Model Assisted Design of Granular Products: Linking Product and Process Models for Wet Granulation

Annual Meeting 2023

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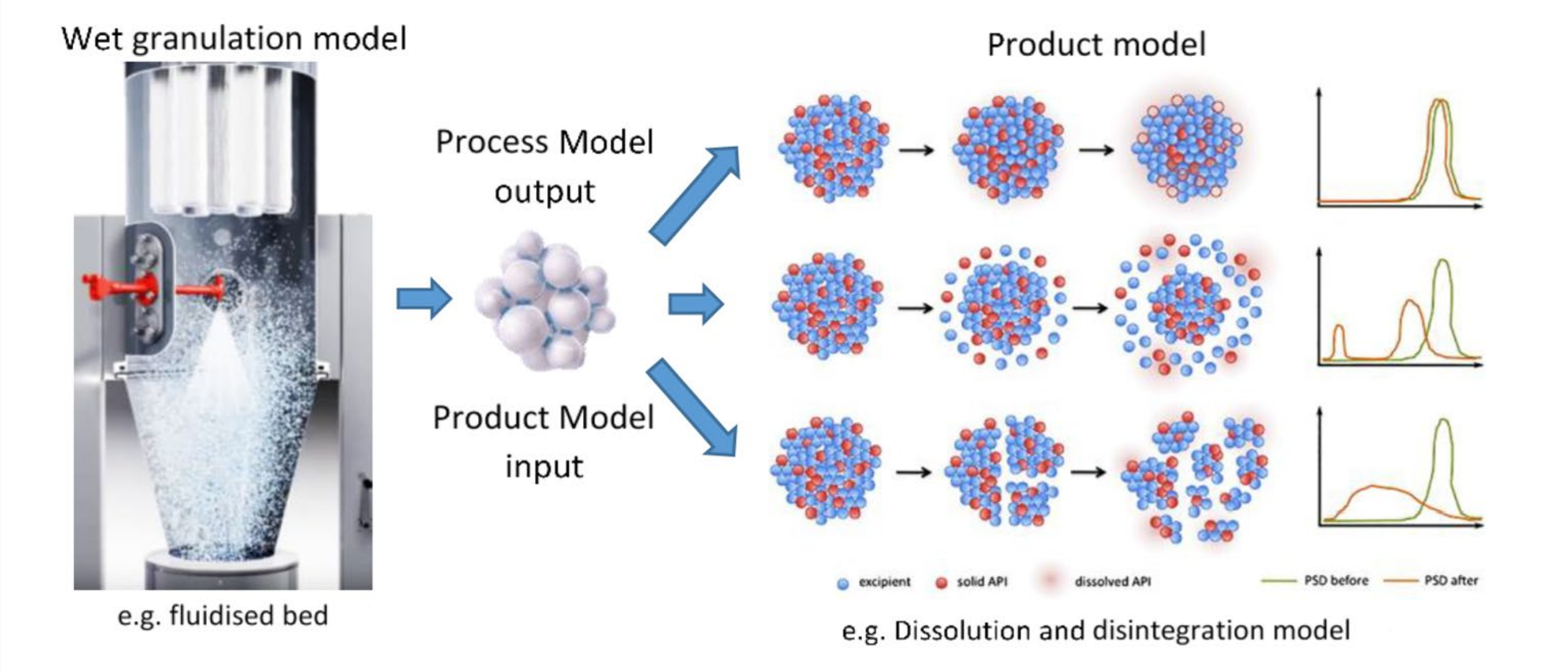
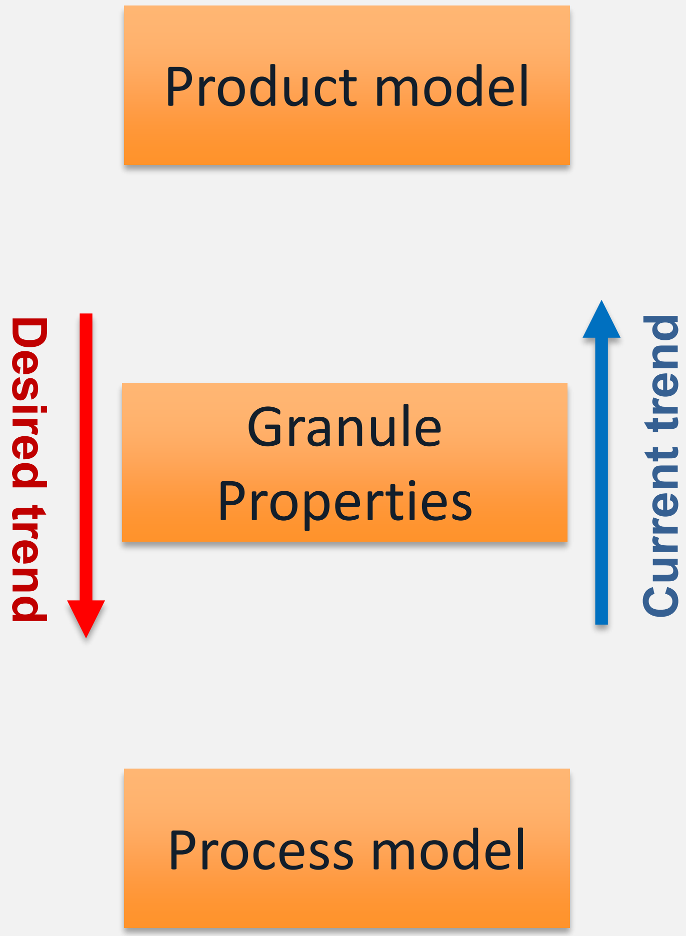
Project overview

