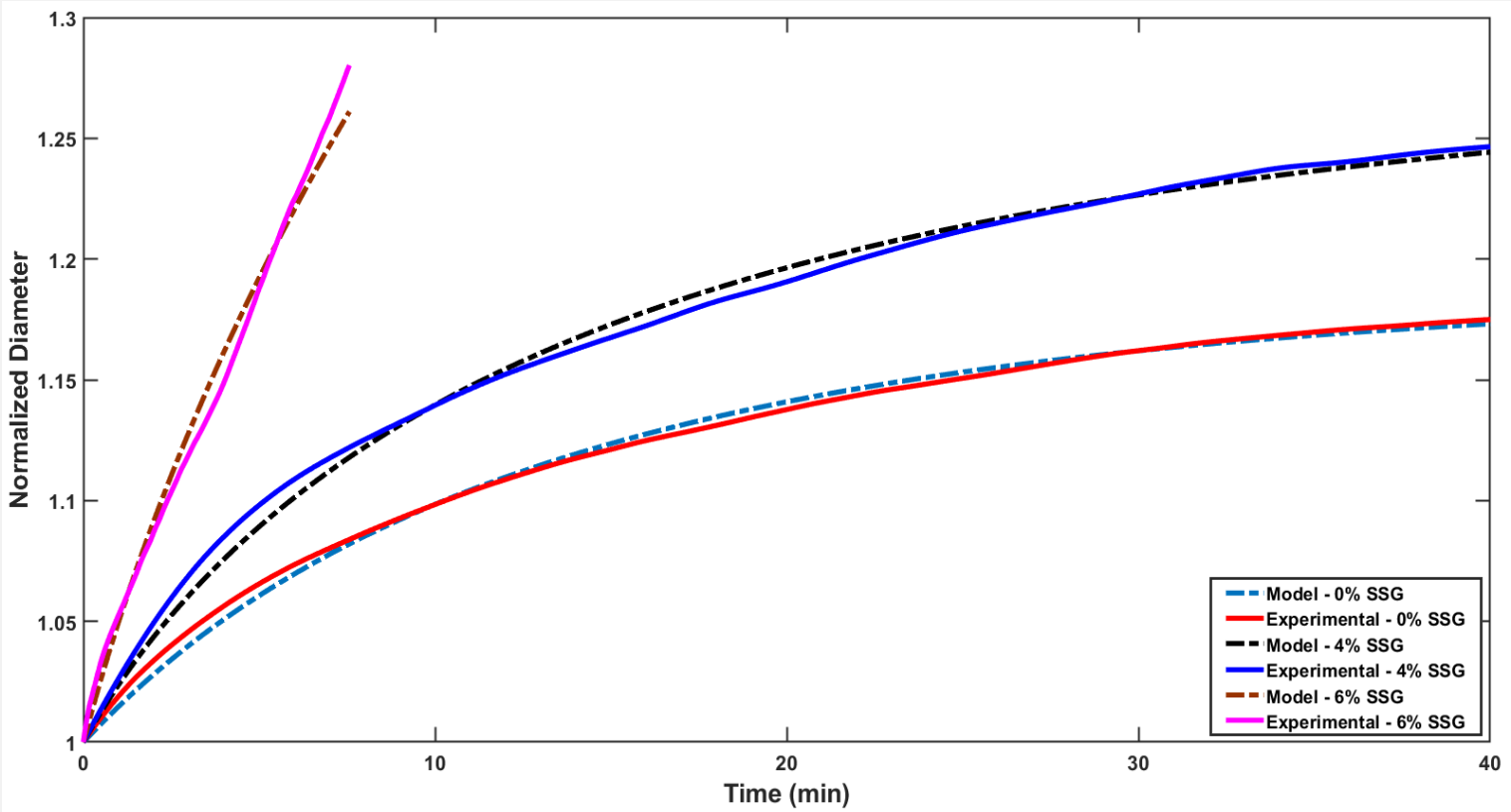
Parameter \ Response	Porosity		Normalized diameter		Mass absorption ratio	
	First Effect	Total Effect	First Effect	Total Effect	First Effect	Total Effect
Superdisintegtant's porosity factor (Γ_{sup})	0.71	0.80	0.67	0.74	0	0
Diffusivity of the disintegrant (D_{sup})	0.06	0.100	0.08	0.11	0.24	0.30
Maximum absorption ratio of the disintegrant (Q_{max}^{sup})	0.13	0.20	0.17	0.23	0.70	0.76

High : Medium : Low :

Parameter Estimation and Validation

- The method to obtain the parameters is least square method

Parameters / Constituent	$D\ (\frac{\mu m^2}{s})$	$Q_{max}\ (\frac{g}{g})$	Γ
MCC	0.35	1.5	0.2
SSG (%4)	1.764	9.292	2.35
SSG (%6)	2.336	9. 891	5.71



- Estimated diffusivity (D) & maximum absorption ratio (Q_{max}) is significantly lower than the literature values, (plasticization effect & pre-disintegration absorption)
- Increase in diffusivity of SSG by increasing SSG content
- Due to low swelling, the model is not able to predict the behavior of granules with 2% SSG.

