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

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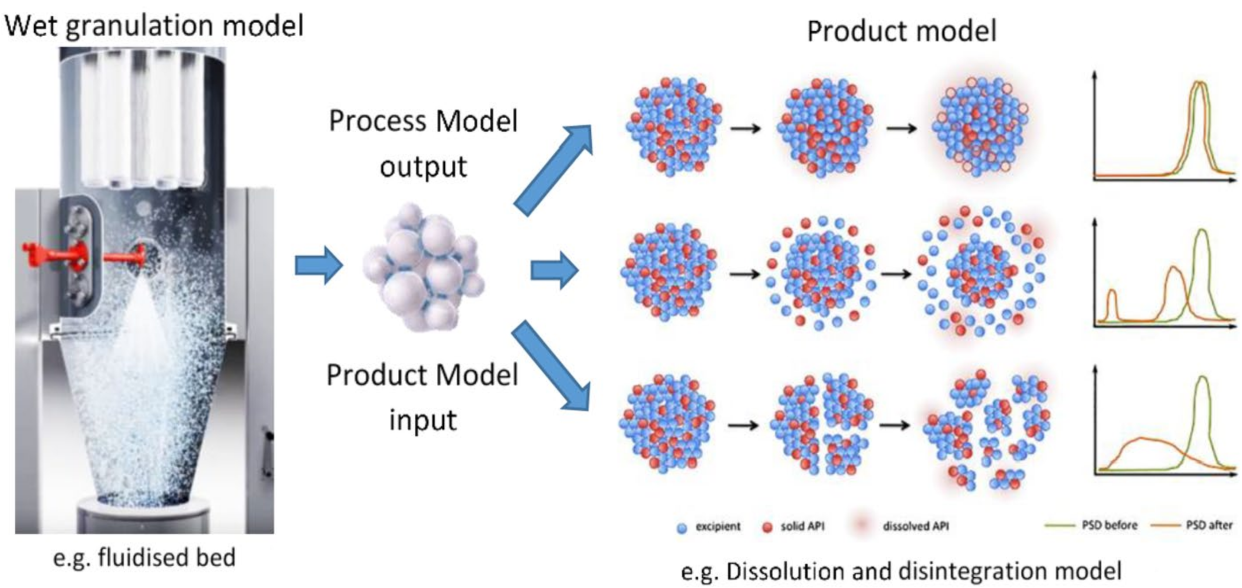
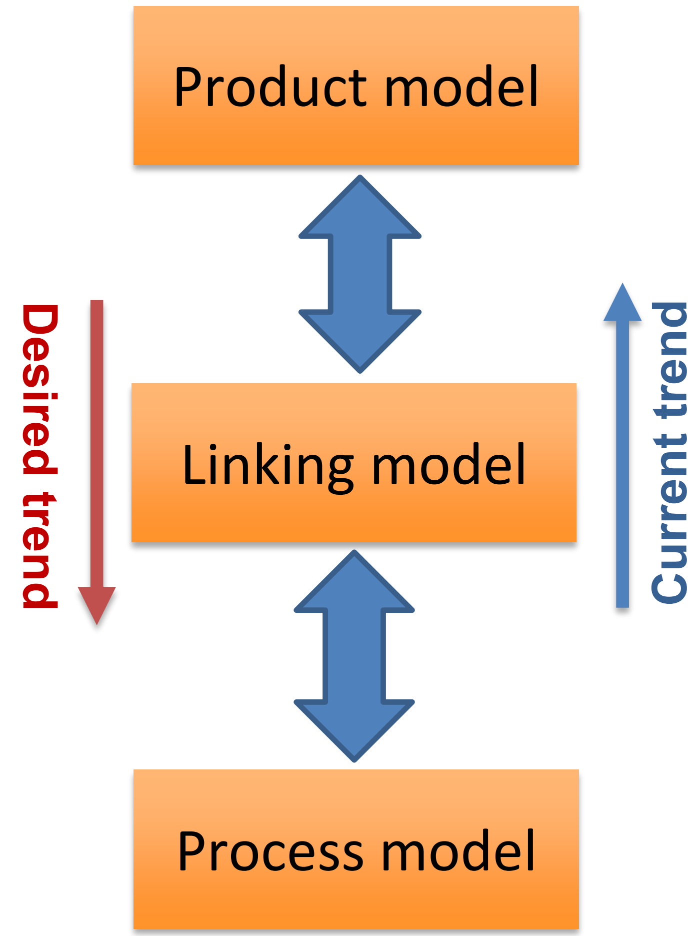
Project overview