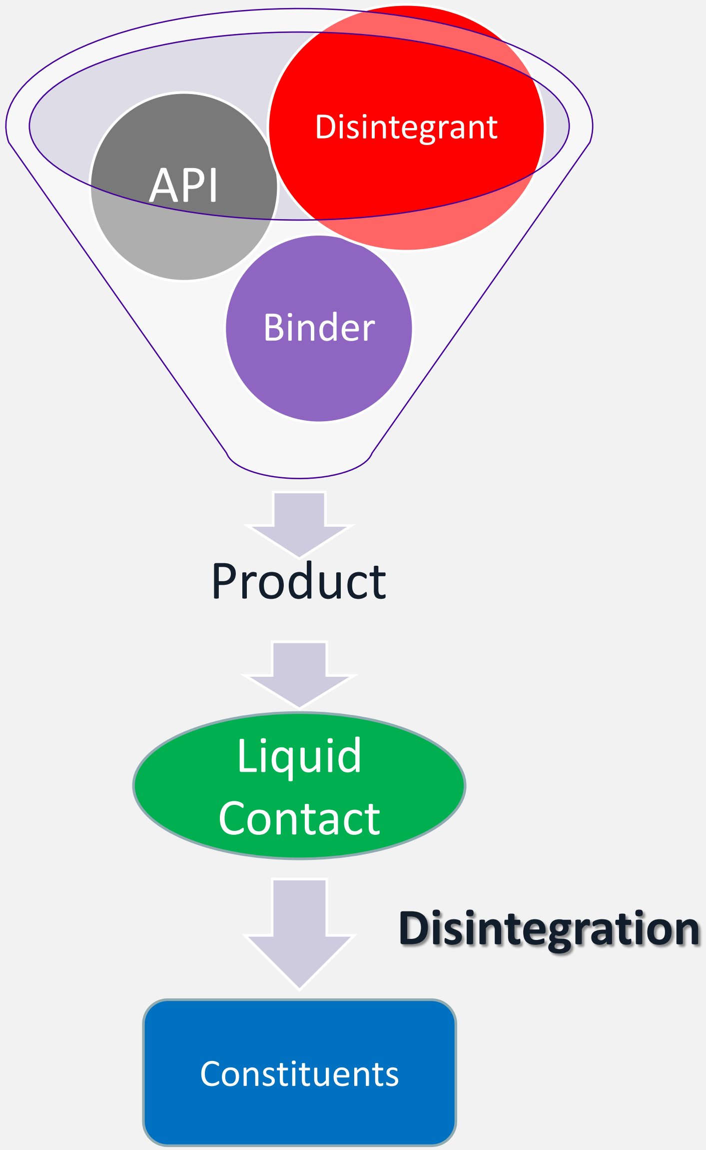




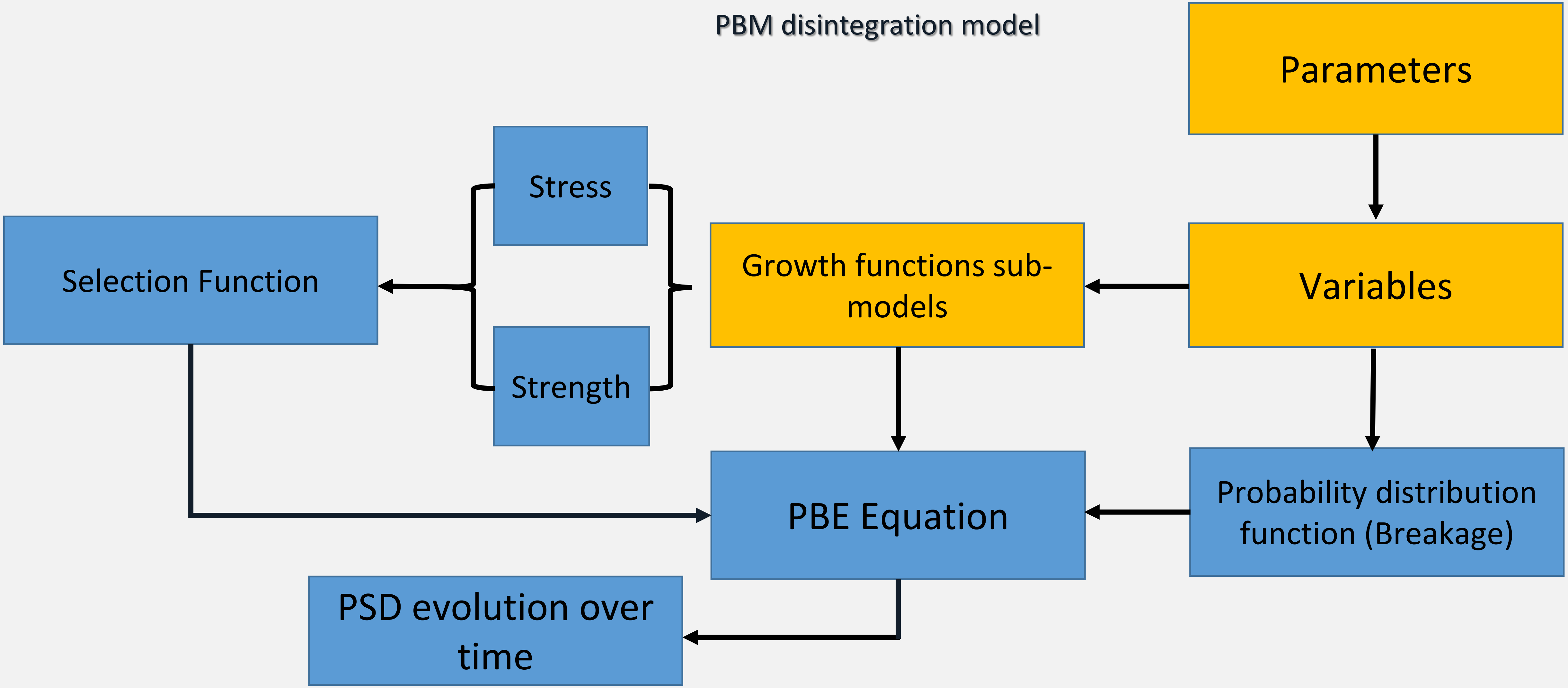
GlattGroup, Glatt Top-Spray granulation process by fluidized bed. (2013)
D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

Granule components

- Active ingredient *(API)*
- Disintegrant (A highly absorbent powder)
- Binder (polymeric)
- A *thermodynamically* compatible liquid



Structure of Models in gPROMS

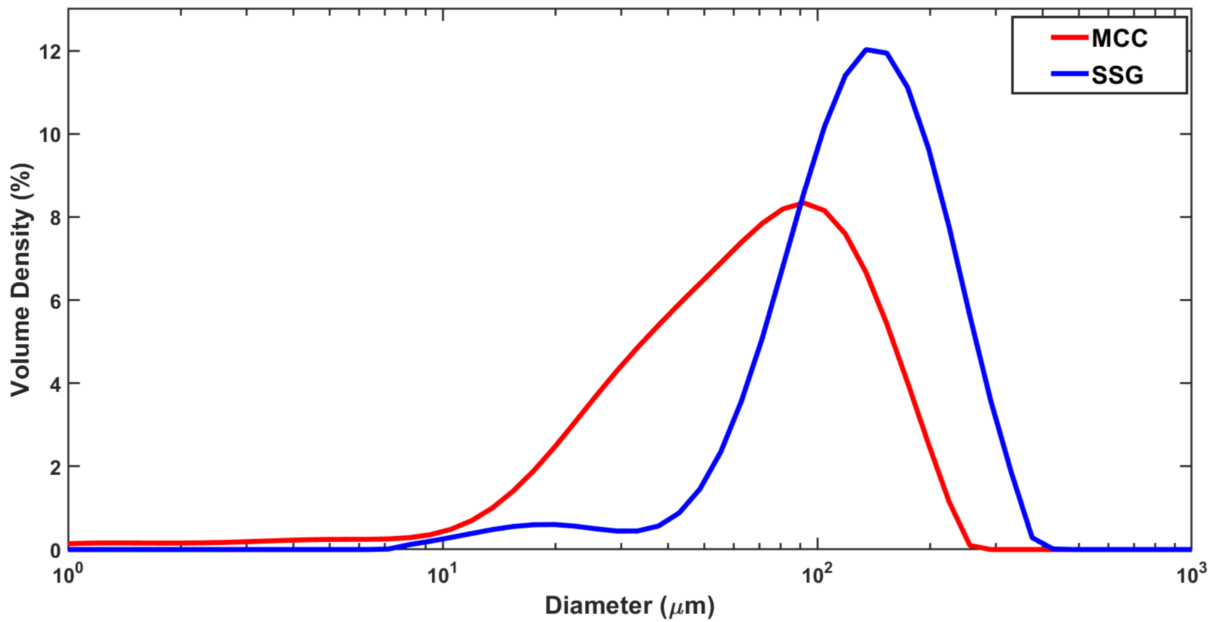


Granulation Experimental Investigation

Materials

Materials	Function	$D_{3,0}$ (μm)	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span	Density ($\frac{g}{cm^3}$)
Microcrystalline cellulose (MCC)	Excipient	103	21	67.5	150	1.9	1.562
Sodium Starch Glycolate (SSG)	Super-disintegrant	171	62.1	131	235	1.32	1.529
HPMC (Pharmacoat 603)	Binder	-	-	-	-	-	-

- Particle Size distributions - Malvern master sizer
- Densities - Helium pycnometry