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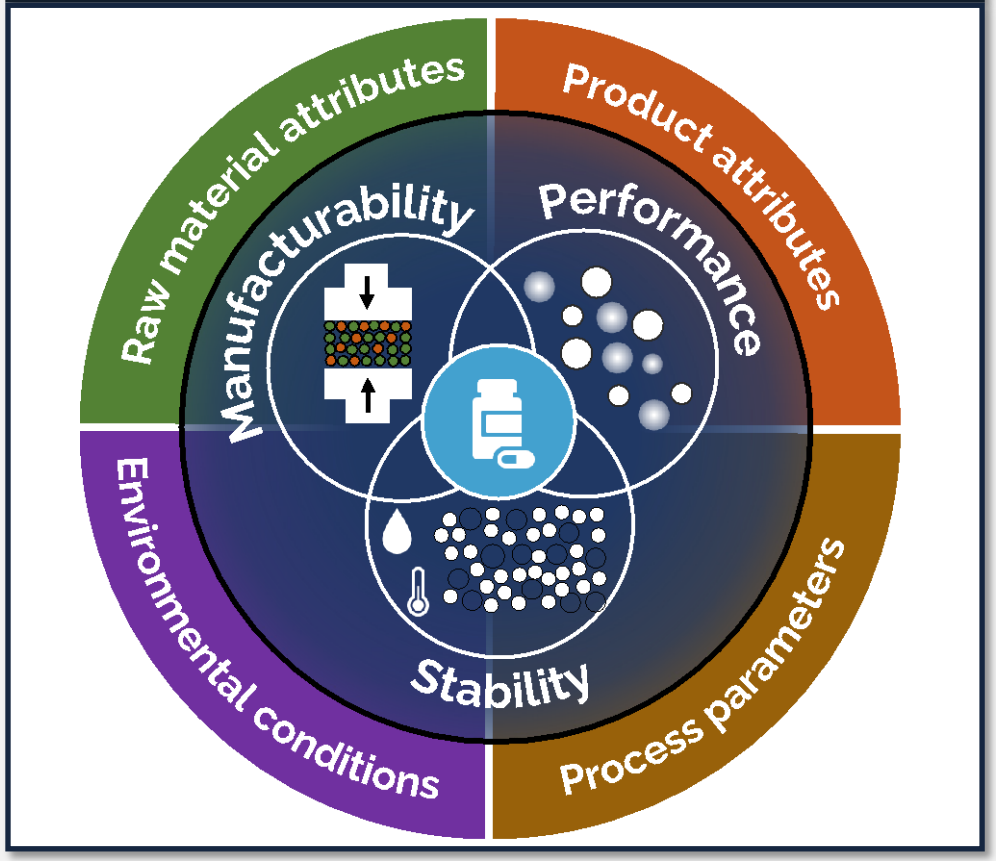
Agile & Flexible Development & Manufacturing

Fundamental Understanding of Relationships



Innovative manufacturing & sensor technologies

Enabler

Enabler

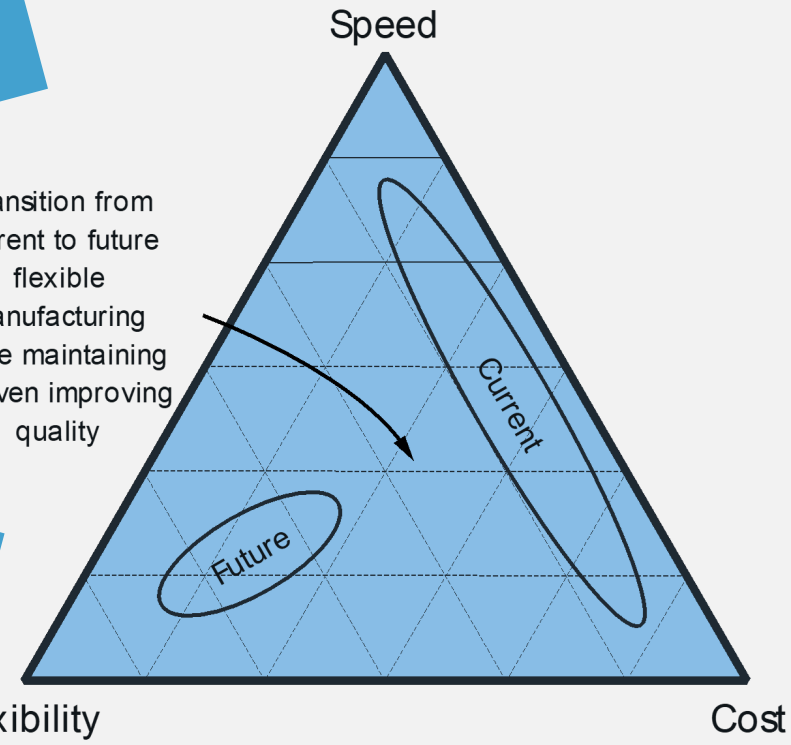
Digital transformation

Enabler

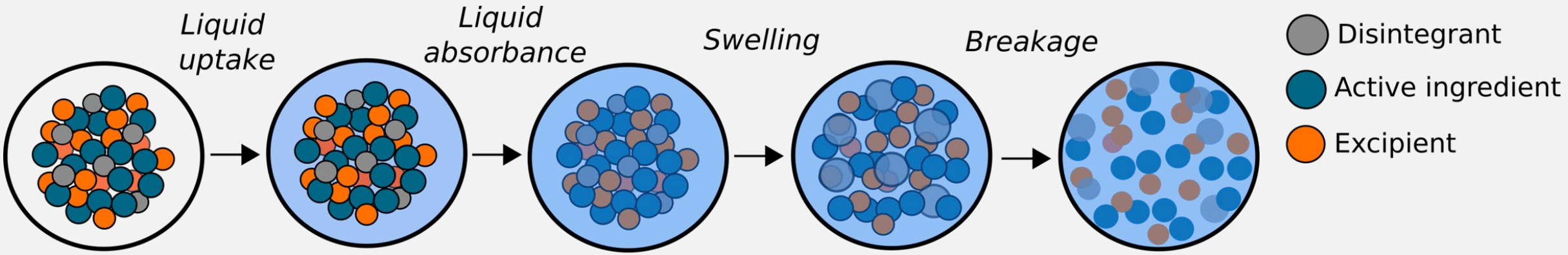
Agile & Flexible Development & Manufacturing

to reduce speed & cost and increase efficiency of how medicines are developed and manufactured to meet changing demands.