GlattGroup, Glatt Top-Spray granulation process by fluidized bed. (2013)

D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

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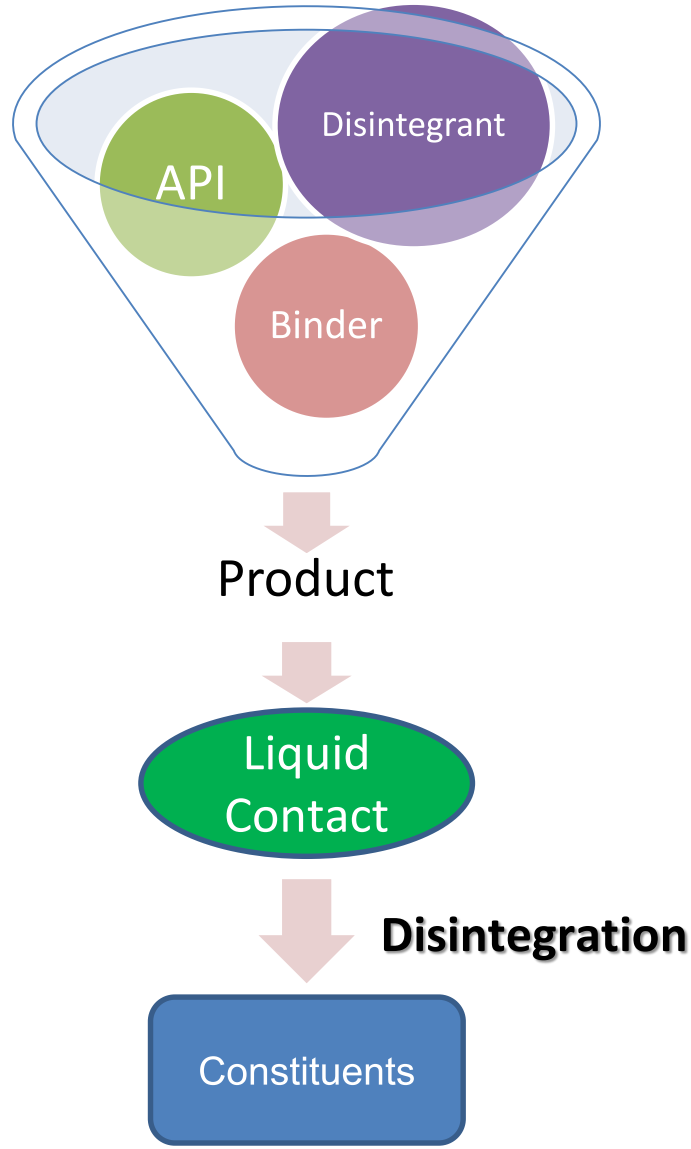
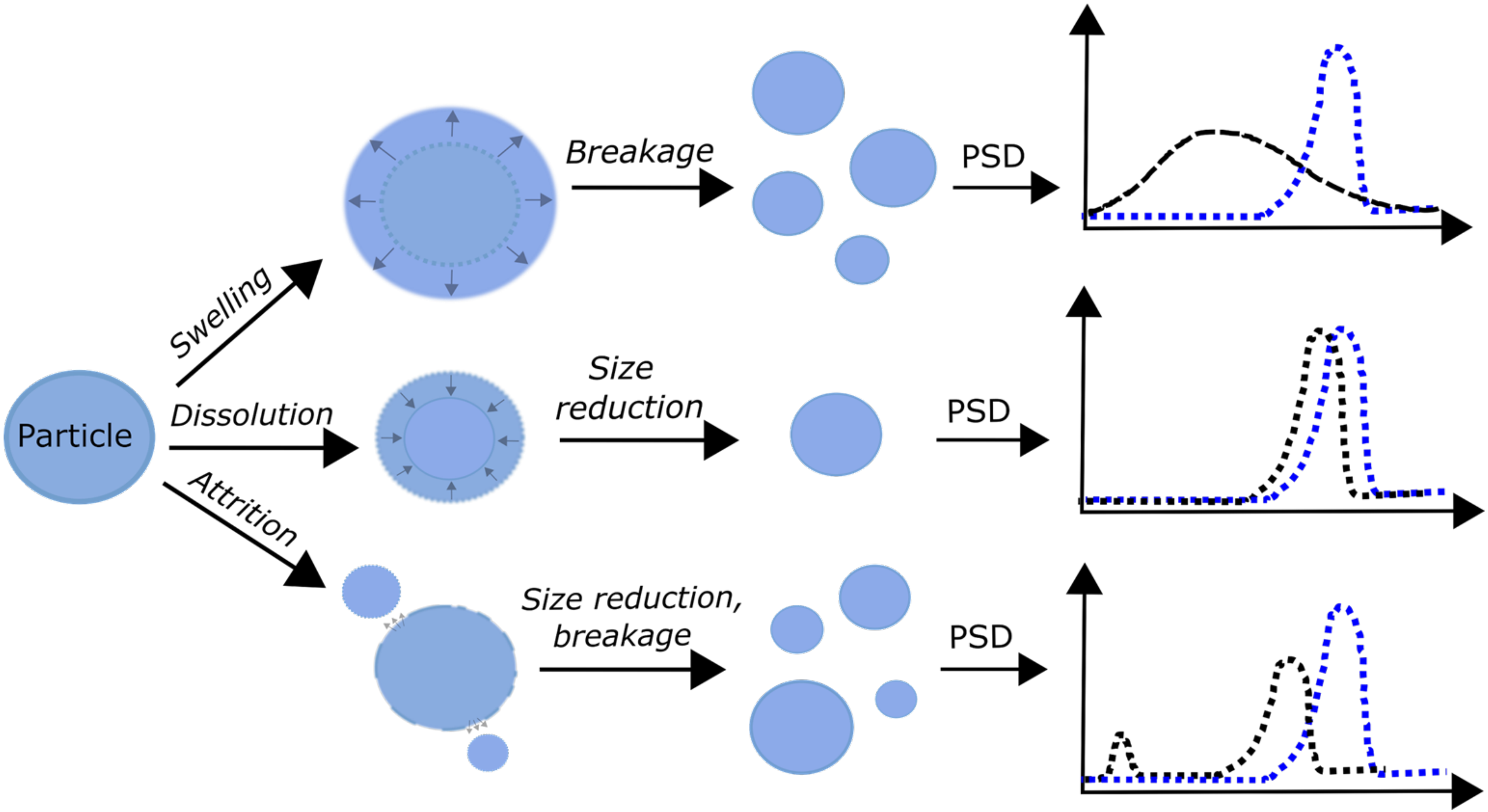
Granule components