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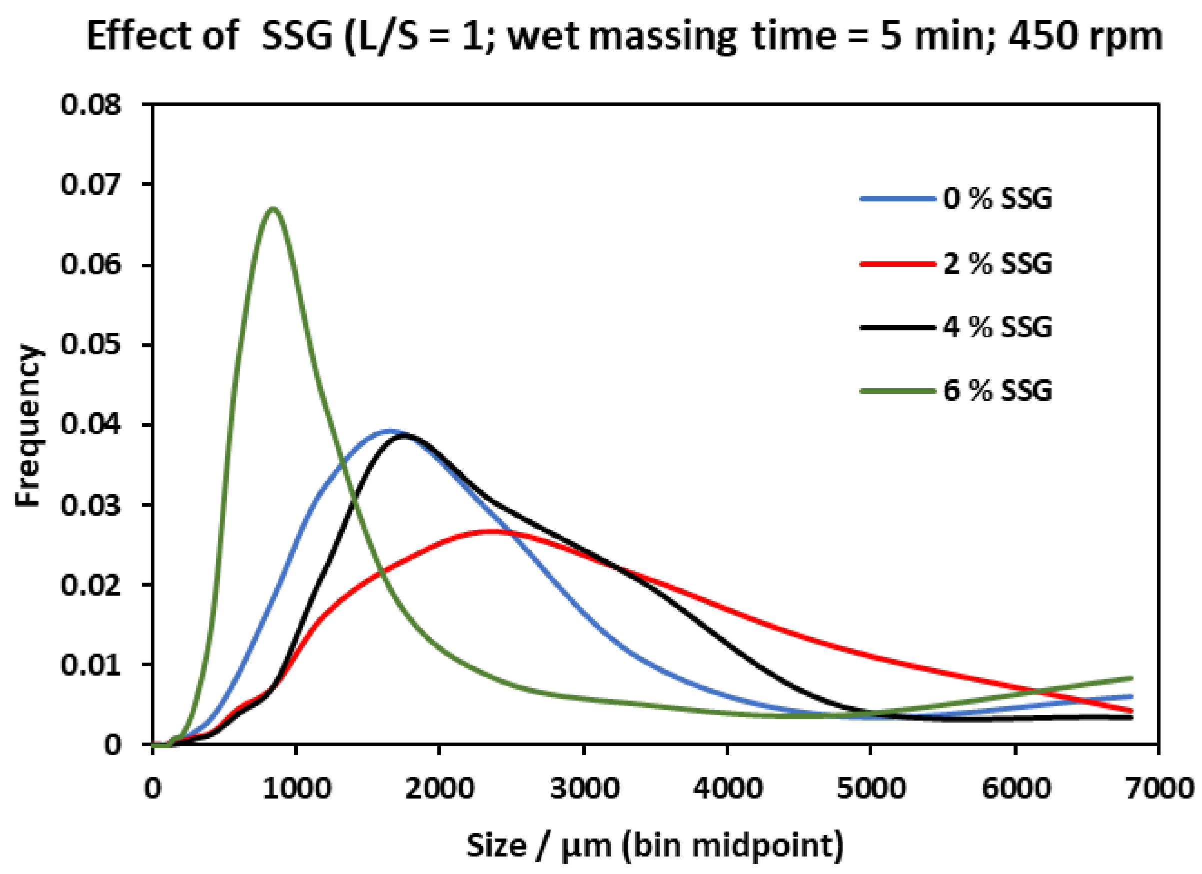
Experimental setup and Formulations

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

- **Optimax**
  - Granule concentration 1.5 % (mg/ml) in 400 ml water at 300 RPM
  - Granule Size = 1- 1.4 mm

EXP ID	Disintegrant conce (%w)	Liquid to solid ratio
5	0	1
6	2	1
7	6	1
4	4	1
8	4	0.8
9	4	0.9

Effect of SSG concentration (EXP ID 5, 6, 7, 4)

Effect of L/S (EXP ID 8, 9)

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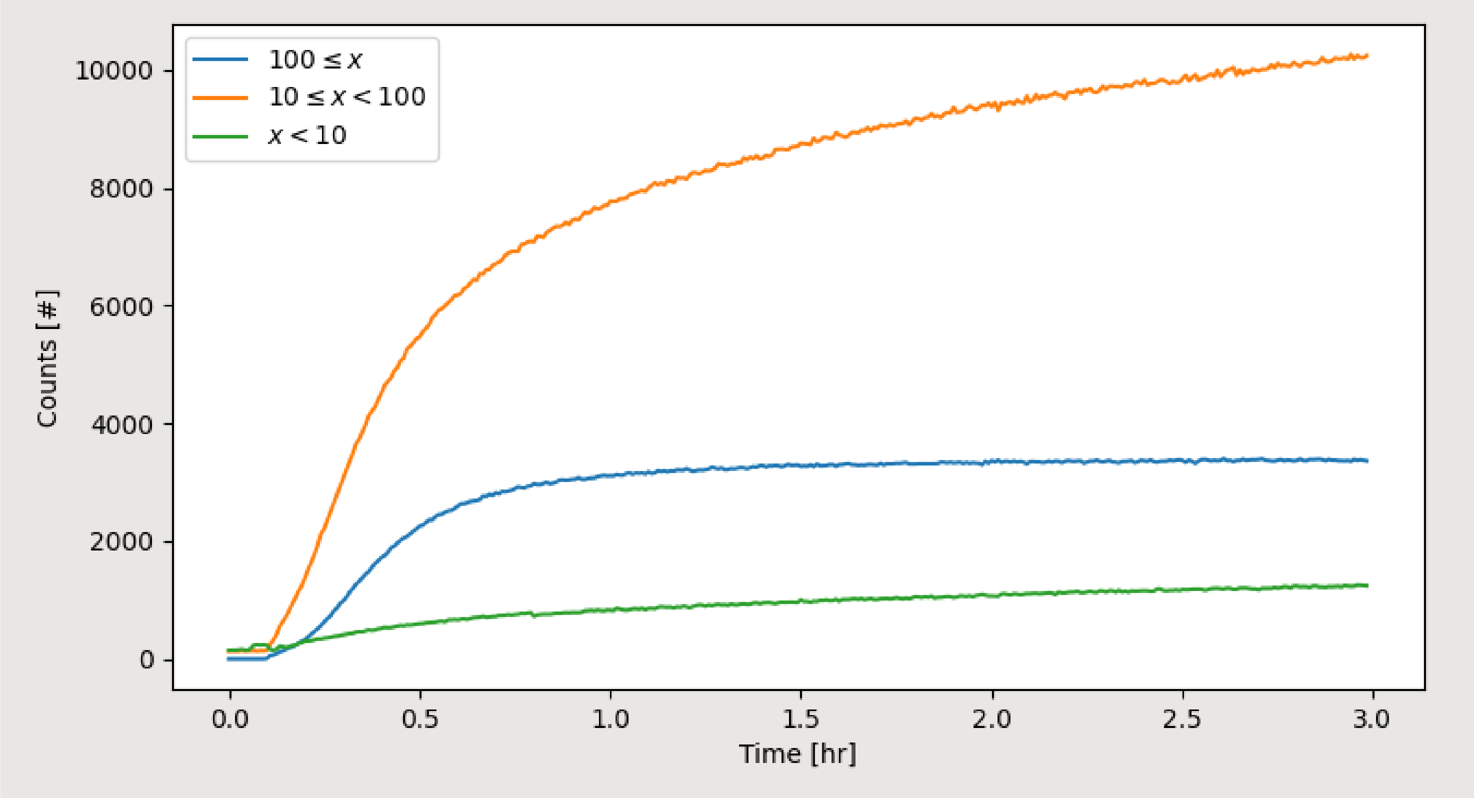
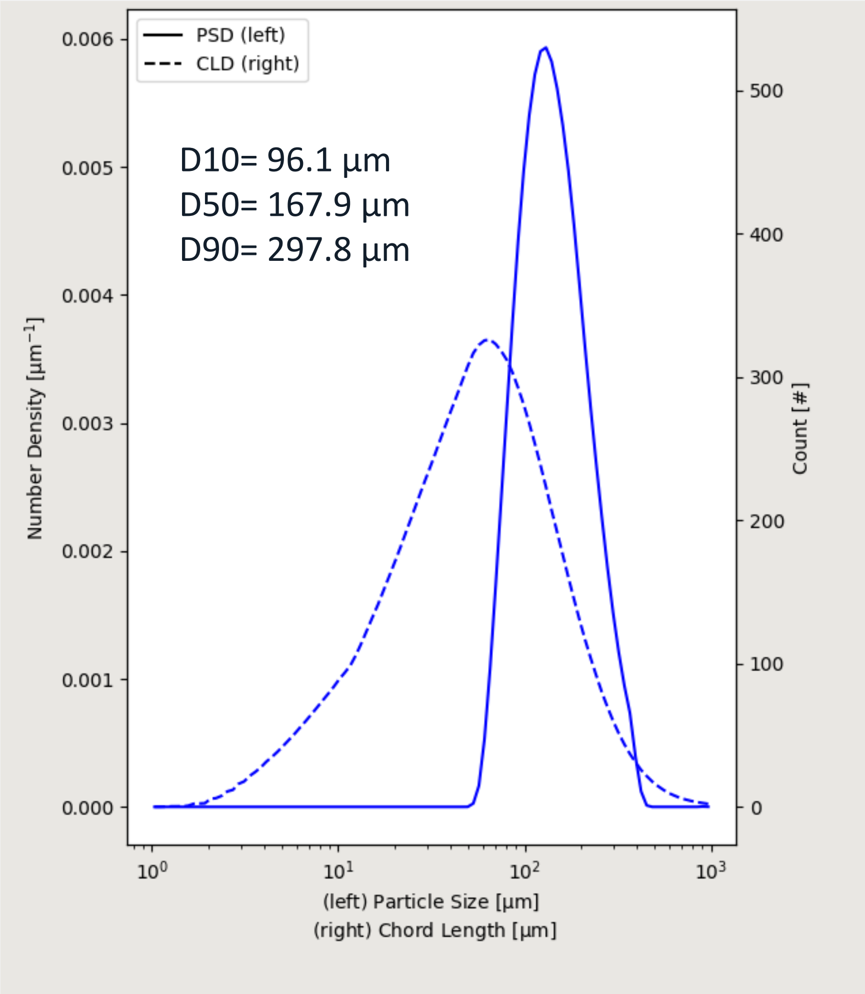
Granule Characterisation G400 FBRM Probe