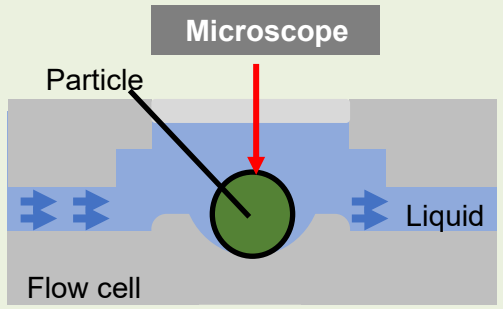
Transition from current to future flexible manufacturing while maintaining or even improving quality



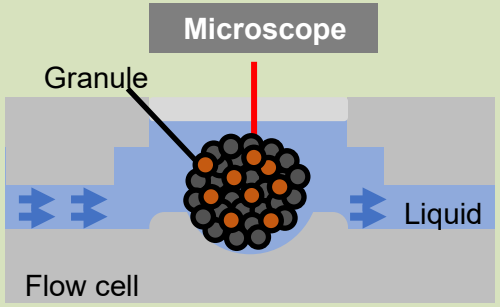
Experimental Investigation



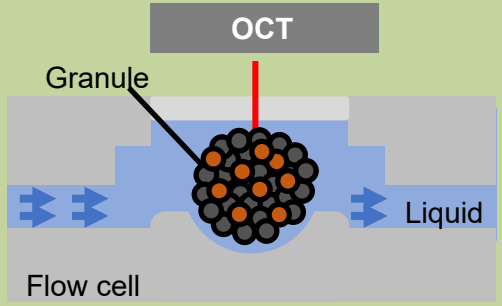
Investigating swelling of single particles particles



Investigating liquid swelling of granules



Investigating liquid liquid uptake and swelling of granules



OCT: optical coherence tomography

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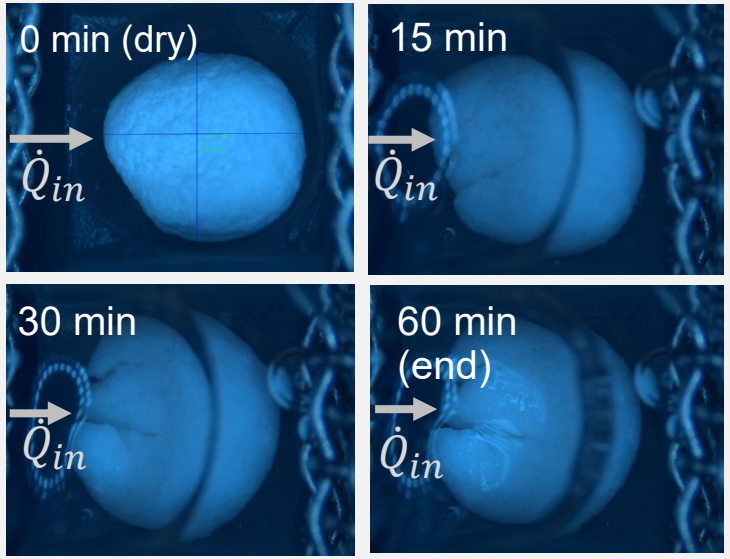
Granule Swelling Characterisation

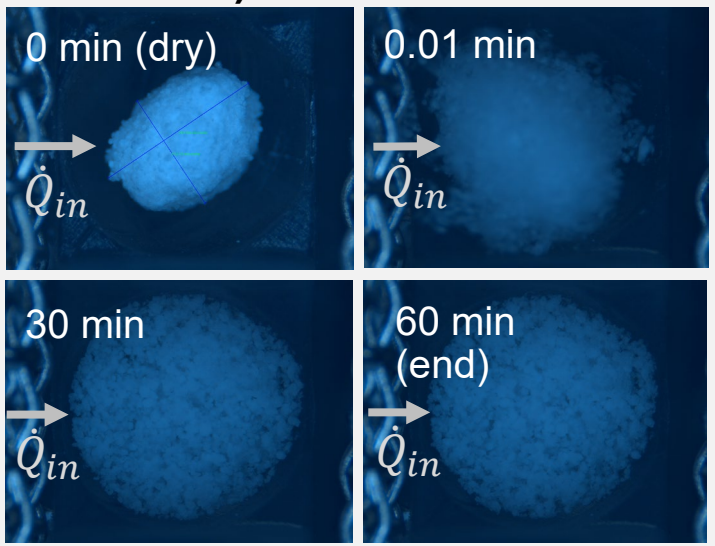
a) MCC



a

- Surface erosion and slow crack propagation observed over time
- No excessiave granule movement, challenges with bubble formation

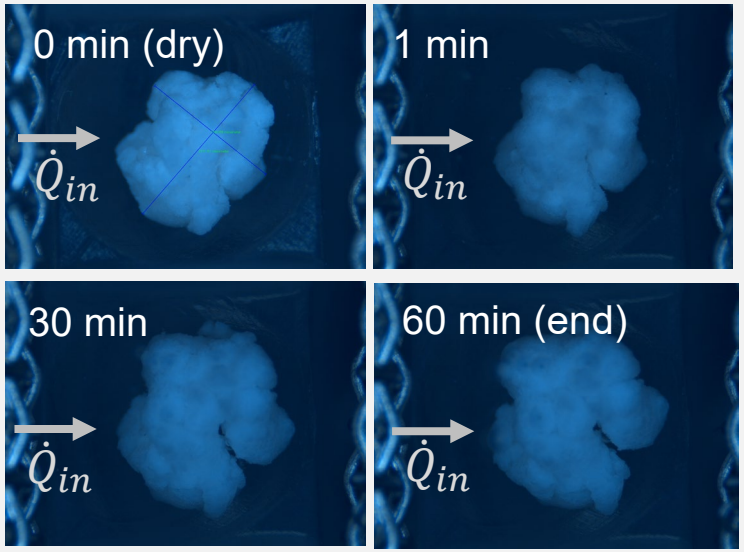
b) MCC + SSG



b

- Adding superdisintegrant caused sudden expansion and swelling over time
- Slow loosening of microstructure and strain recovery observed

