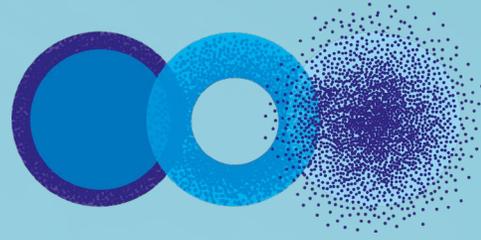




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# Model Driven Design of Formulated Products

Rachel Smith

Department of Chemical and Biological Engineering  
The University of Sheffield

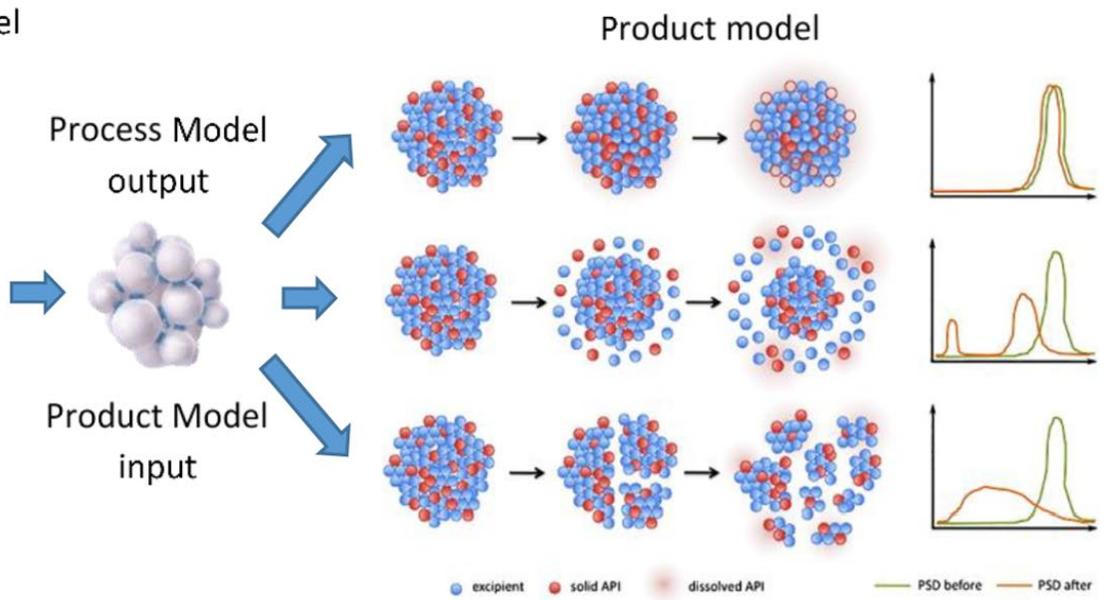
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# Process-product relationship in disintegration