SSG Concentration = 4% and L/S = 1

a) Particle count vs time



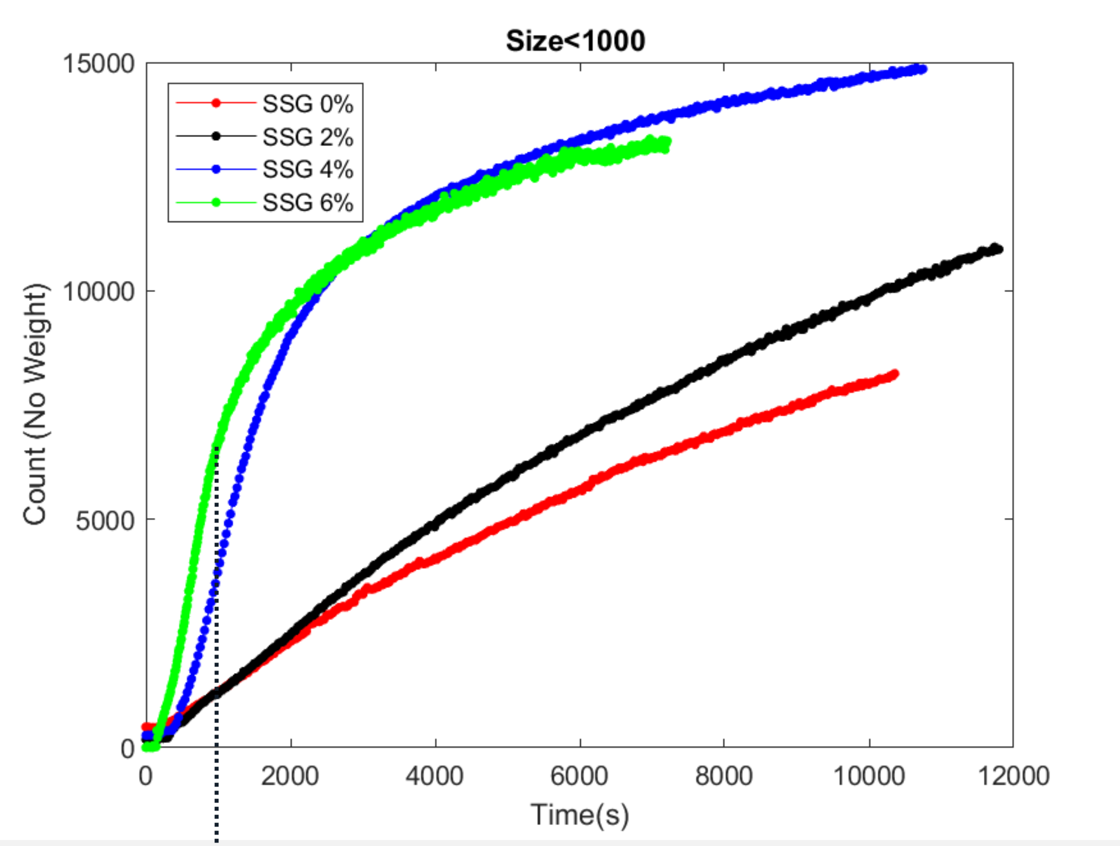
b) Number density vs PSD/CLD



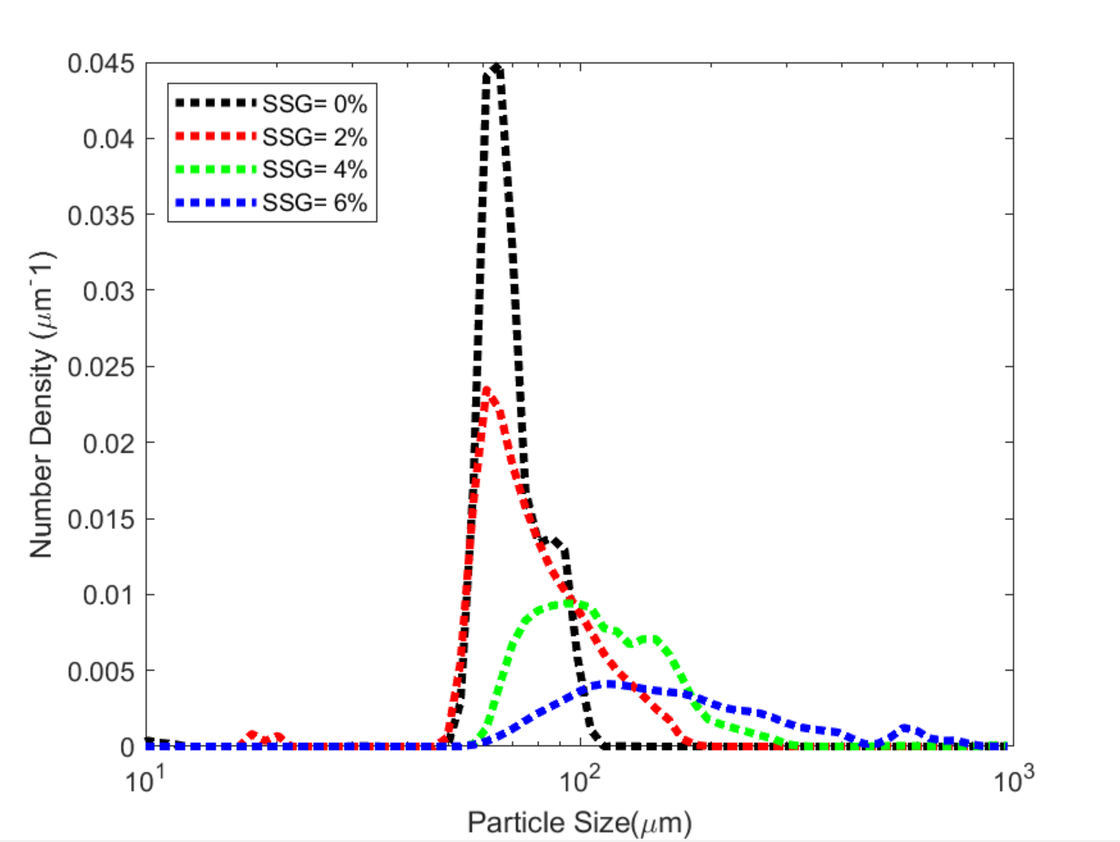
Granule Characterisation - G400 FBRM Probe

Effect of SSG Concentration (L/S = 1)