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



Processes in disintegration



D. Smrčka, J. Dohnal, F. Štěpánek, European Journal of Pharmaceutics and Biopharmaceutics, 106 (2016)

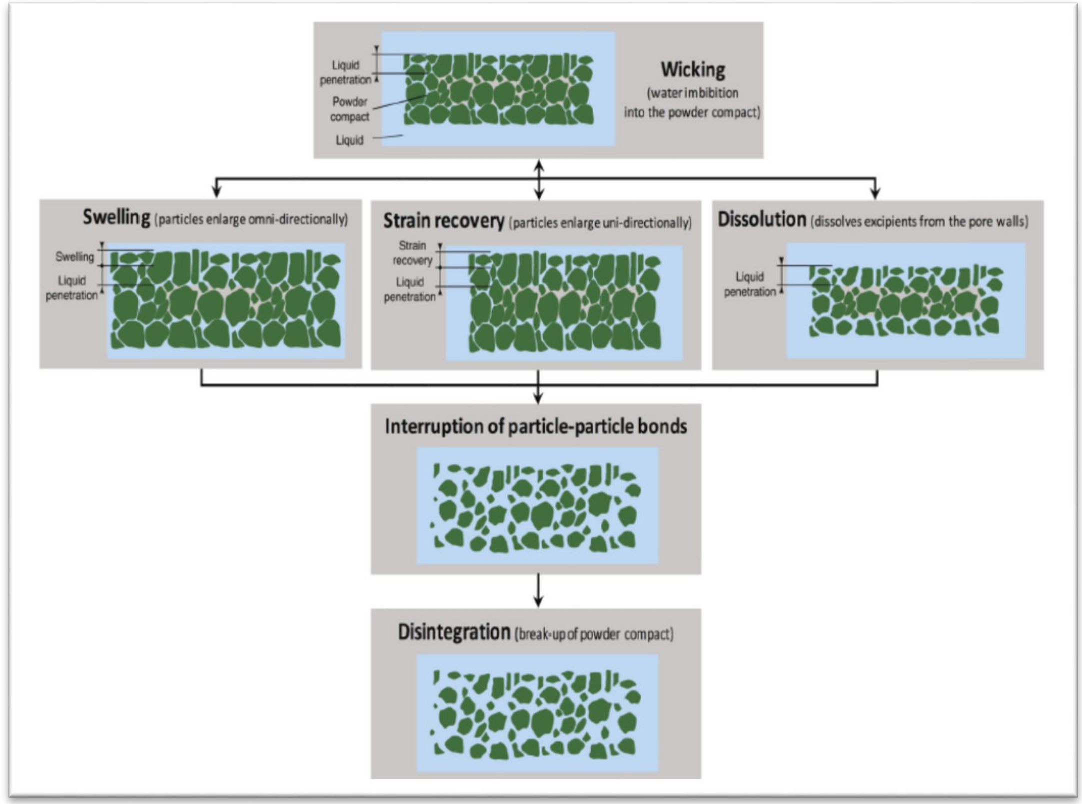
1. Liquid uptake:
   - i) Diffusion
   - ii) Capillary

2. Liquid absorbance or contact

3. Swelling, Strain recovery, Dissolution, Erosion (Degradation or Attrition)

4. Stress build-up

5. Breakage



D. Markl, J.A. Zeitler, Pharm. Res., 34 (2017).

Swelling

- Liquid penetration (Darcy's law):

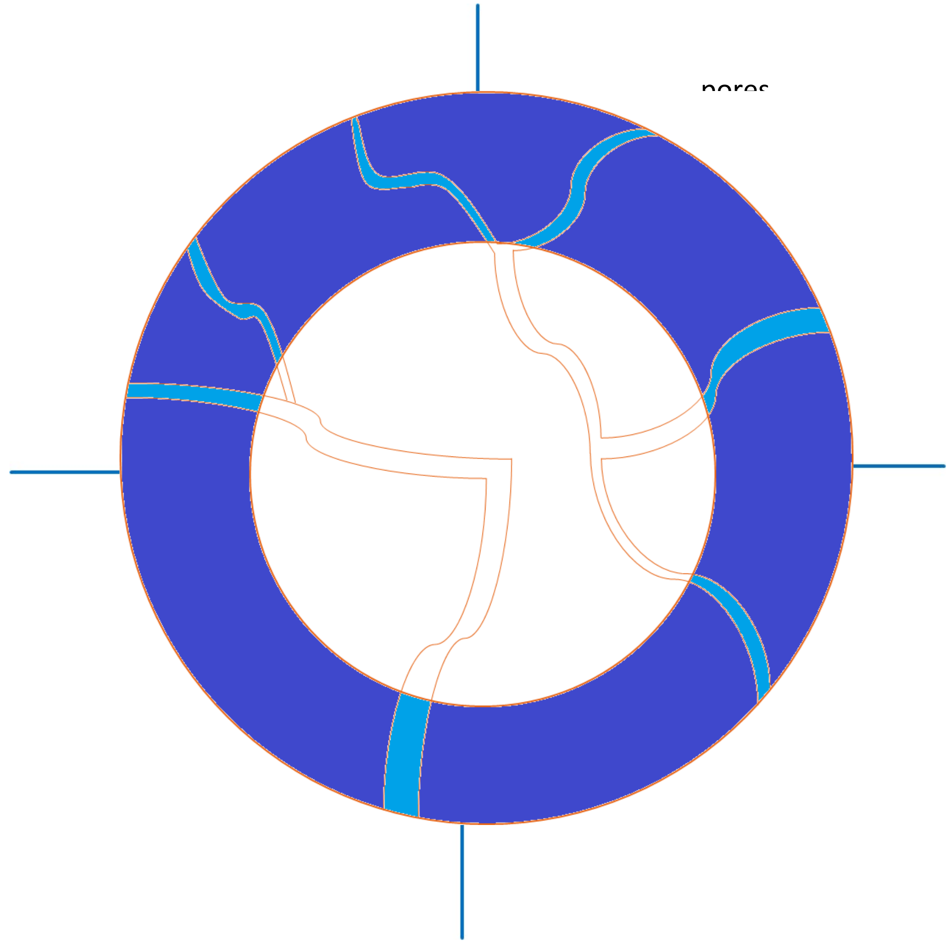
$$\varepsilon_l(\overrightarrow{v_l} - \overrightarrow{v_s}) = -\frac{k}{\eta}\nabla P$$