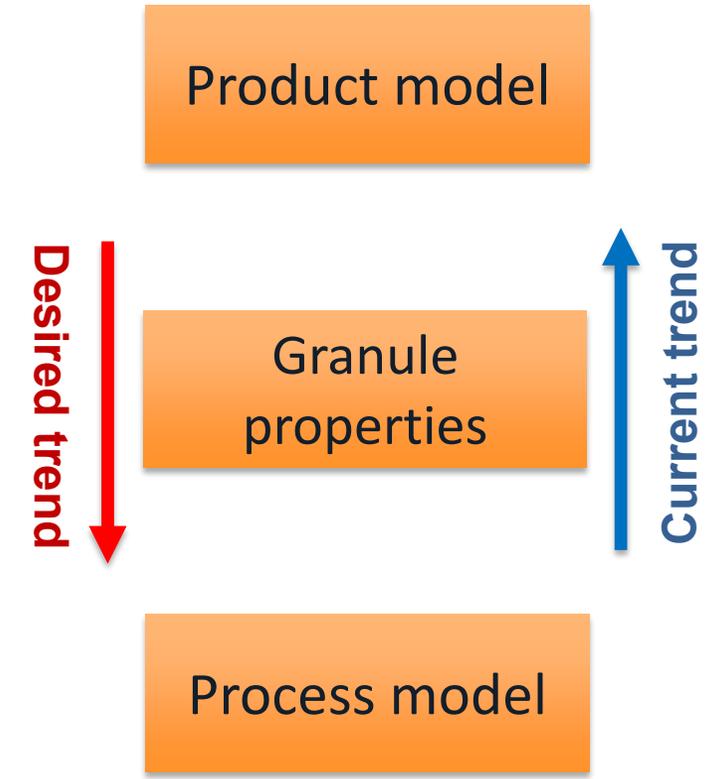
Wet granulation model



e.g. fluidised bed



e.g. Dissolution and disintegration model



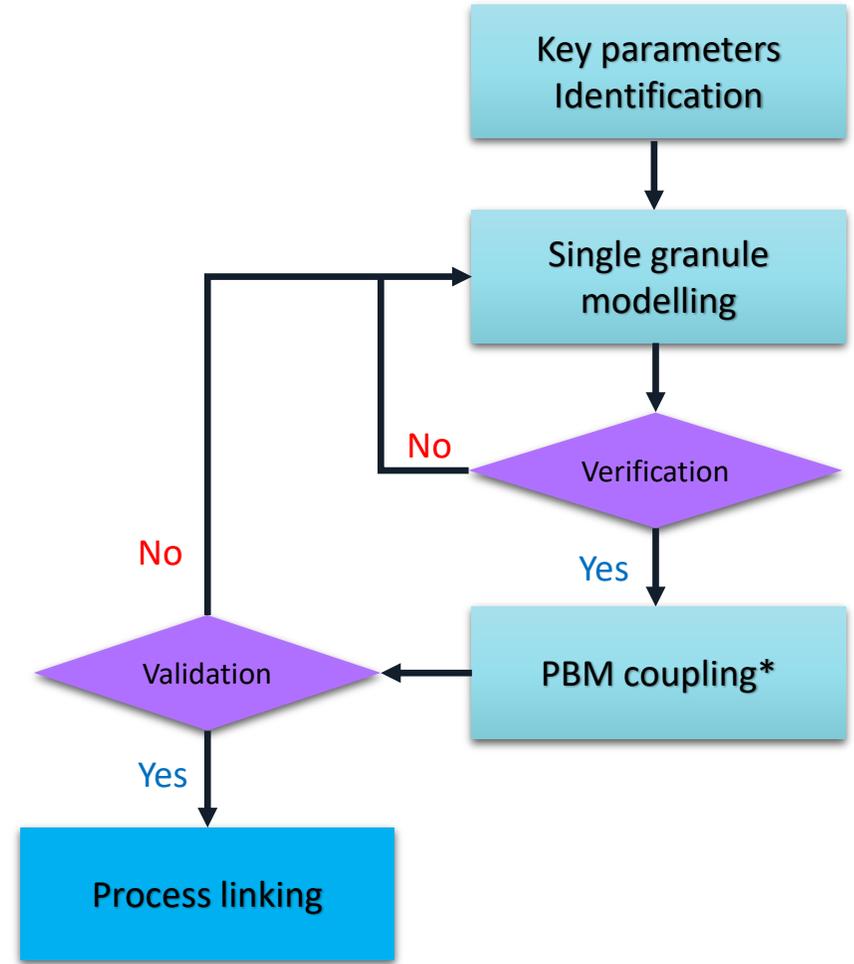
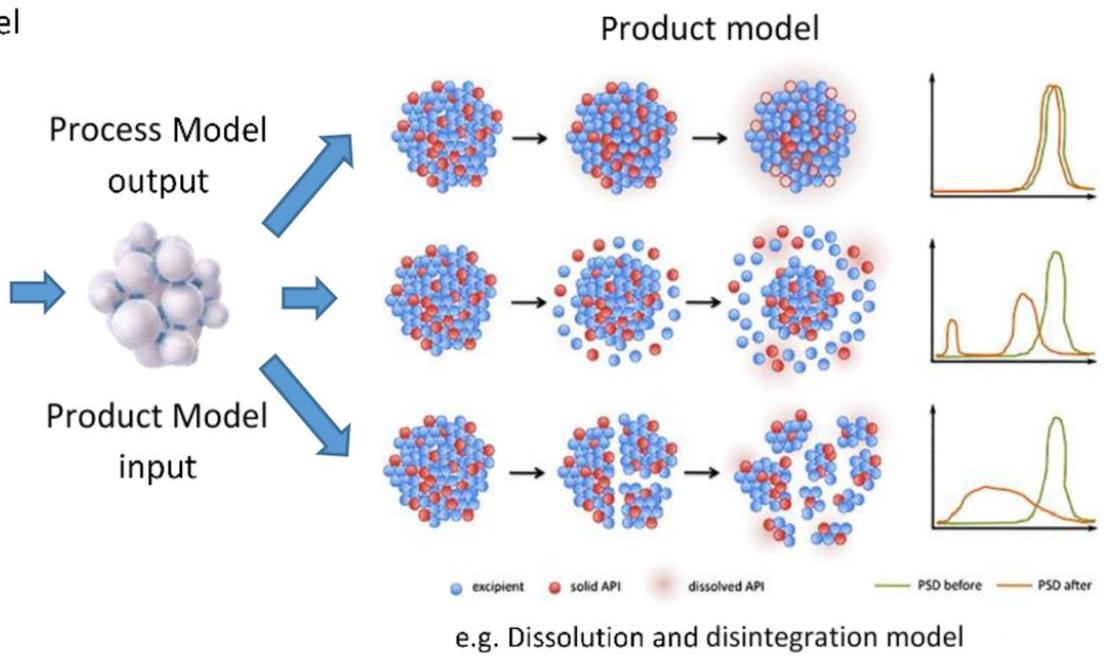
GlattGroup, Glatt Top-Spray granulation process by fluidized bed. (2013)  
 D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

# Process-product relationship in disintegration

Wet granulation model



e.g. fluidised bed

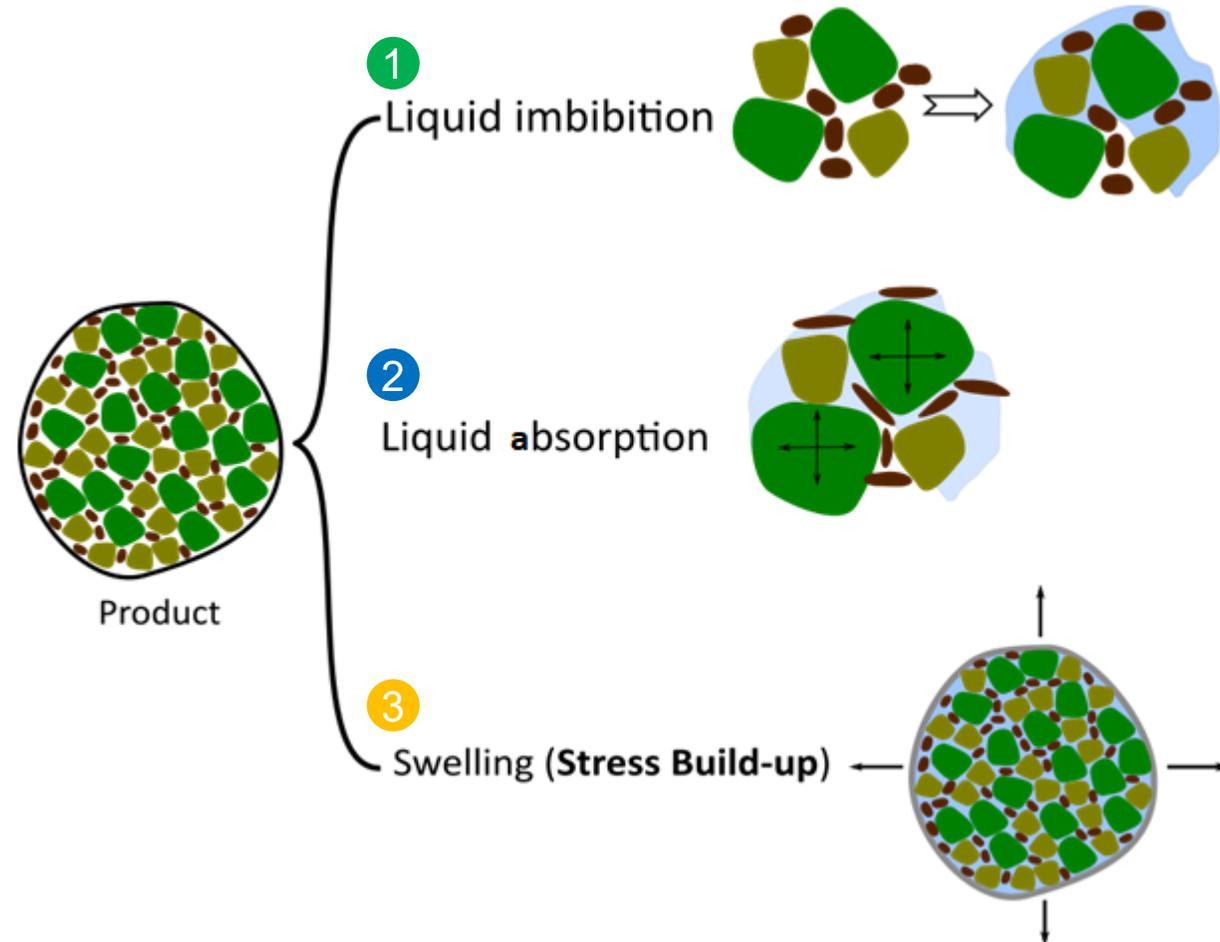


GlattGroup, Glatt Top-Spray granulation process by fluidized bed. (2013)  
 D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