a) Particle count vs time



b) Number density vs PSD

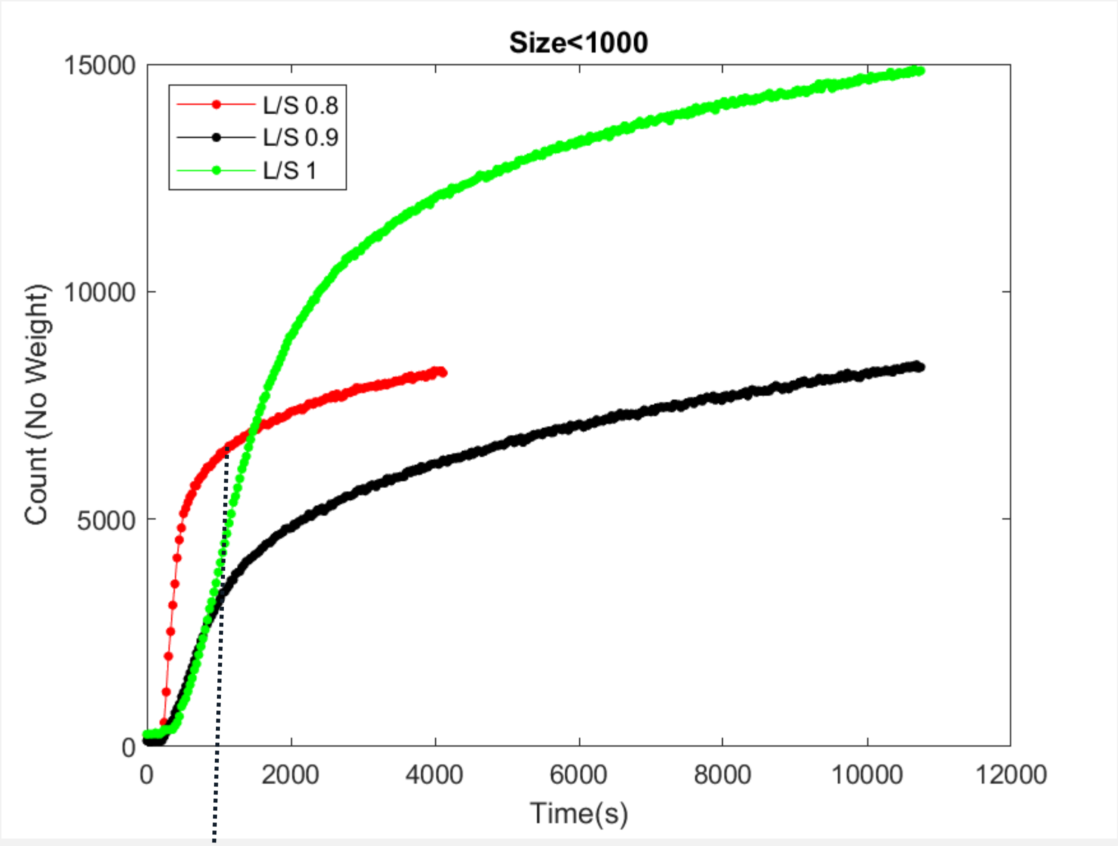


Time = 1000 sec

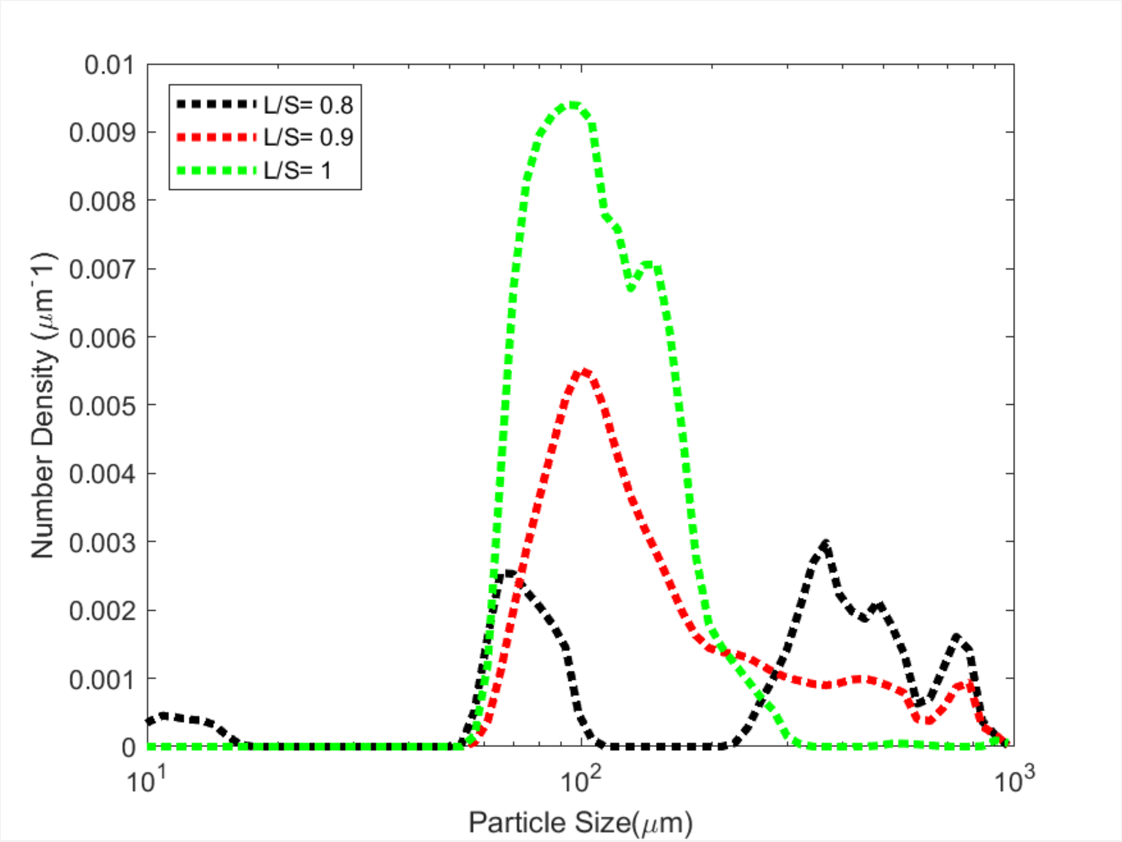
Granule Characterisation - G400 FBRM Probe