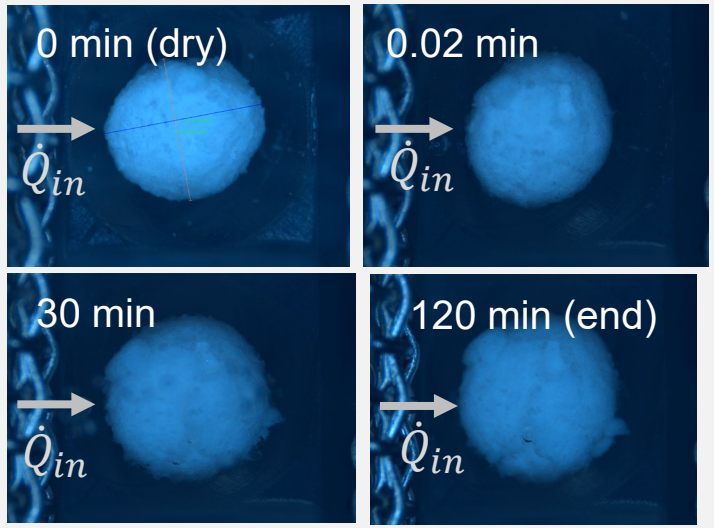
c) Aspirin + MCC



c

- Aspirin added to MCC (no superdisintegrant)
- Erosion and crack propagation observed with slow swelling

d) Aspirin + MCC + SSG

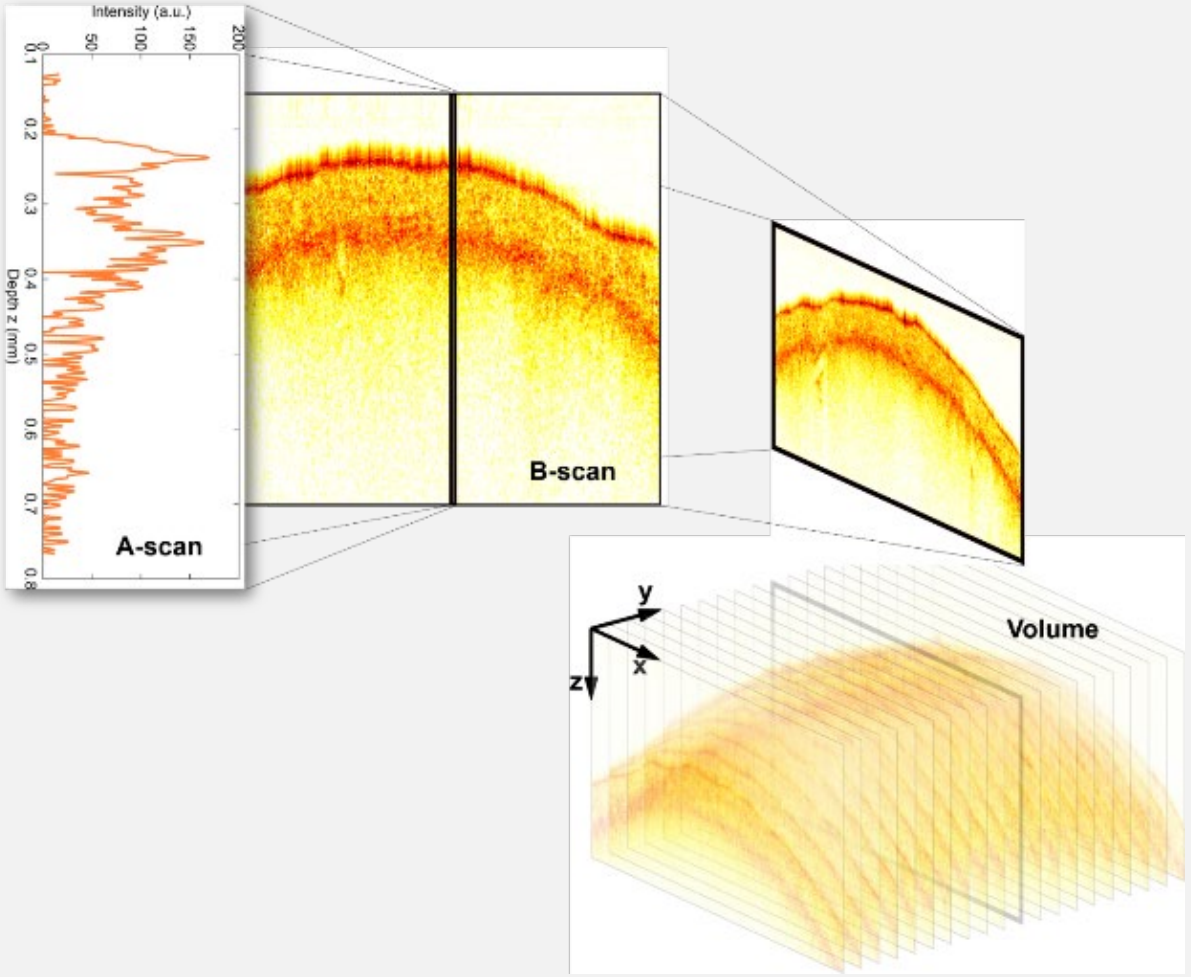


d

- Aspirin added to MCC (no superdisintegrant)
- Erosion and crack propagation observed with slow swelling

Optical Coherence Tomography for Material Characterisation

- Optical coherence tomography is a non-destructive, contactless and fast method to resolve sub-surface structures.
- It generates 1D, 2D and 3D depth profiles within seconds.
- Acquisition rate of 1D profiles can be as high as 230 kHz (→ 230 cross-sectional images per second)