# Single granule swelling model

## Part 1: Modelling

# Mechanisms



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

$$\left(\frac{dV_l}{dt}\right)_{sin} = 4\pi R^2 \frac{k_{per}}{\eta} \lim_{r \rightarrow R} \frac{\partial P_c}{\partial r} - \underbrace{\sum n_{p,i} \frac{dV_{p,i}}{dt}}_{\text{Total liquid absorbance by the solid phase}}$$

$V_l = \varepsilon S V$

**2**

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

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

**3**

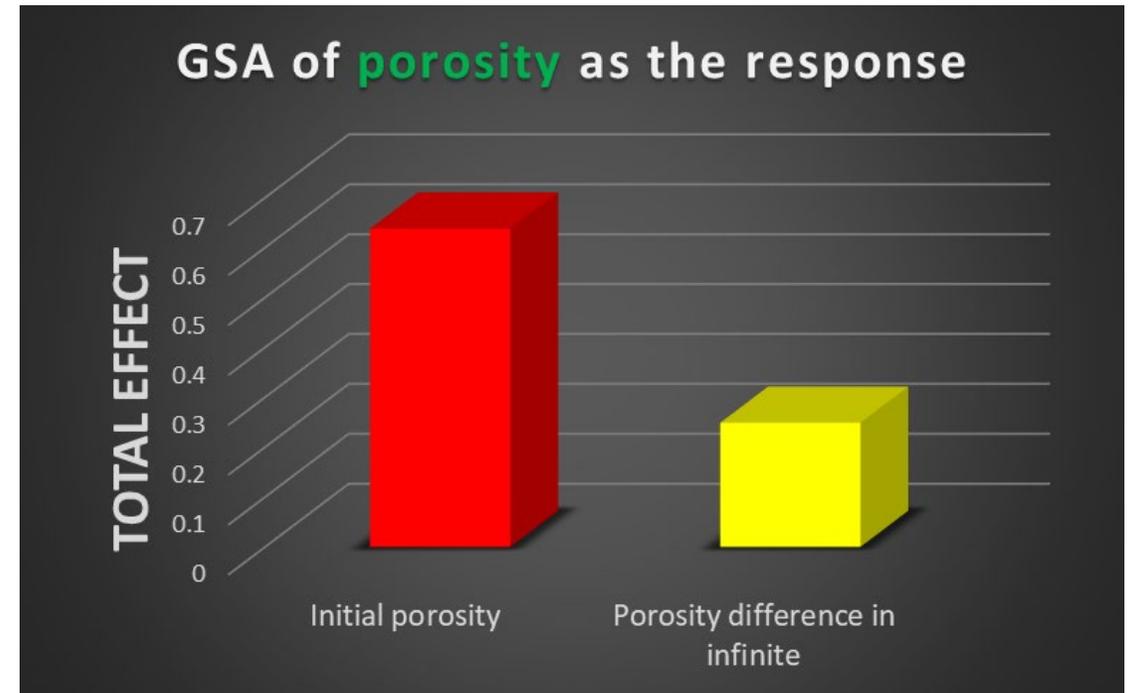
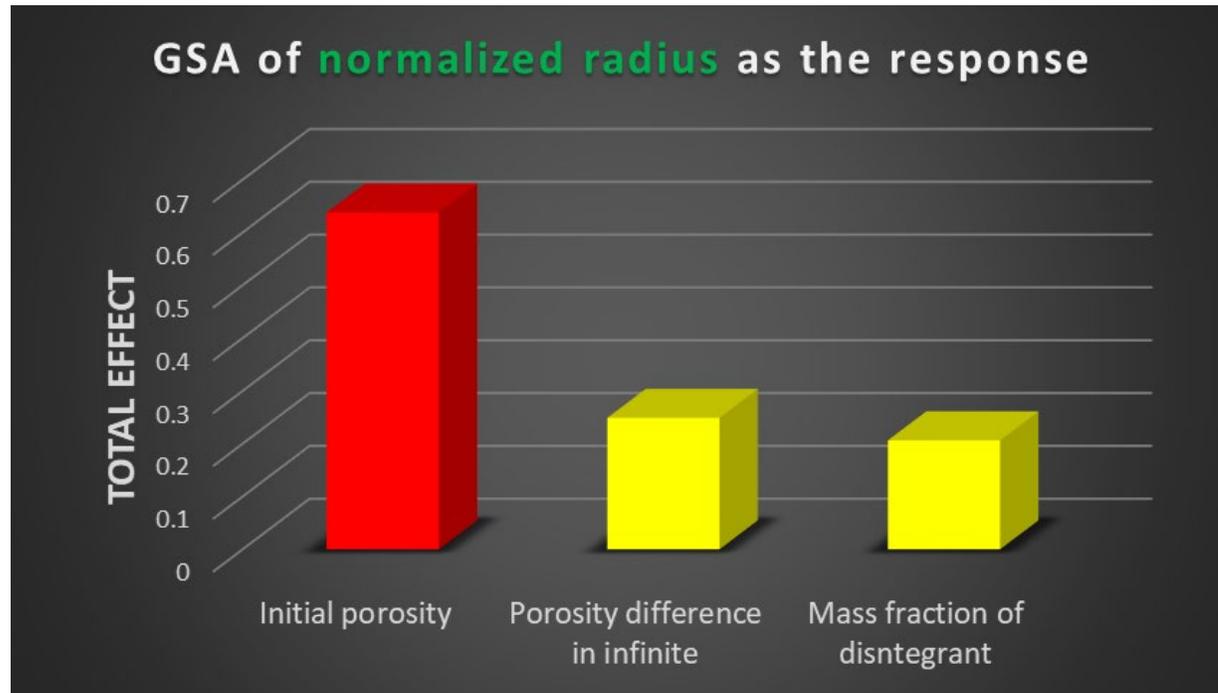
$$\frac{\varepsilon - \varepsilon_0}{\Delta \varepsilon_\infty} = 1 - (1 - \hat{m}_s)^\beta \rightarrow \text{Dependency of porosity on mass absorption ratios of solid phase}$$

$$\hat{m}_s = \frac{\sum w_i Q_i^{abs} - 1}{\sum w_i Q_i^{max} - 1}$$

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

$t$ : time,  $R$ : granule radius,  $\varepsilon$ : porosity,  $S$ : saturation,  $V$ : volume,  $V_l$ : volume of liquid in granule,  $k_{per}$ : permeability,  $P_c$ : capillary pressure,  $n_{p,i}$ : number of  $i^{\text{th}}$  component in the solid  
 $V_{p,i}$ : volume of a single  $i^{\text{th}}$  component particle,  $V_{s,i}$ : volume of  $i^{\text{th}}$  component in the granule,  $V_{binder}$ : volume of the binder in the granule,  $x_{v,i}$ : volume fraction of  $i^{\text{th}}$  component in the solid  
 $Q_i$ : mass absorption of  $i^{\text{th}}$  component,  $\Gamma_i$ : porosity factor of  $i^{\text{th}}$  component,  $\varepsilon_0$ : initial porosity,  $\Delta \varepsilon_\infty$ : porosity difference at infinite,  $\rho_{s,i}$ : density of  $i^{\text{th}}$  component,  $\hat{m}_s$ : normalized liquid uptake  
 $w_i$ : mass fraction of components,  $\rho_l$ : fluid density,  $V_{p,i}(0)$ : initial volume of a single  $i^{\text{th}}$  component particle