- Liquid absorbance-diffusion:

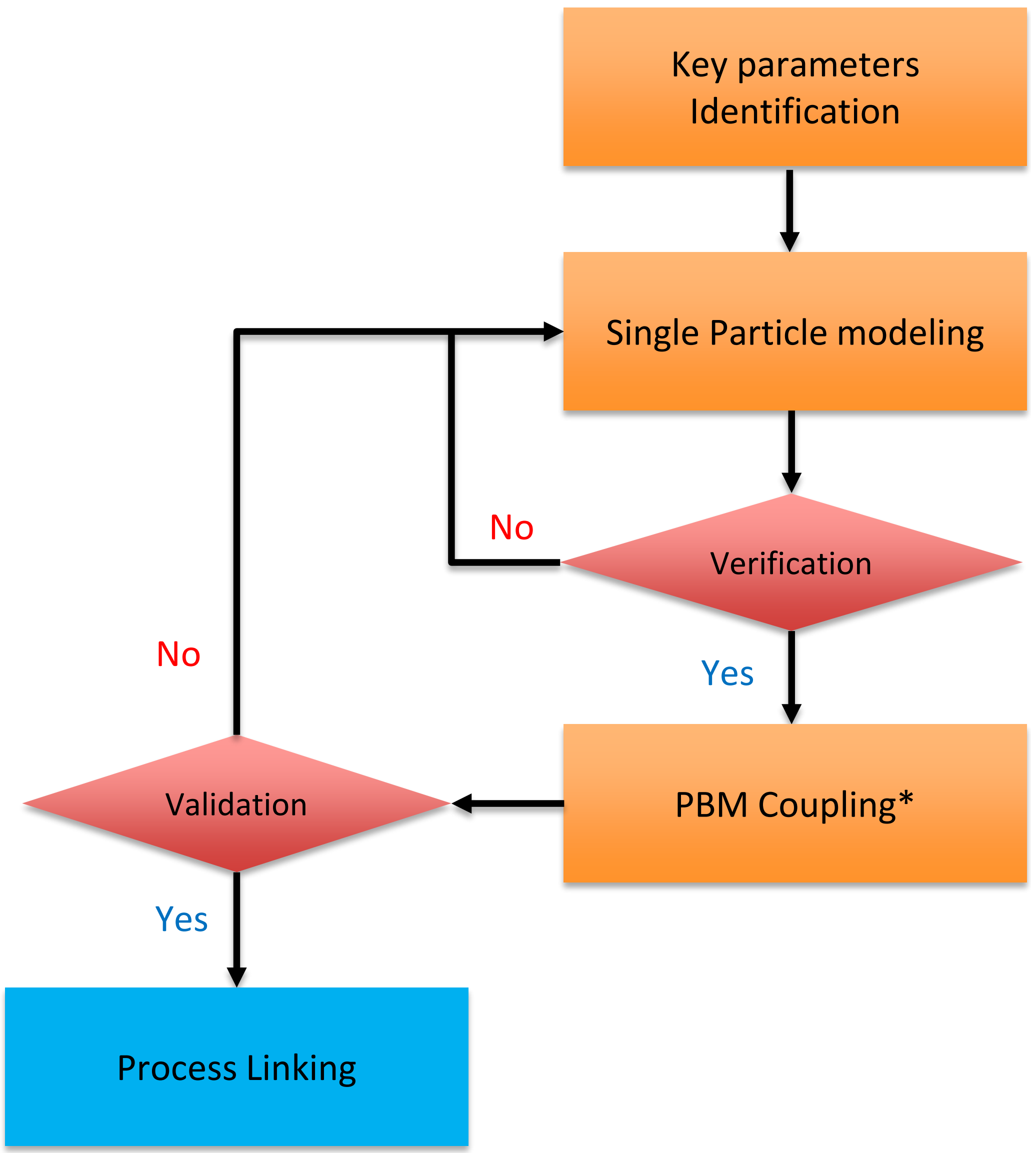
$$\frac{\partial \varepsilon_l}{\partial t} + \nabla.(\varepsilon_l \overrightarrow{v_l}) = -q$$