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

a) Particle count vs time

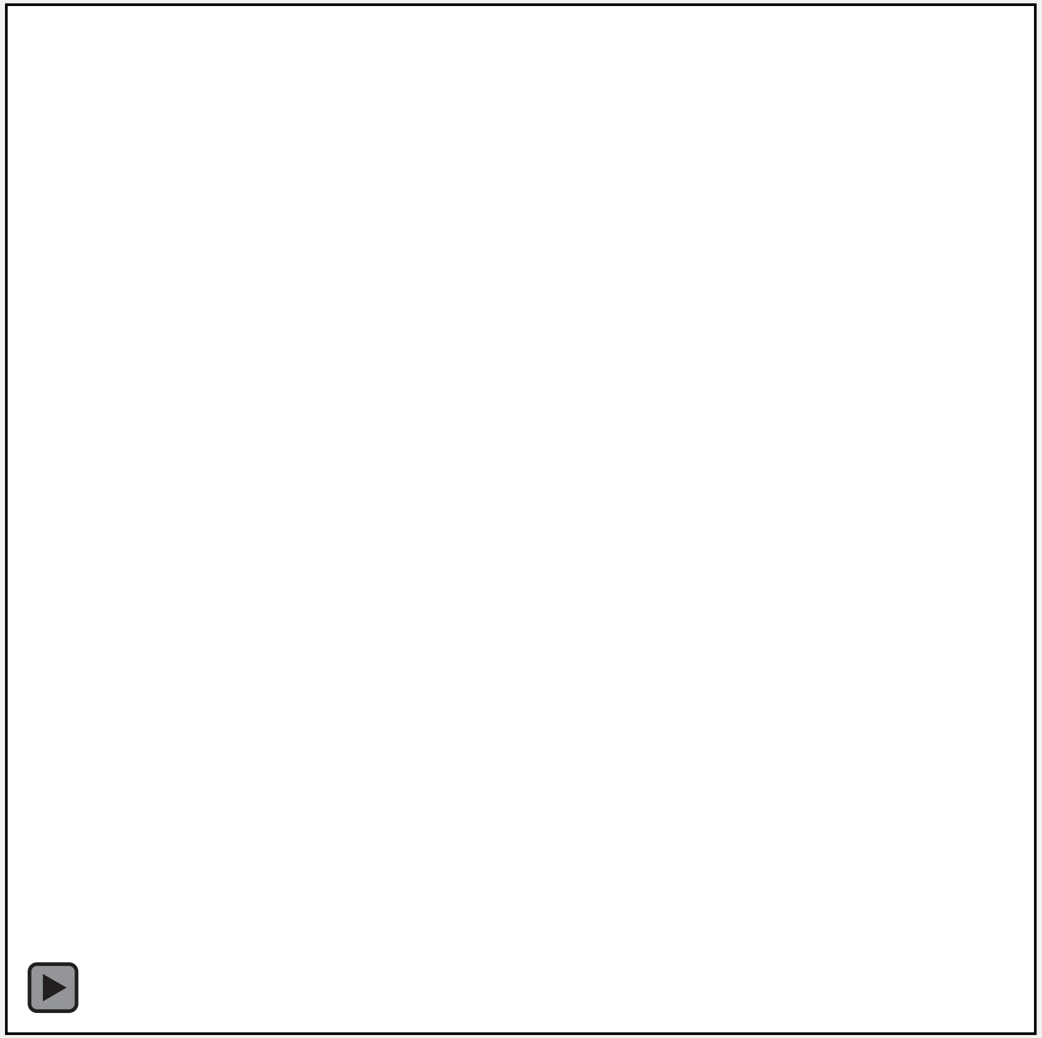


b) Number density vs PSD

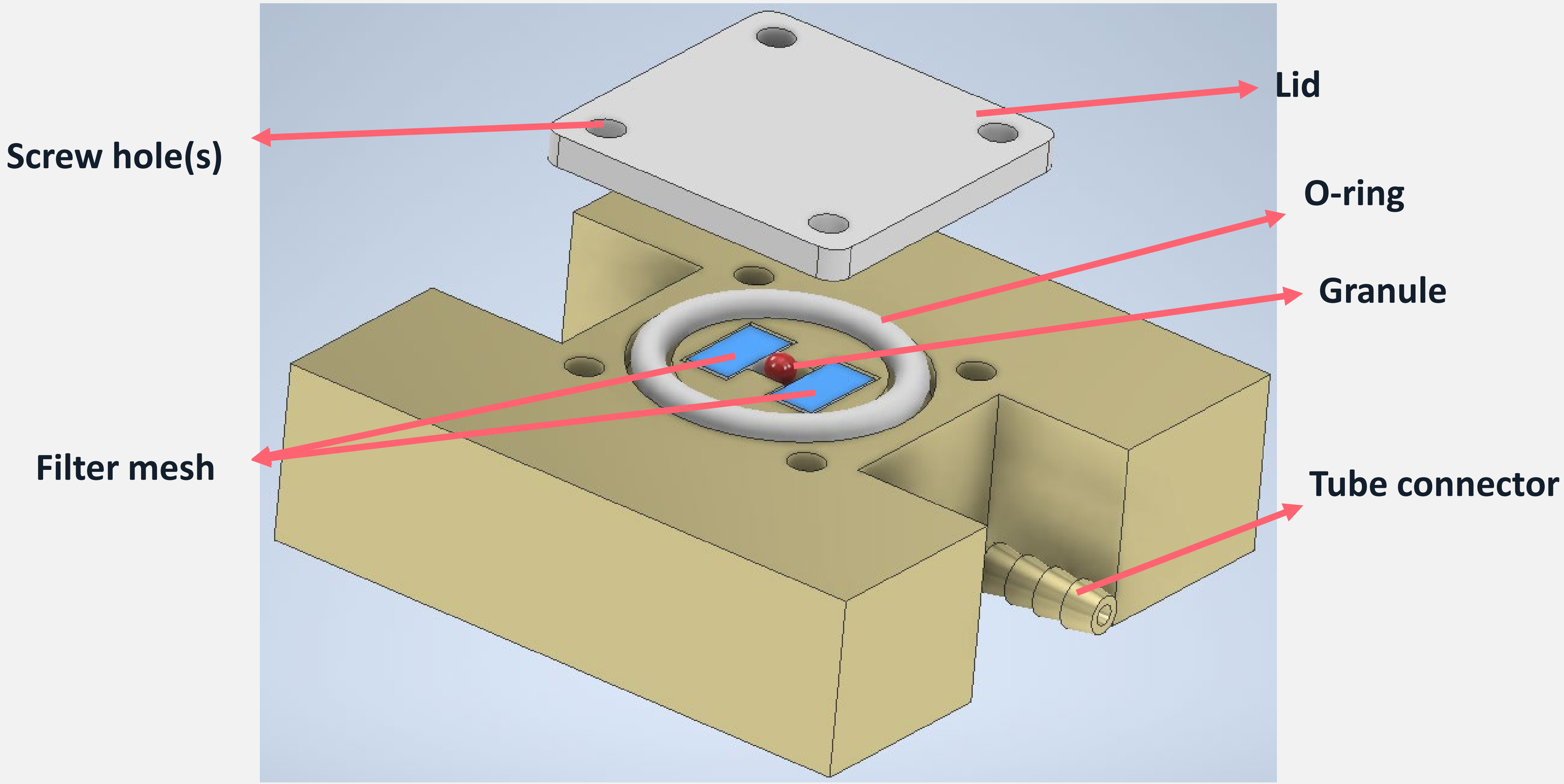


Time = 1000 sec

Blaze Probe: Disintegration mechanism (L/S = 0.8, SSG = 4%)



Granule Swelling Characterisation – Flow Cell



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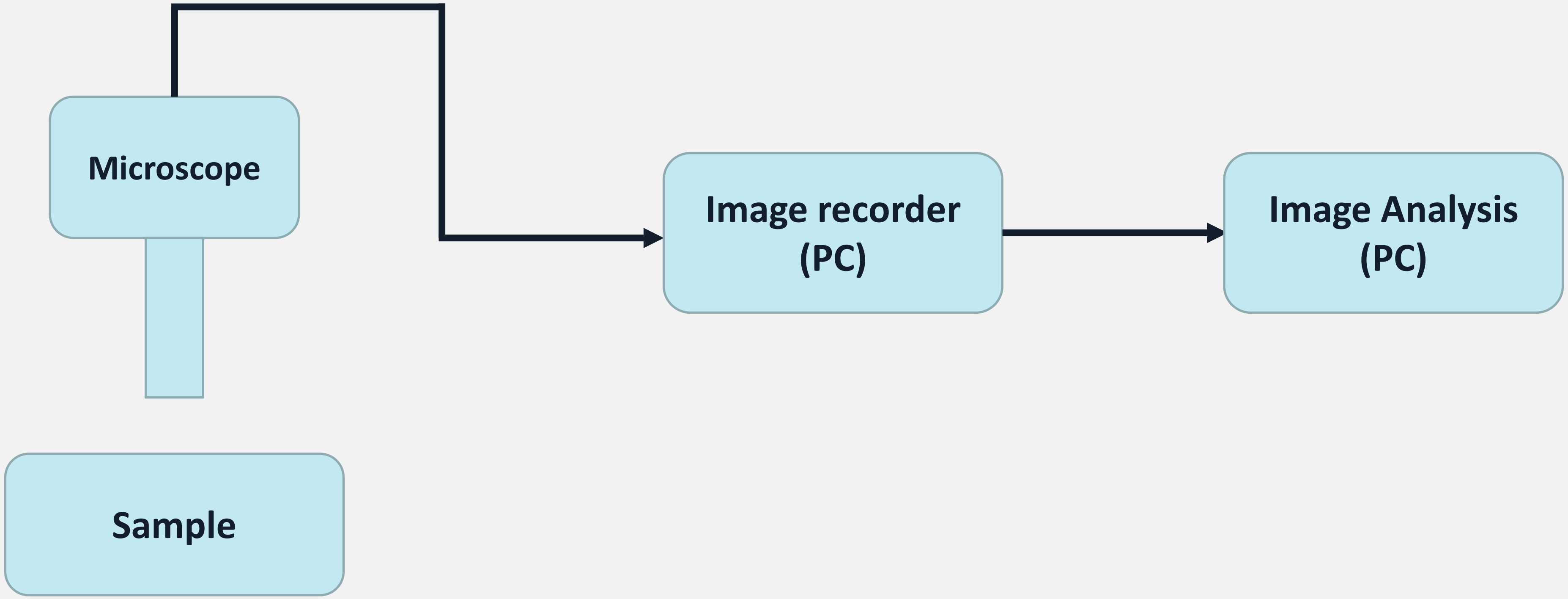
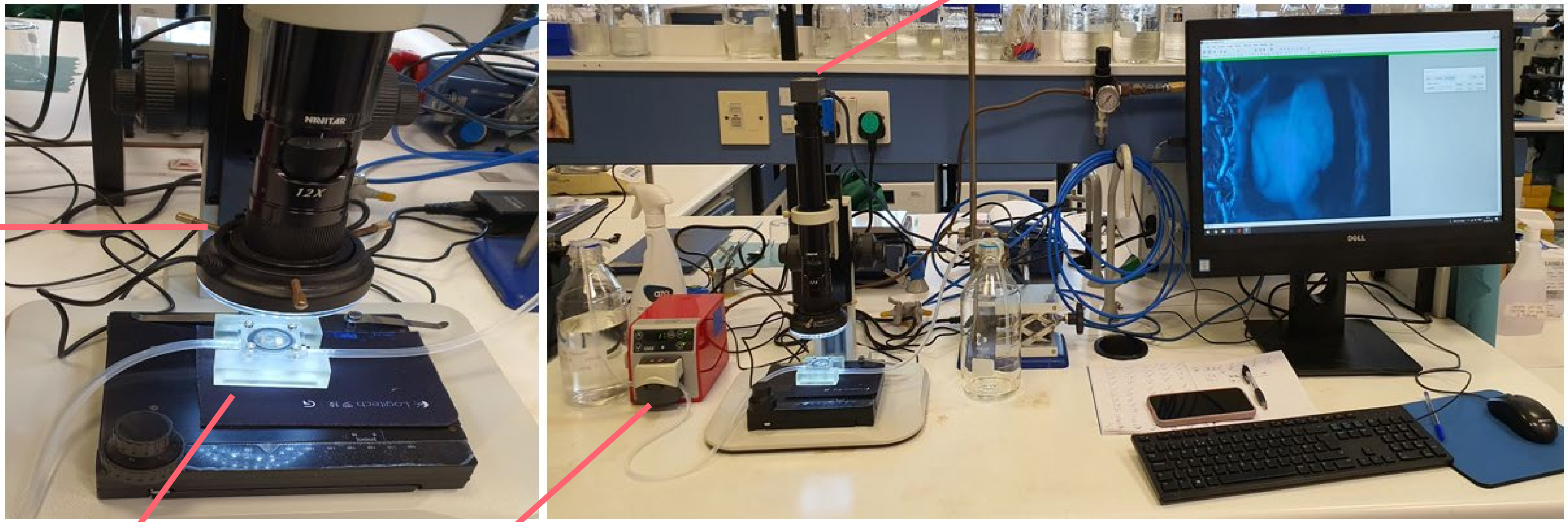