# GSA for mono-sized single granule swelling model



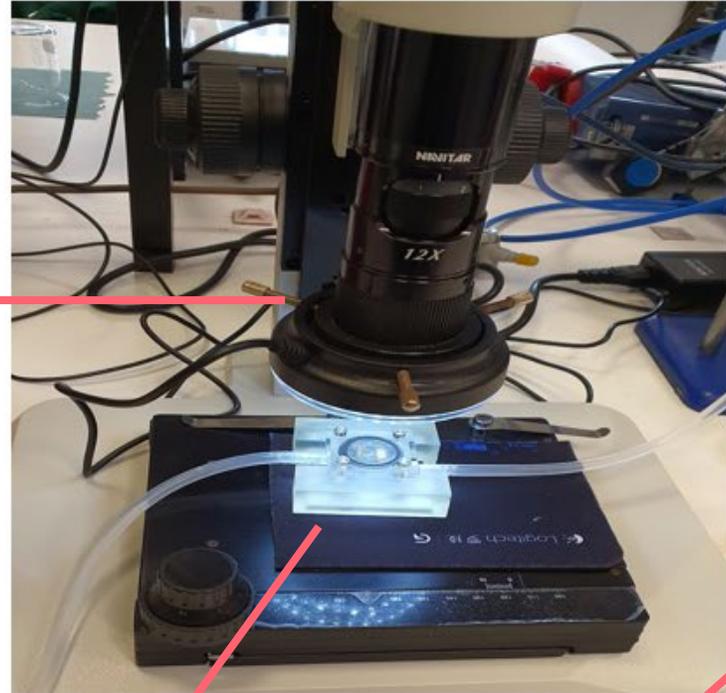
# Single granule swelling model

## Part 2: Experimental

# Granule swelling characterisation – flow cell

Optical microscope

Image capturing camera

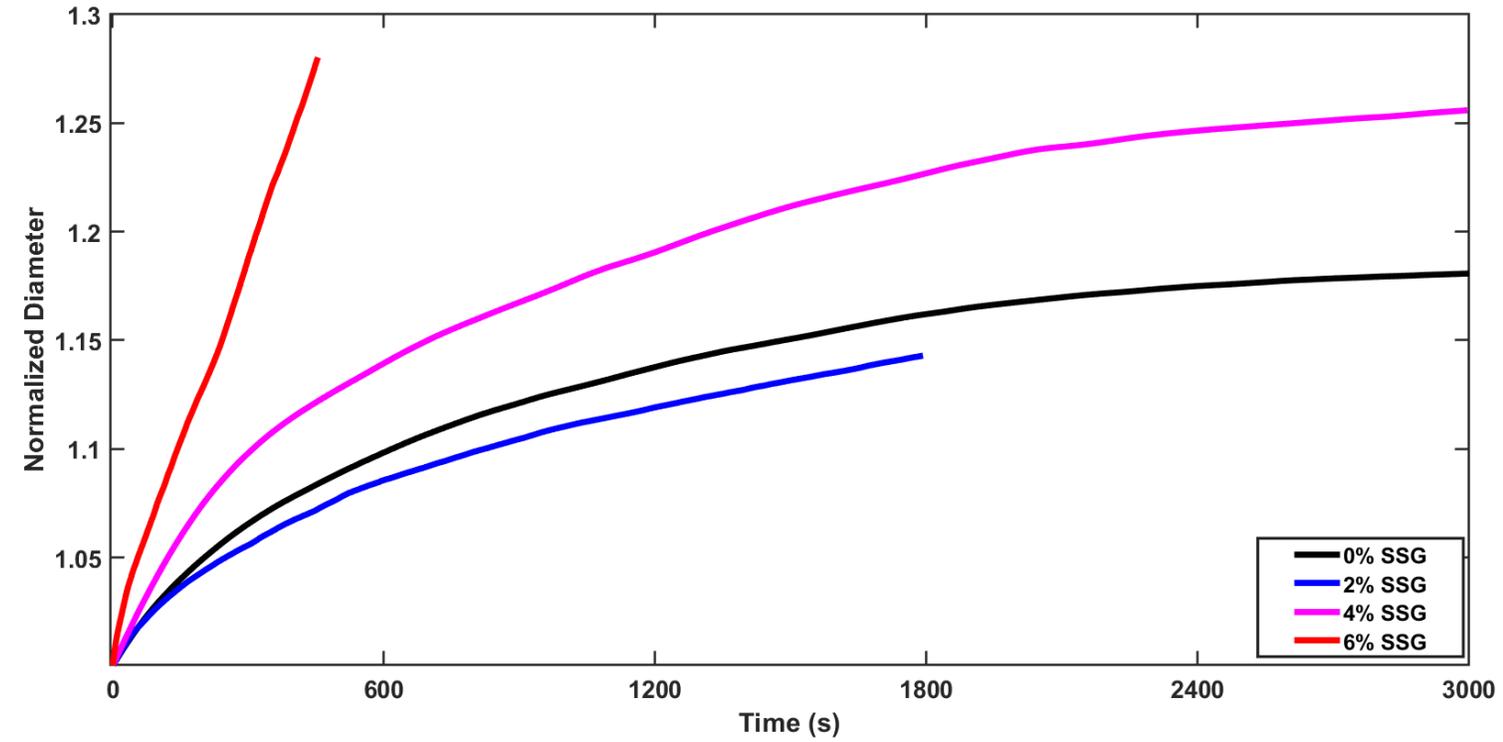


Flow cell

Peristaltic Pump

# Granule swelling characterisation – flow cell

- Granule Size = 1- 1.4 mm
- SSG = 0 % , L/S =1, HPMC Conc = 12.5%

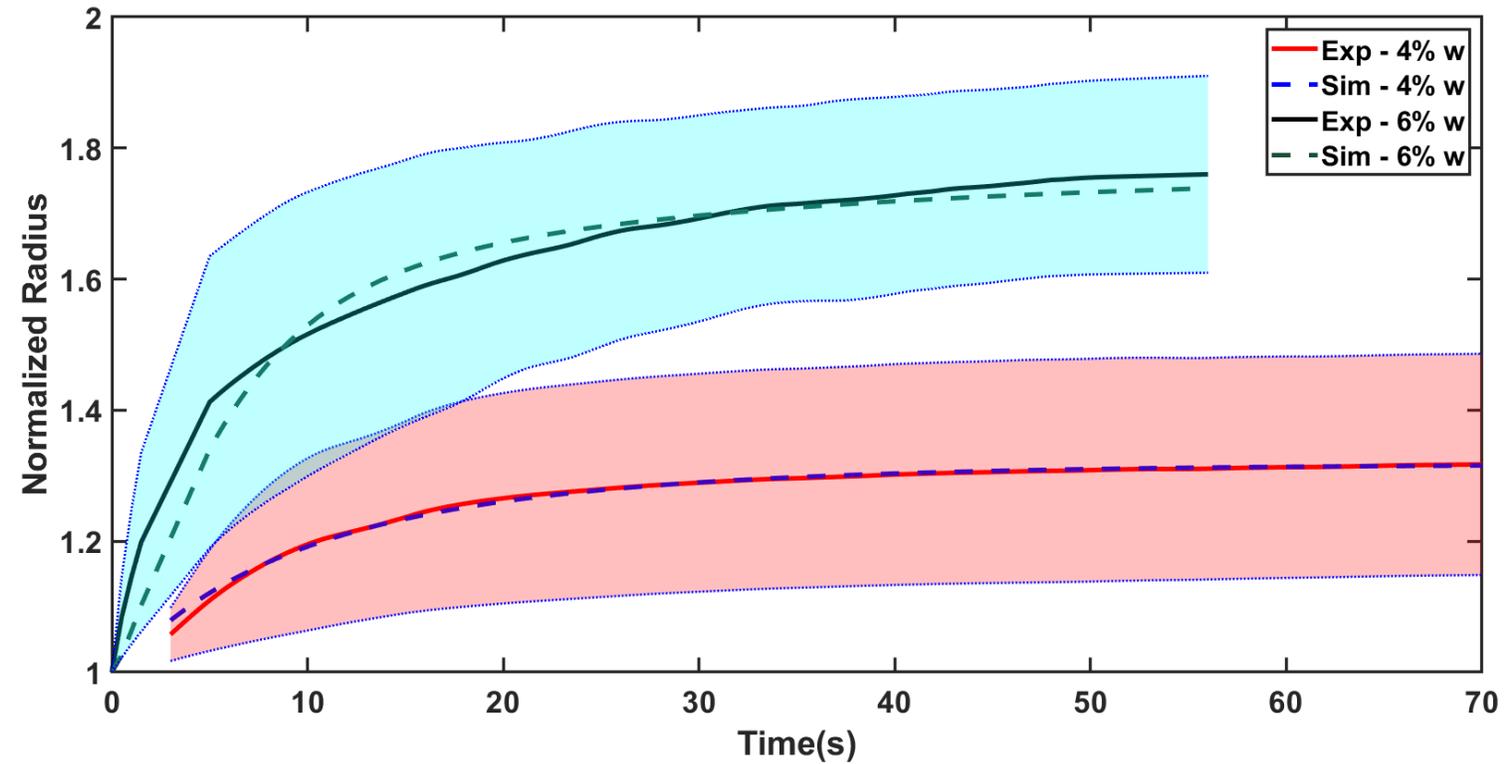


# Single granule swelling model

## Part 3: Validation

# Parameter Estimation and Validation

Excip	SSG	HPMC	$D_{dis}$	$D_{exc}$	$Q_{exp}$	$\Delta\epsilon_{\infty}$