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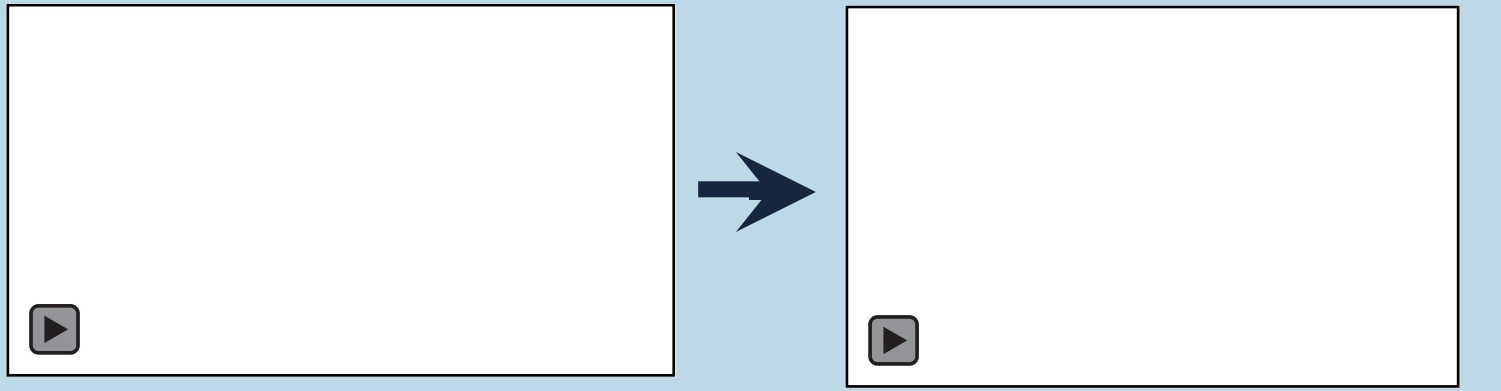
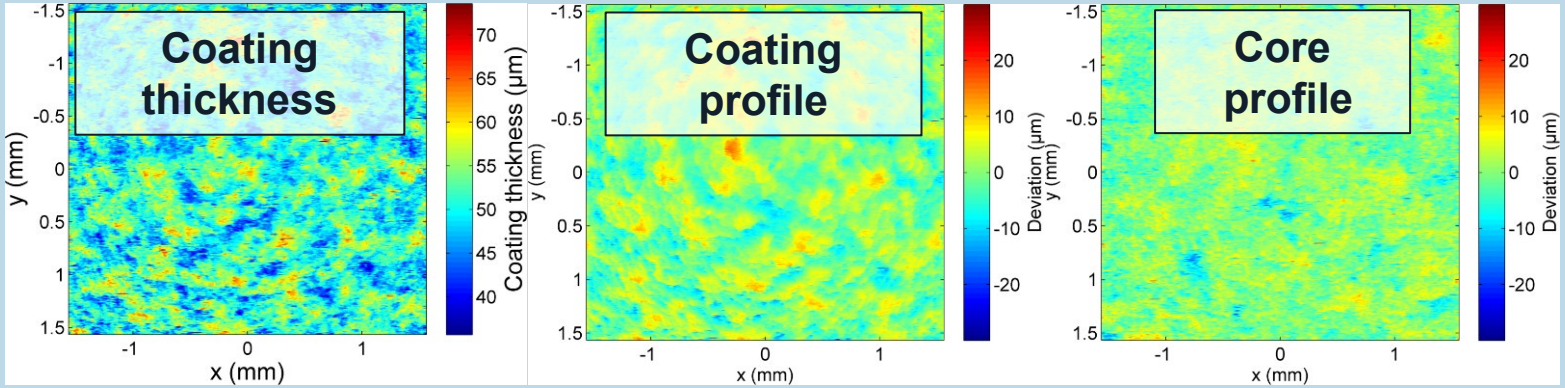
Selected Application of OCT Tablet Coating Thickness Characterisation

Tablet Coating Characterisation





Pellet Coating Characterisation

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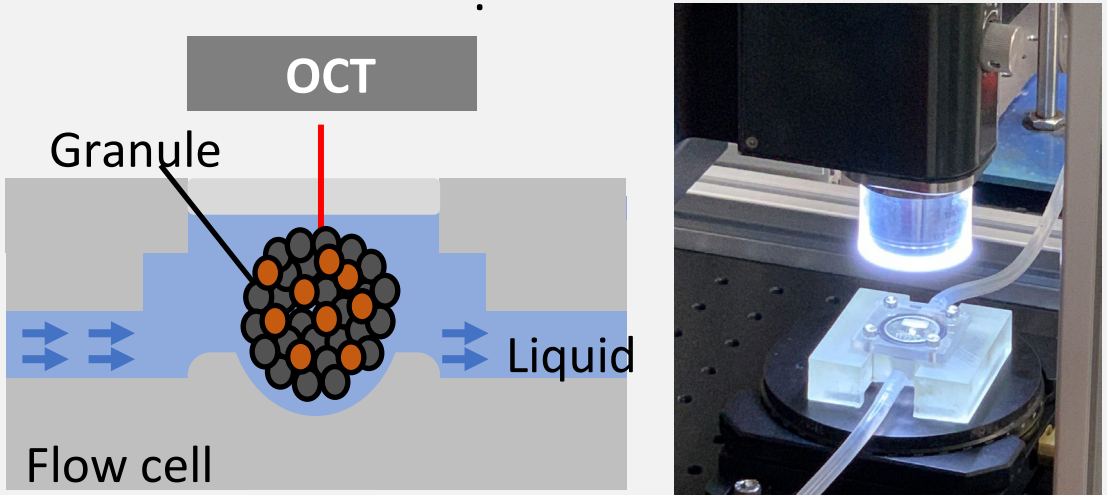
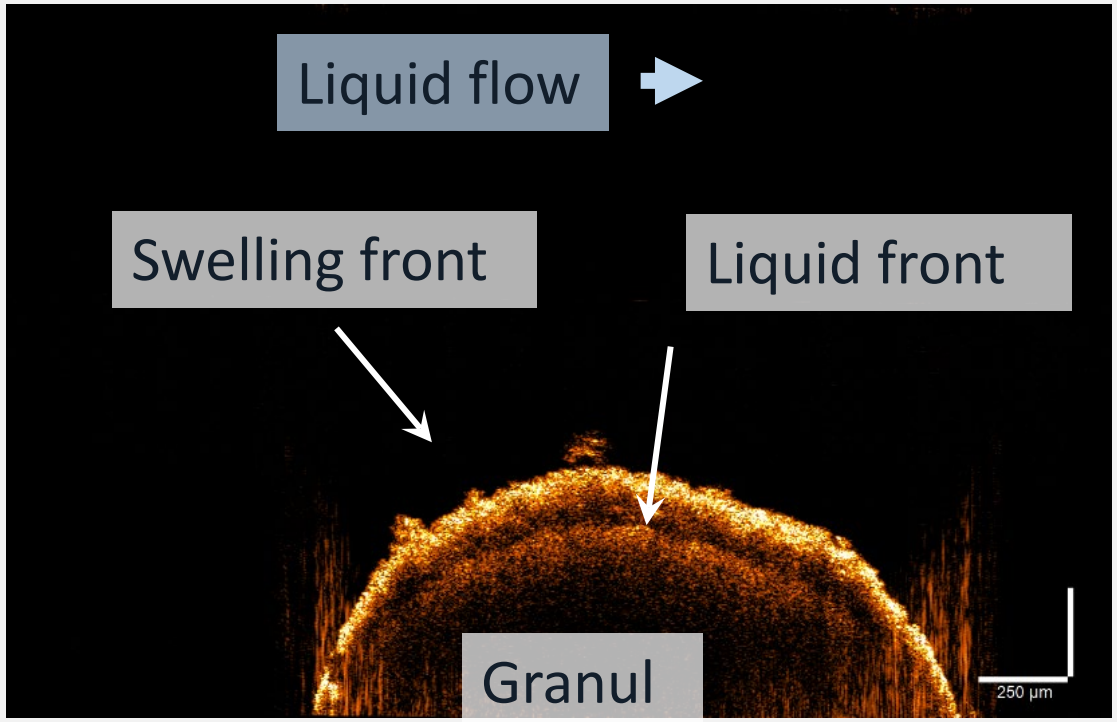
Disintegration Analysis using Optical Coherence Tomography