- Solid deformation (Equation of motion):

$$\nabla.\sigma = \nabla P$$



Product model design



Input

i. (Initial) Granule size
ii. (Initial) Primary particle size
iii. (Initial) Porosity
iv. (Initial) Saturation

Single Granule Model →

Output

i. Granule size
ii. Primary particle size
iii. Porosity
iv. Saturation
v. Internal stress

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Model assumptions

1. Granules and primary particles (disintegrants) are both **spherical**
2. The liquid penetration to the center of the granule (first step of liquid uptake) is **much faster** than the liquid absorbance.
3. The porosity and saturation is **uniform** through out the granule and is a function of time and granule size
4. The solid acts like a **semi-linear elastic body** with displacement only in **radial direction**
5. Stress build-up and tensile strength is **uniform** through out the granule and is a function of time and granule size
6. The PBM considers only **growth** and **breakage disintegration** mechanisms

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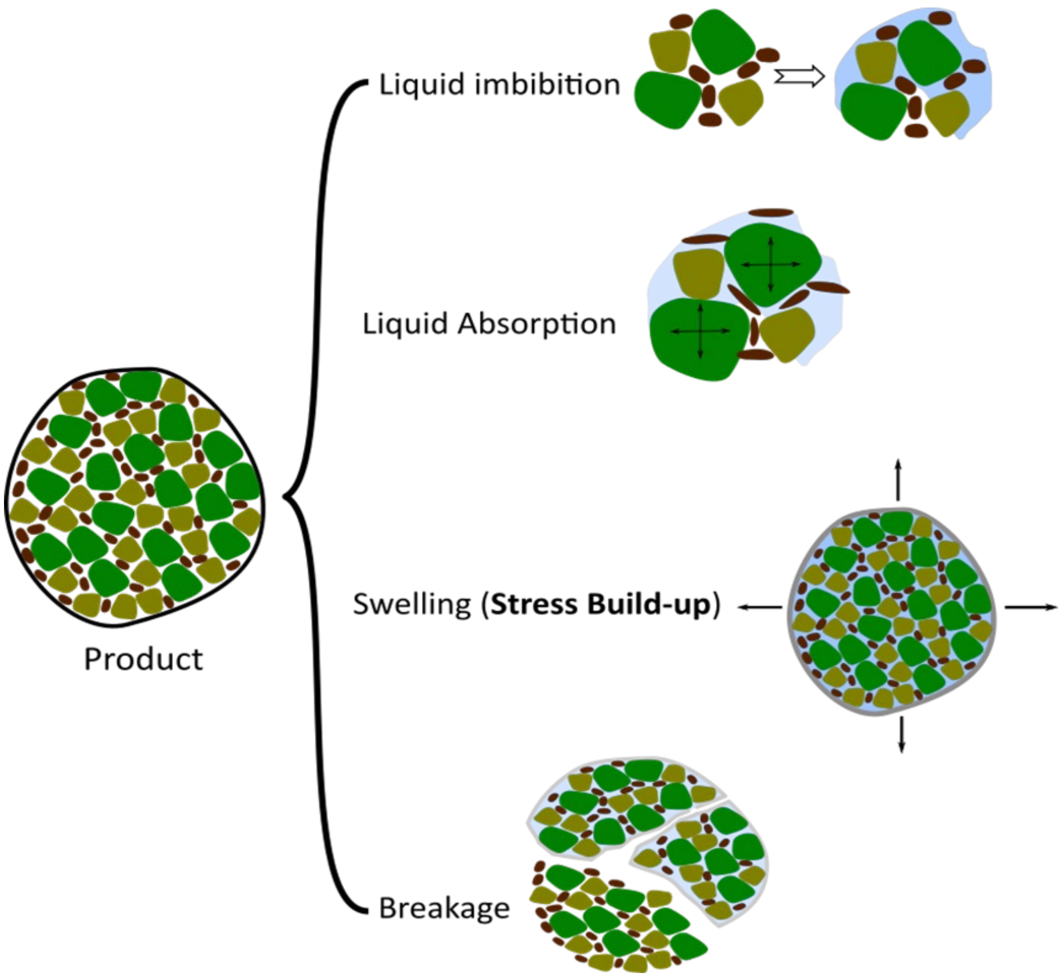
Single granule model