DCPA	4%	12.5%	231	0	1	0.26
DCPA	6%	12.5%	231	0	1	0.33
MCC	0%	12.5%	-	0.38	1.36	0.04
MCC	4%	12.5%	1.2	0.38	1.36	0.05
MCC	6%	12.5%	8	0.38	1.36	0.07
MCC	0%	5%	-	0.31	1.21	0.05
MCC	2%	5%	0.8	0.31	1.21	0.06
MCC	4%	5%	15	0.31	1.21	0.09
MCC	6%	5%	44	0.31	1.21	0.1

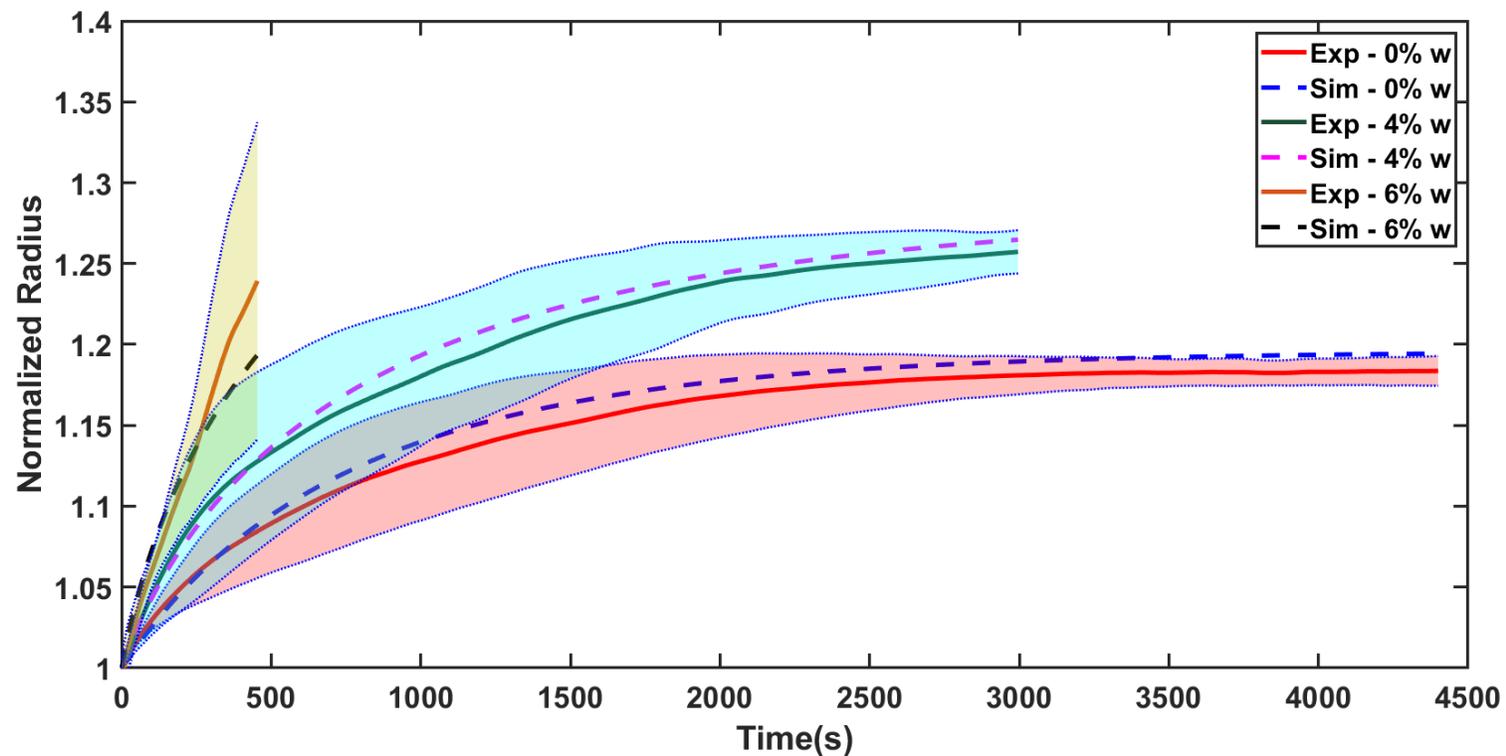


Swelling prediction of **DCPA** granules with **12.5%** concentration of binders

- No change to the diffusivity and maximum absorption ratio of the disintegrant due to lack of plasticization effect