OCT conditions:

- Lens: 18 mm focal length
- Burst of images collected upon liquid addition and granule events
- Only 2D images analysed

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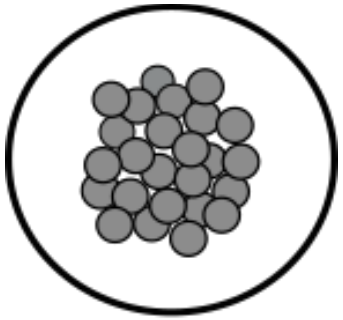
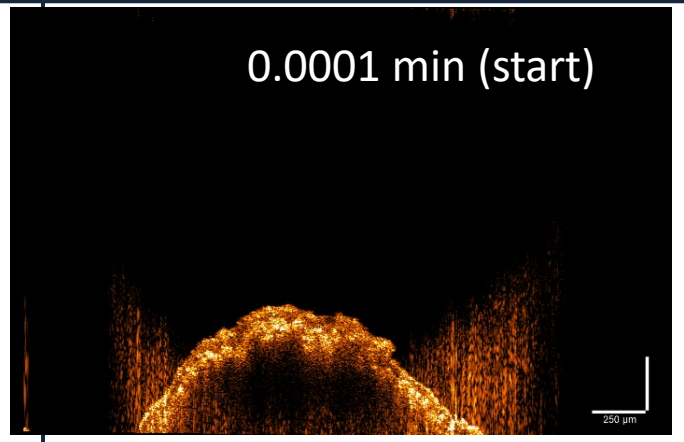
Disintegration Analysis Microcrystalline Cellulose