Granule Swelling Characterisation – Flow Cell

Image capturing camera

Optical microscope



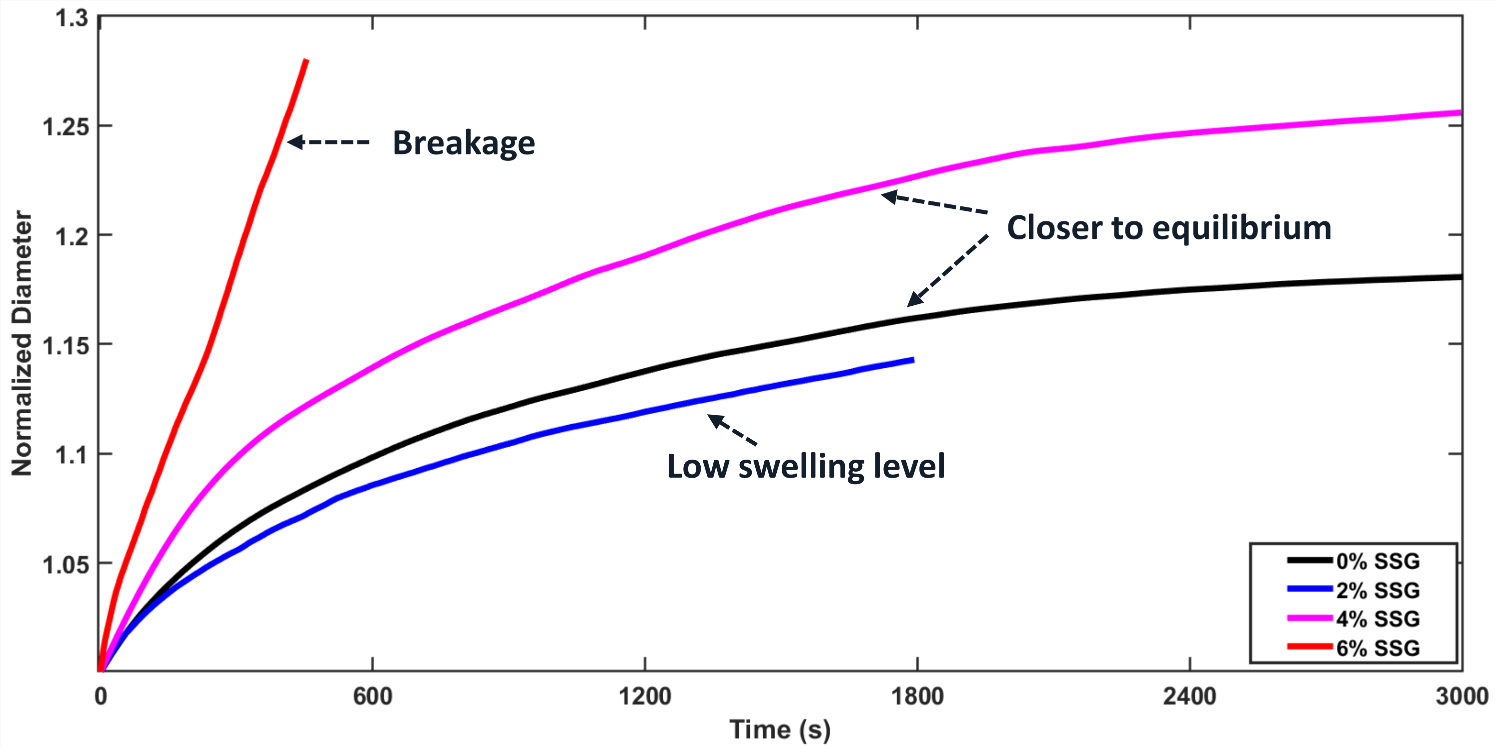
(a) (b)

Flow cell

Peristaltic Pump

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



Modelling and Validation

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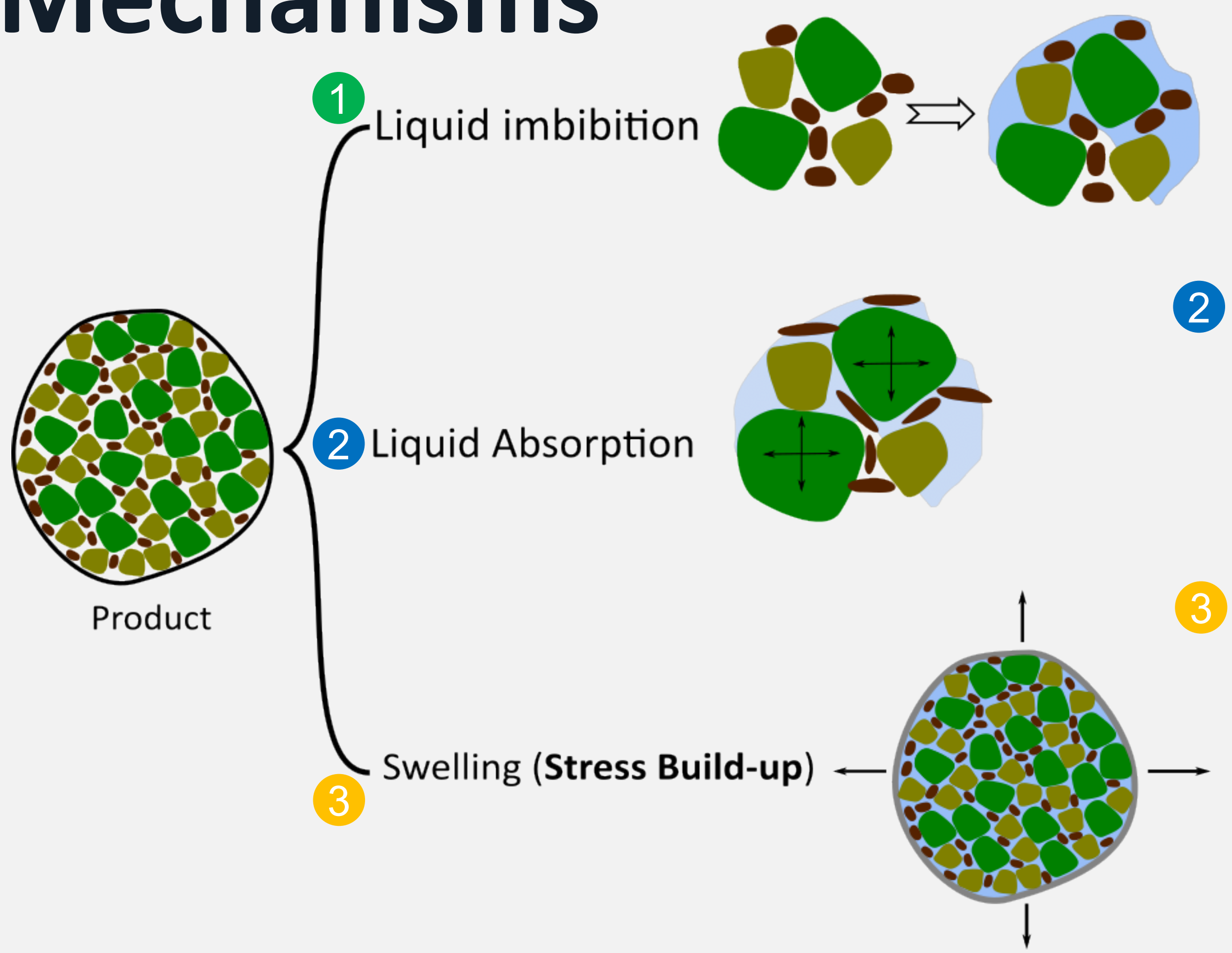
Mechanisms