## Parameter Estimation and Validation

Excip	SSG	HPMC	$D_{dis}$	$D_{exc}$	$Q_{exp}$	$\Delta\epsilon_{\infty}$
DCPA	4%	12.5%	231	0	1	0.26
DCPA	6%	12.5%	231	0	1	0.33
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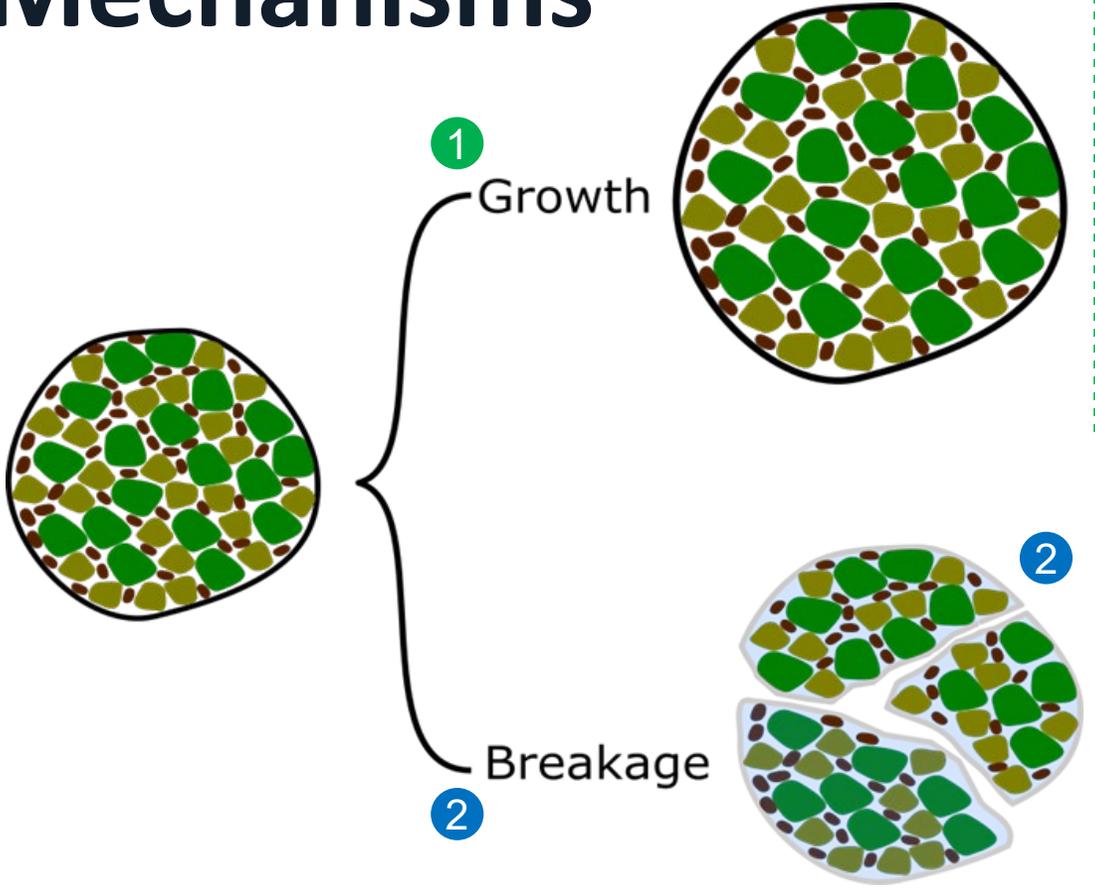
Swelling prediction of **MCC** granules with **12.5%** concentration of binders

- Decrease in reported values of diffusivity and maximum absorption ratio due to plasticization effect and pre-disintegration absorption
- Increase in diffusivity of SSG by increasing SSG content

# Population balance disintegration model

## Part 1: Modelling

# Mechanisms



1

$$G_R(R, t) = \frac{R}{3} \left( \frac{G_\varepsilon(R, t)}{1 - \varepsilon(R, t)} + \frac{\sum x_{n,i} G_{V_{p,i}}(R, t)}{\sum x_{n,i} V_{p,i}(R, t)} \right)$$

$$G_{V_{s,i}}(R, t) = n_p(R, t) x_{n,i} G_{V_{p,i}}(R, t)$$

$$G_{V_l}(R, t) = 2\pi \frac{\varepsilon(R, t) R^3}{\tau_{sat}(\varepsilon(R, t), R, \bar{R}_p(R, t))} \left( \frac{1 - \hat{S}_a(R, t)}{\hat{S}_a(R, t) + b} \right) - n_p(R, t) \sum x_{n,i} G_{V_{p,i}}(R, t)$$