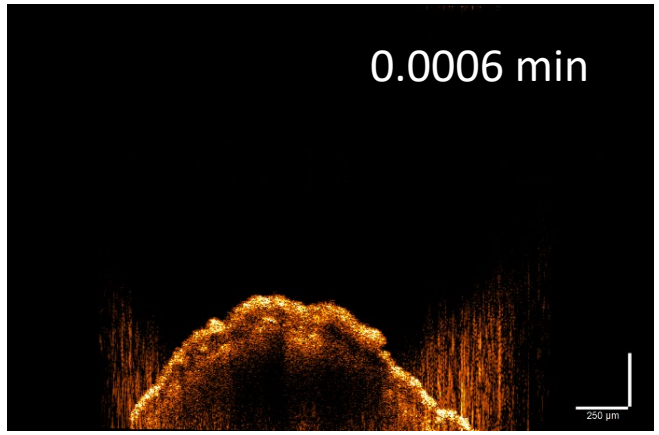
Product Structure	Surface Imaging

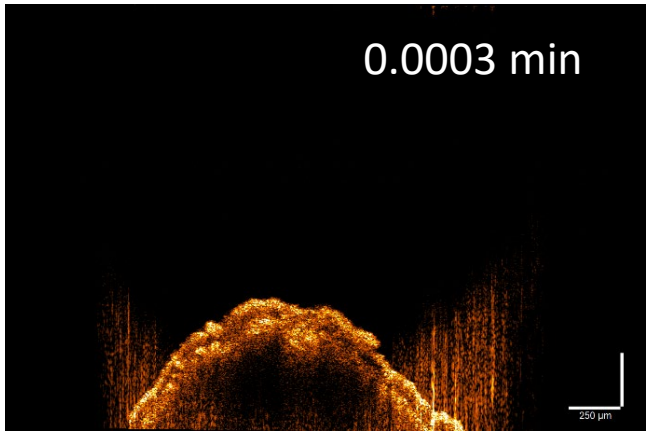


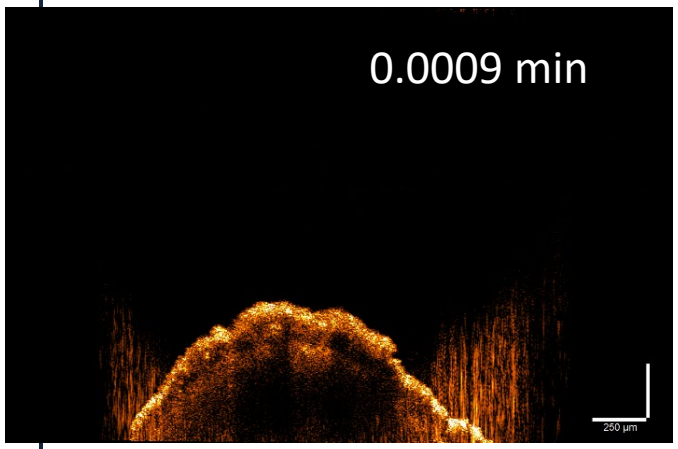
D_p (*mm*) = 2.3

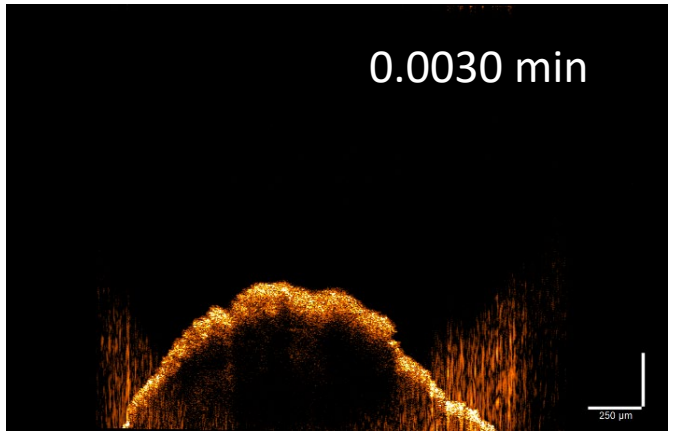
ε (%) = 47 MCC

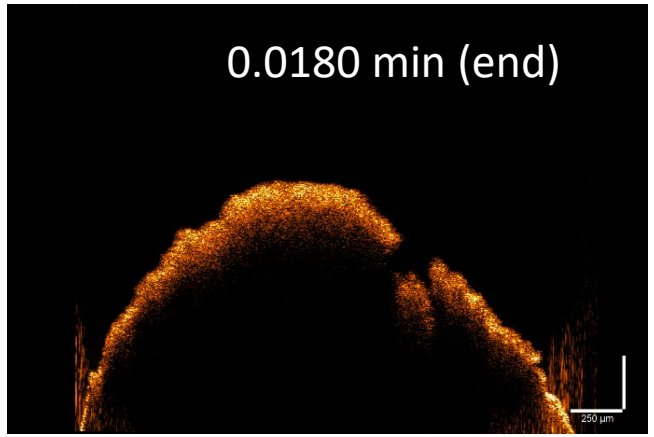




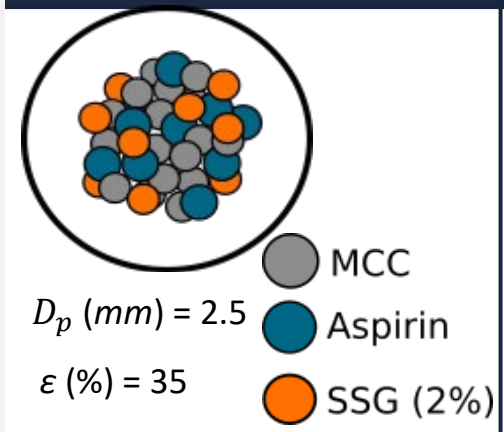
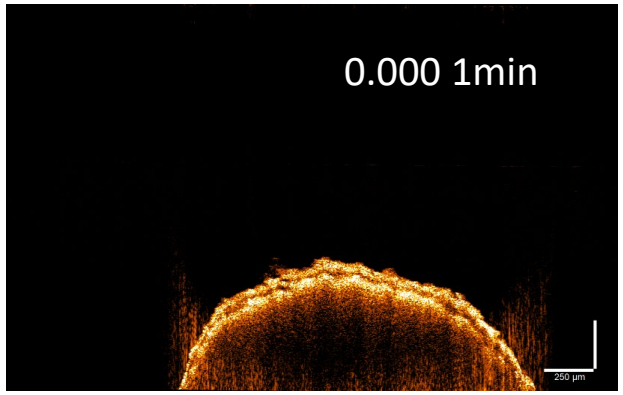
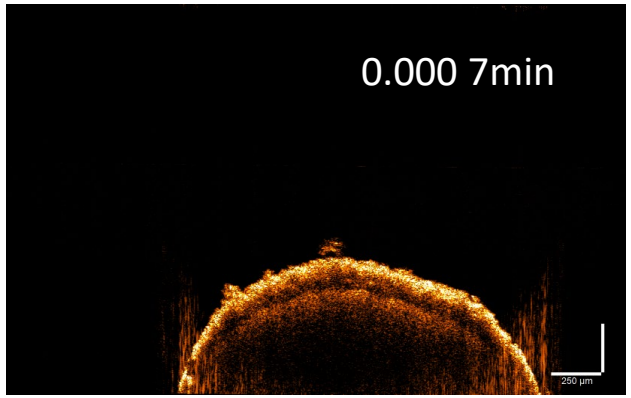
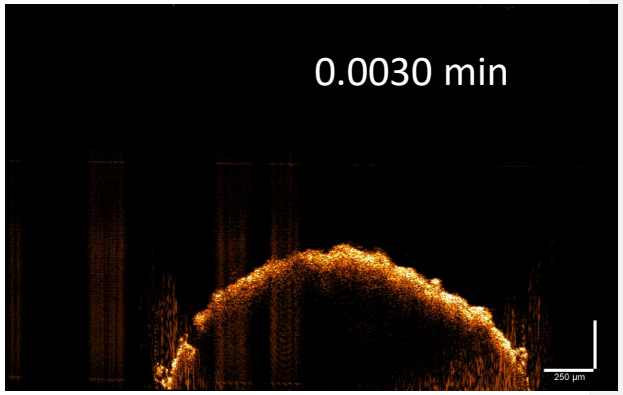
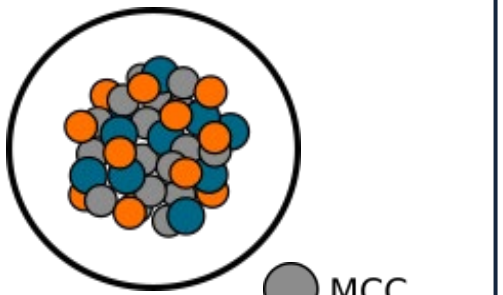
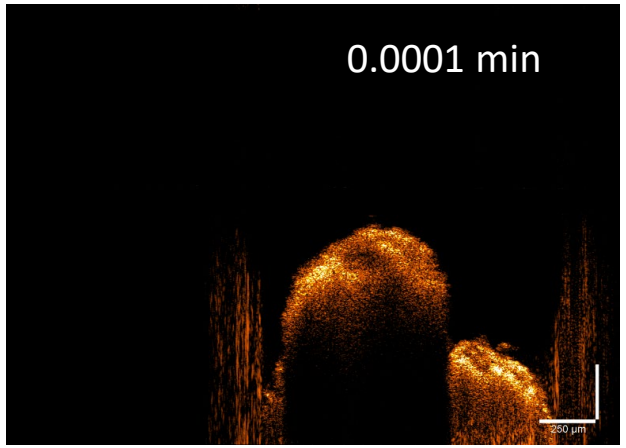
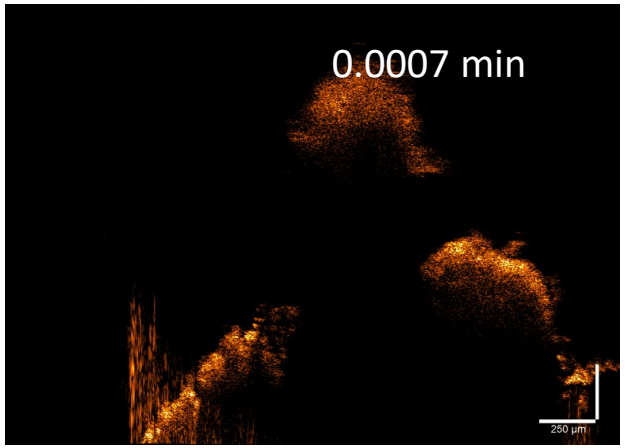
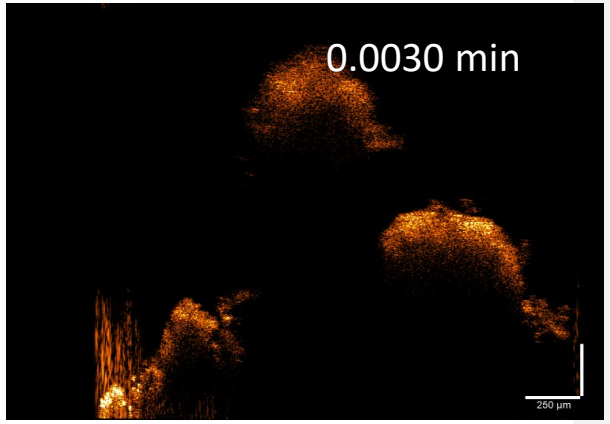