$$G_{V_l} = 4\pi R^2 \frac{k_{per}}{\eta} \frac{\partial P_c}{\partial r}\bigg|_{r\to R} - V(1-\varepsilon)G^*_{R_p}$$

$$G_{V_s} = V(1-\varepsilon)G^*_{R_p}$$

$$G_{V_{ini}} \approx -\left(\frac{\partial V}{\partial t}\right)_{V_{ini}} \left(\frac{\partial V_{ini}}{\partial V}\right)_t \approx -G_V\left(\frac{\partial V_{ini}}{\partial V}\right)_t$$

$$G_{n_p} = 0$$

$$\bar{\sigma}_{rr} > \sigma_c$$

G_{V_l}: liquid volume growth rate, R: granule radius, k_{per}: permeability, η: liquid viscosity, P_c: capillary pressure, V: granule volume
ε: porosity, $G^*_{R_p}$: logarithmic liquid absorbance rate, G_{V_s}: solid volume growth rate, V_{ini}: volume of granules at zero stress state
$G_{V_{ini}}$: growth rate of volume of granule at zero stress state, t: time, G_V: granule growth rate, $\bar{\sigma}_{rr}$: radial internal stress, σ_c: tensile strength,
G_{n_p}: growth rate of number of primary particles per granule

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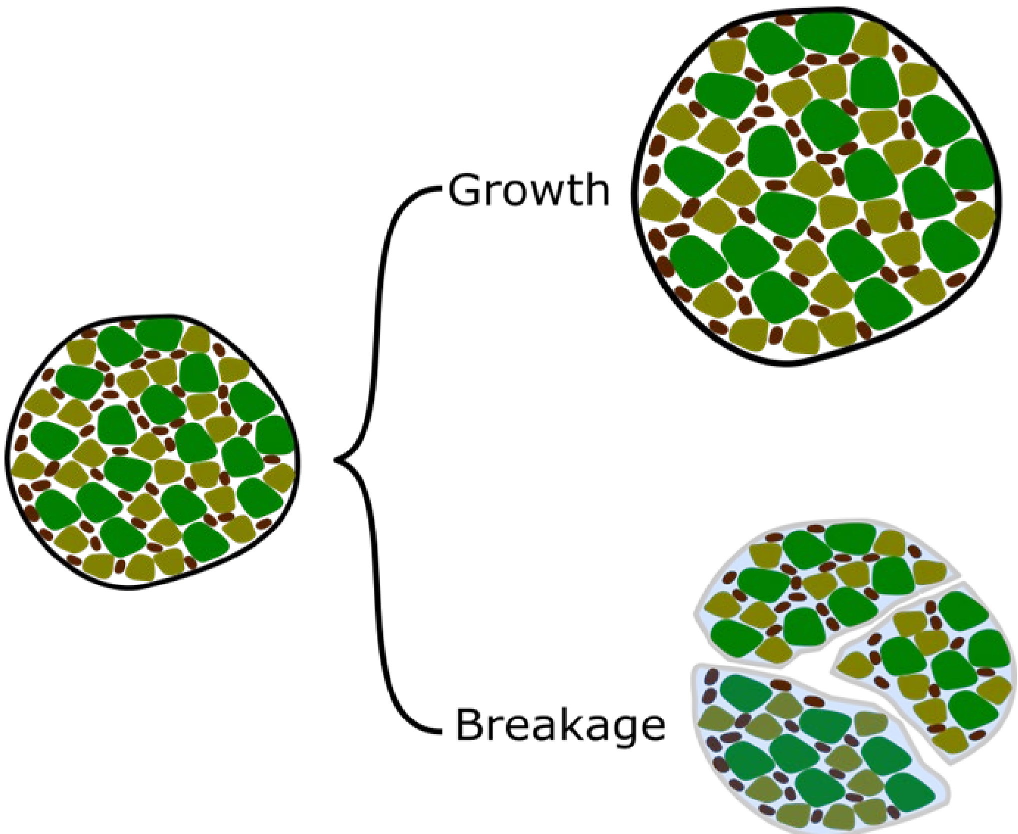
Population balance model