2

$$\psi(R) = \frac{1}{\tau_b} \left( \frac{\sigma_{str}}{\sigma_c} \right)_n$$

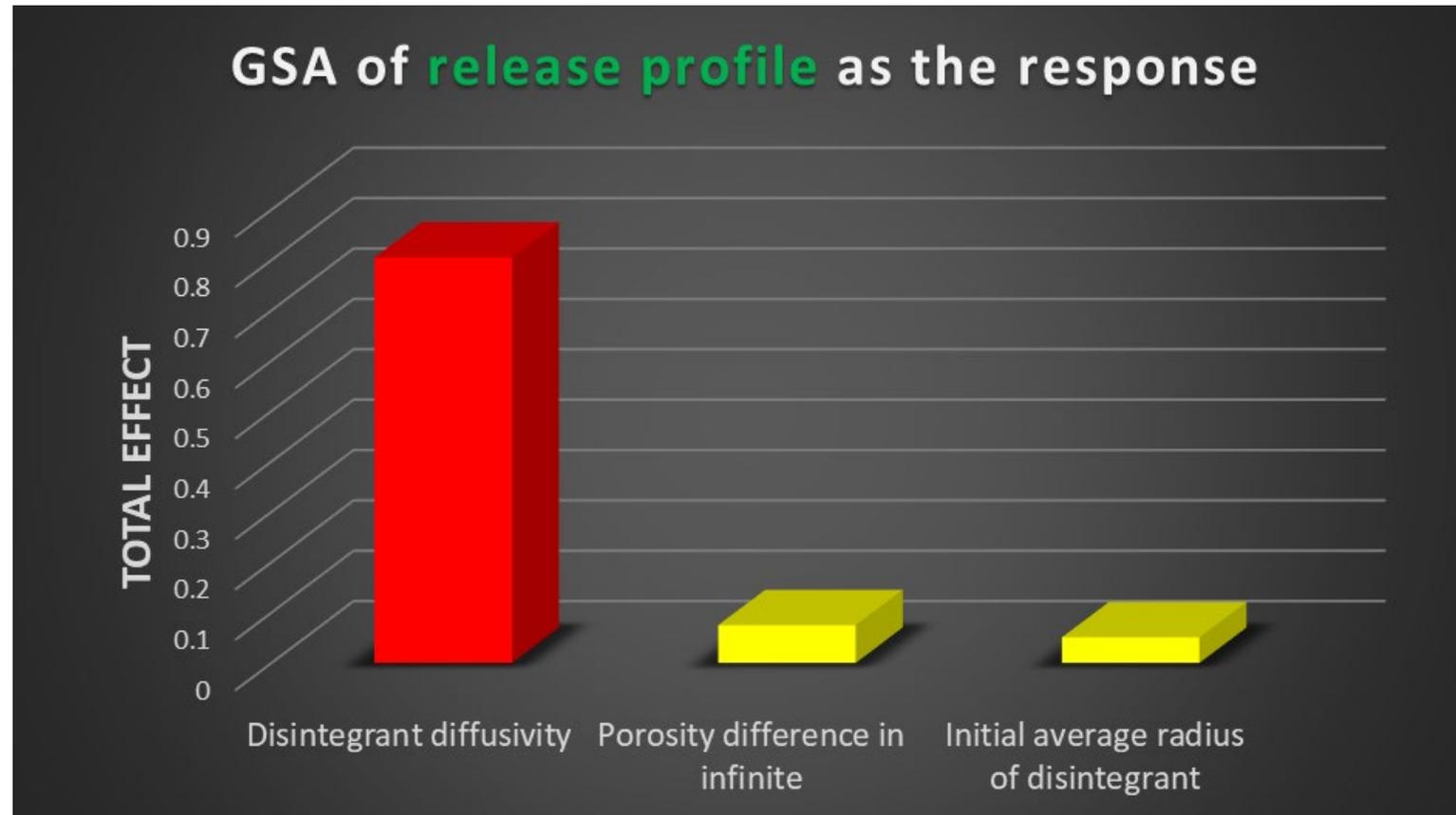
$$b_i(r|R) = n_p(R, t) x_{n,i} f_i(R, r, t)$$

Model implemented in Siemens PSE gPROMS

$t$ : time,  $R$ : granule radius,  $\varepsilon$ : porosity,  $\hat{S}_a$ : saturation,  $G_R$ : Growth term for size,  $G_{V_{s,i}}$ : Growth term for solid components,  $G_\varepsilon$ : Growth term for porosity,  $G_{V_l}$ : Growth term for liquid content,  $n_p$ : density function of swelling granules,  $G_{V_{p,i}}$ : Growth term for single particle of a component,  $x_{n,i}$ : number fraction of  $i^{th}$  component in the solid  
 $\psi$ : selection function,  $\tau_b$ : inherent breakage time,  $\sigma_{str}$ : swelling stress,  $b_i$ : breakage probability function of  $i^{th}$  component,  $f_i$ : number-based size distribution of original component

# GSA for population balance disintegration model

Factor : Release profile  $\left(1 - \frac{\int_{R_{min}}^{\infty} n_g(R,t)n_p(r,t)dR}{\int_{R_{min}}^{\infty} n_g(R,0)n_p(r,0)dR}\right)$