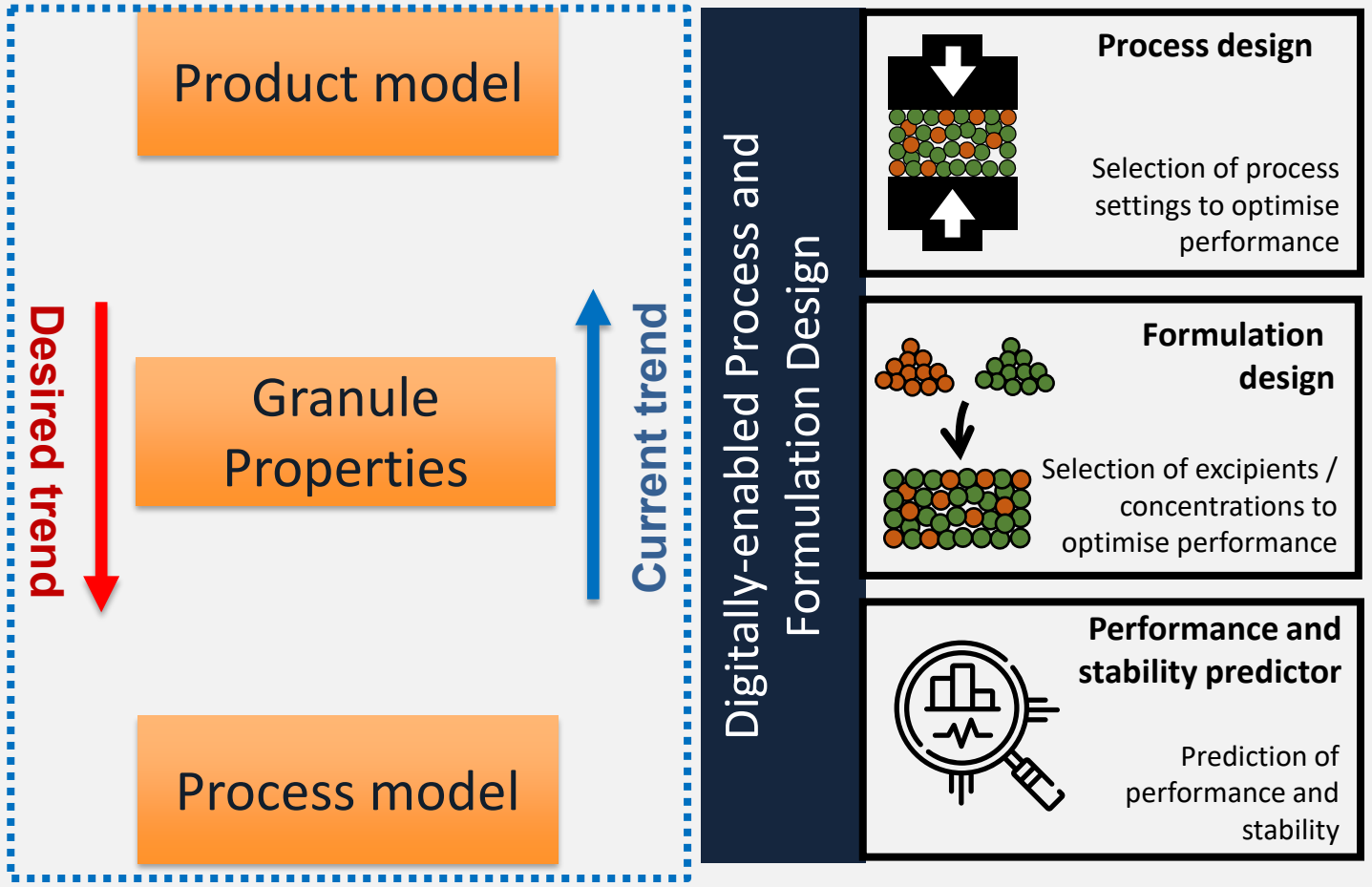


Disintegration Analysis Apsirin and Excipients

Product Structure	Surface Imaging
 D_p (mm) = 2.5 ε (%) = 35	  
 D_p (mm) = 2.5 ε (%) = 52	  

Summary

- Experimental investigation (High shear mixer) for the impact of varying binder (SSG) concentration and L/S ratio on the critical quality attribute (PSD), granule diameter
- Single granule model: global sensitivity analysis and parameter ranking
- Model well predicts the swelling behaviors of the investigated formulations (except 2% SSG, due to low level of swelling)



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Thank you!

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