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

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

$$V_l = \varepsilon S V$$

Total liquid absorbance by the solid phase

2

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

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

3

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

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

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

Dependency of porosity on mass absorption ratios of solid phase

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 i^th component in the solid
$V_{p,i}$: volume of a single i^th component particle, $V_{s,i}$: volume of i^th component in the granule, V_{binder}: volume of the binder in the granule, $x_{v,i}$: volume fraction of i^th component in the solid
Q_i: mass absorption of i^th component, Γ_i: porosity factor of i^th component, ε_{max}&ε_{min}: minimum and maximum porosity, $\rho_{s,i}$: density of i^th component
ρ_l: fluid density ,$V_{p.i}(0)$: initial volume of a single i^th 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	-

Parameter Estimation Procedure

Step 1: Perform GSA on the model to determine the most important parameters

Pick reasonable value for non-important parameters	Parameter estimation for important parameters

↓

Step 2: Image Analysis on Single Granule Swelling Model

Saturation related parameters	Porosity related parameters

↓

Step 3: PSD measurement (FBRM) on PBM Disintegration Model

PBM related parameters

GSA for single granule swelling model: Process Parameters

1. The type of sensitivity analysis is called Variance based Indices
2. The sample generating algorithm is Quasi random (Sobol) sampling
3. The Response variable for sensitivity analysis is normalized size R/R_0 and porosity
4. The total number of simulation used for GSA is 6000

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

High : (red) Medium : (yellow) Low : (green)

GSA for single granule swelling model: Porosity related Parameters

1. Variance based Indices was used as the technique for GSA
2. Quasi random (Sobol) sampling is the sample generating algorithm
3. The response variable for sensitivity analysis is normalized radius R/R_0, porosity and absorption ratio of the superdisintegrant averaged over time
4. The total number of simulation used for GSA is 7500

Parameter \ Response	Porosity		Normalized diameter		Mass absorption ratio	
	First Effect	Total Effect	First Effect	Total Effect	First Effect	Total Effect
Superdisintegrant'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

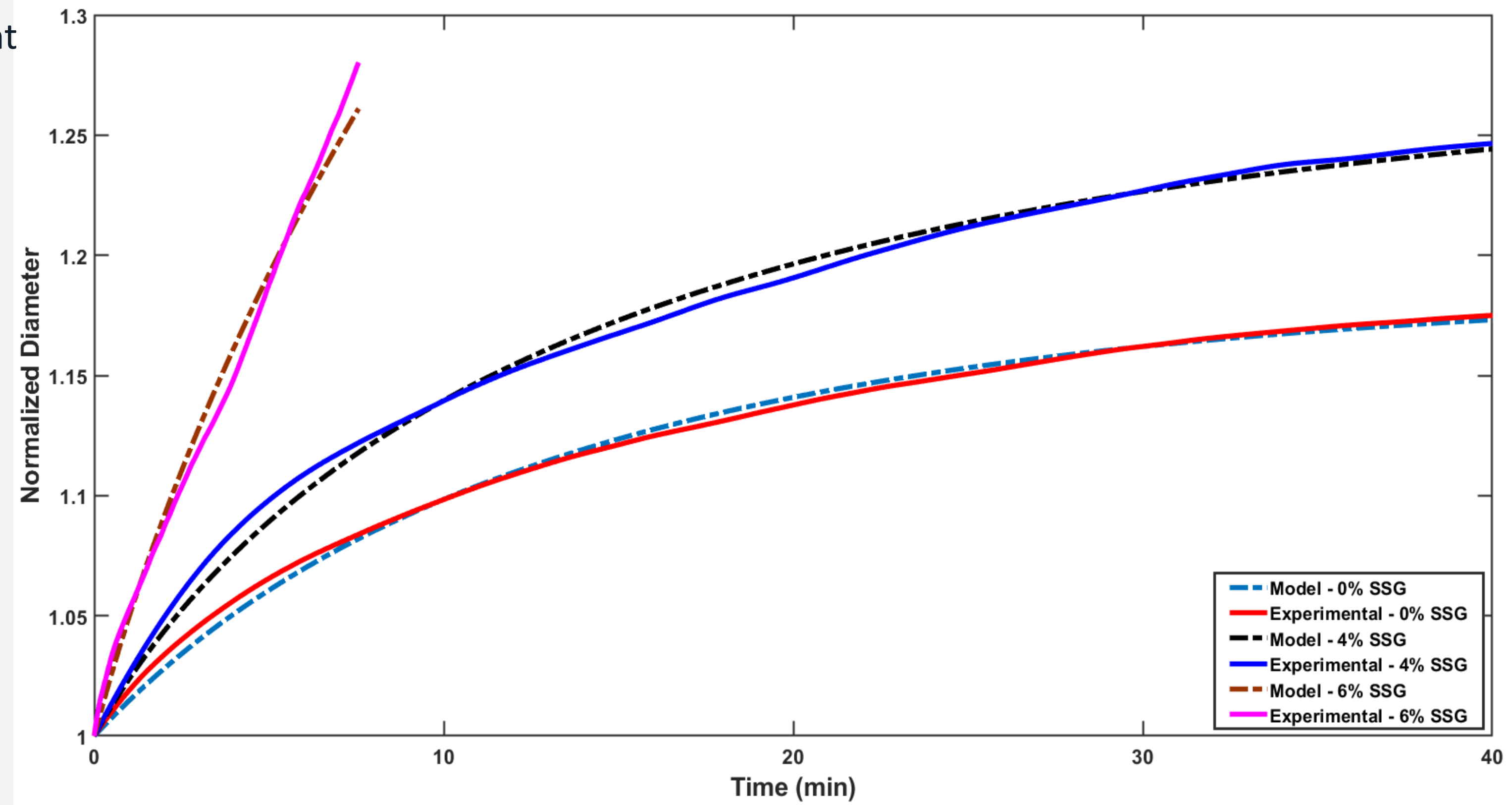
High : (red) Medium : (yellow) Low : (green)

Parameter Estimation and Validation

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

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

Parameter estimation : least square method



Summary

- Experimental investigation was performed using High shear mixer with Microcrystalline cellulose (MCC), Sodium Starch Glycolate (SSG) and HPMC (Pharmacoat 603) as formulation material

- Investigated the impact of varying binder (SSG) concentration and L/S ratio on the critical quality attributes (CQA’s) such as particle size distribution (PSD) and granule size

- Global sensitivity analysis:
  - Process parameters: initial porosity & initial primary particle sizes have the most impact on CQA
  - Porosity related parameters: Superdisintegrant’s porosity factor followed by its maximum absorption ratio and diffusivity.

- Model well predicts the swelling behaviors of the investigated formulations except the granules with 2% SSG, due to low level of swelling.

Next steps

1. Validating of Population Balance Model (PBM)
2. Complete the development of the model in gPROMS Formulated Products
3. Calibrate the high shear granulation process model
4. Link the process model to the disintegration model

Publications/Conferences

1. A Mechanistic Model for Swelling Driven Disintegration of Granular Products (plan to submit to Pharmaceutics August 2023)
2. Granulation Workshop, June 2023
3. International Congress on Particle Technology PARTEC, September 2023

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