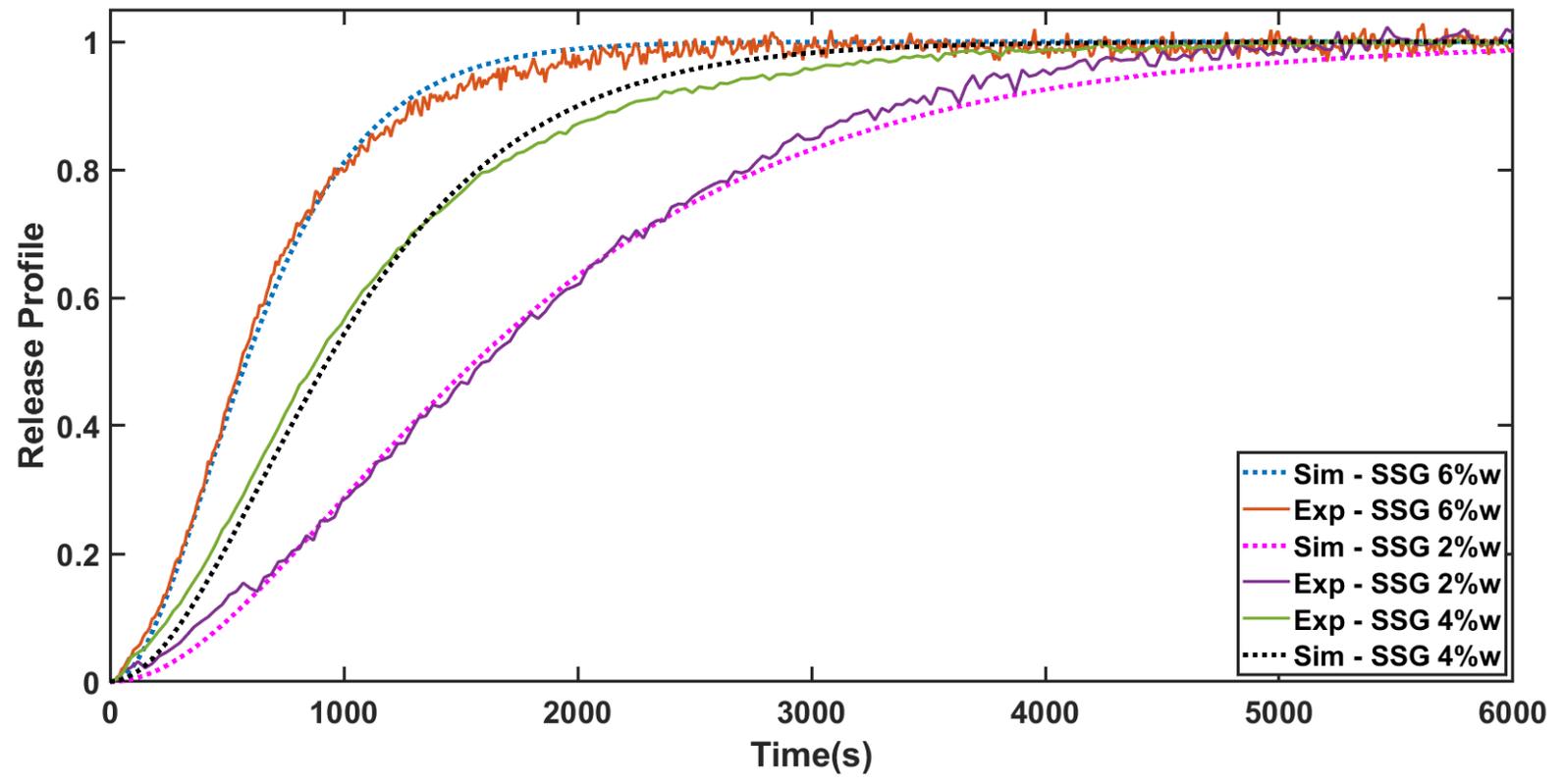
GSA from Siemens PSE gPROMS

# Population balance disintegration model

## Part 2: Validation

## Parameter estimation and validation

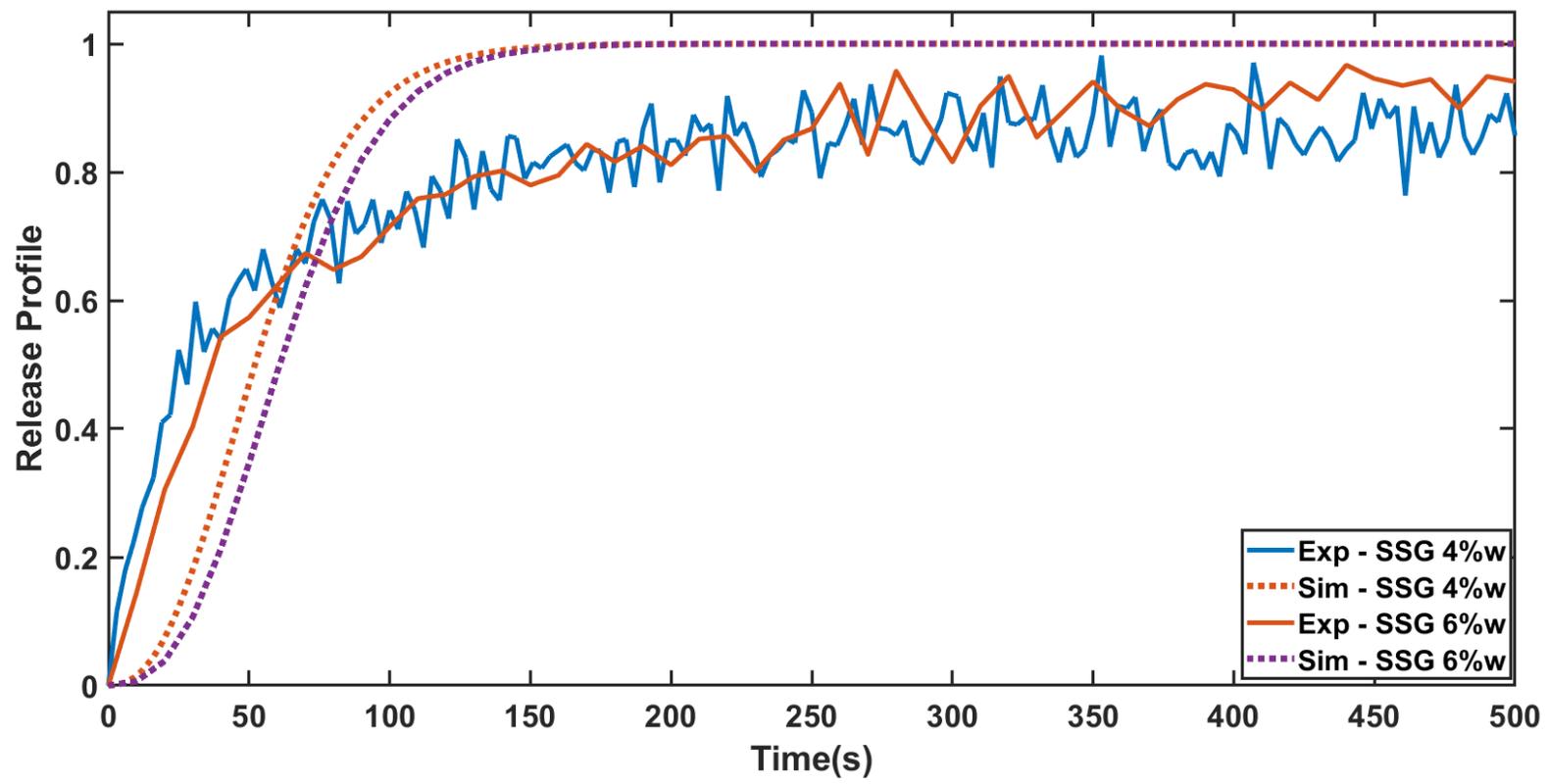
Excip	SSG	HPMC	$\tau_b$ (s)	$R^2$
DCPA	4%	12.5%	18	0.21
DCPA	6%	12.5%	18	0.67
MCC	0%	12.5%	—	—
MCC	2%	12.5%	1113	0.99
MCC	4%	12.5%	524	0.99
MCC	6%	12.5%	326	0.99
MCC	0%	5%	—	—
MCC	2%	5%	—	—
MCC	4%	5%	644	0.78
MCC	6%	5%	176	0.68



Release profile prediction of **MCC** granules with **%12.5** binder concentration

## Parameter estimation and validation

Excip	SSG	HPMC	$\tau_b$ (s)	$R^2$
DCPA	4%	12.5%	18	0.21
DCPA	6%	12.5%	18	0.67
MCC	0%	12.5%	—	—
MCC	2%	12.5%	1113	0.99
MCC	4%	12.5%	524	0.99
MCC	6%	12.5%	326	0.99
MCC	0%	5%	—	—
MCC	2%	5%	—	—
MCC	4%	5%	644	0.78
MCC	6%	5%	176	0.68



Release profile prediction of **DCPA** granules

## Summary

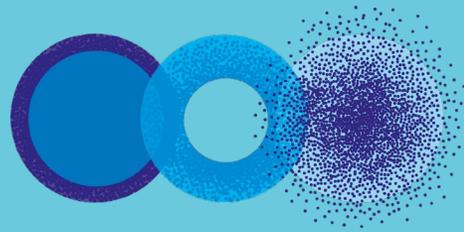
- A mechanistic model for swelling driven granule disintegration and dispersion has been developed and implemented.
- Developed novel experimental validation methods for model validation and parameterization, for both early-stage granule swelling, and bulk granule disintegration and dispersion.
- Demonstrated the ability of the model to predict granule swelling and the evolving granule disintegration.
- Detailed investigation of model sensitivity to parameters.

## Planned Further Work

- Develop a surrogate model for the Granule Disintegration Model.
- Validate and Parameterize the Population Balance Model for High Shear Wet Granulation.
- Link the wet granulation model with the granule disintegration model.
- Solve the inverse problem → specify process parameters to give desired granule disintegration characteristics.



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- **Bindhu Gururajan from Novartis**
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this project**

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