$$G_V = \frac{dV}{dt} = V(G^*_{R_p} - \frac{G_\varepsilon}{1-\varepsilon})$$

$$S(V,t) = K_b \left(\frac{\bar{\sigma}_{rr}}{\sigma_c} - 1\right)^{n_b} H(\bar{\sigma}_{rr} - \sigma_c)$$

$$b(V|U) = \frac{p}{U} \frac{\Gamma\big((c+1)p\big)}{\Gamma(c+1)\Gamma\big((c+1)(p-1)\big)} (1 - \frac{V}{U})^{(c+1)(p-1)-1} (\frac{V}{U})^c$$

V, U: granule volume, t: time, G_V: granule growth rate, $G^*_{R_p}$: logarithmic liquid absorbance rate, ε: porosity

G_ε: porosity growth rate, S: selection function, $\bar{\sigma}_{rr}$: radial internal stress, σ_c: tensile strength, H: step function

K_b, n_b: selection function parameters, b: probability distribution function, p, c: probability distribution function parameters

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PBM framework

Variables:

Main:
Granule volume V

Lumped ($\boldsymbol{M}$):

- Granule porosity ε
- Granule saturation s
- Number of disintegrant particle in the granule n_p
- Volume of granule at zero stress state V_{ini}

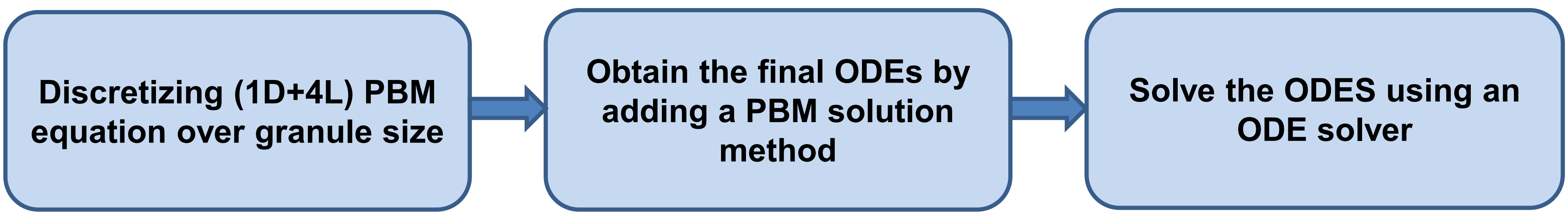
$$\frac{\partial n(V,\boldsymbol{M},t)}{\partial t} = -\frac{\partial}{\partial V}\left(G_v n(V,\boldsymbol{M},t)\right) - S(V,\boldsymbol{M},t)n(V,\boldsymbol{M},t) + \int_V^{V_{max}} S(U,\boldsymbol{M},t)b(V|U)\,n(U,\boldsymbol{M},t)dU$$

n: number density function, t: time, G_V: Growth term related to the size, S: selection function, b: probability distribution function

PBM solution methodology

Solution method:

1. Obtain the equations which relate the lumped parameters to the granule size[1]
2. Discretise the granule size range, and express the differential equations (PDEs) as a set of ordinary differential equations (ODEs) based on the method described by Hounslow et al 2001[1]
3. Solve the set of ODEs using a robust ODE solver (e.g. Backward differentiation Formula (BDF))

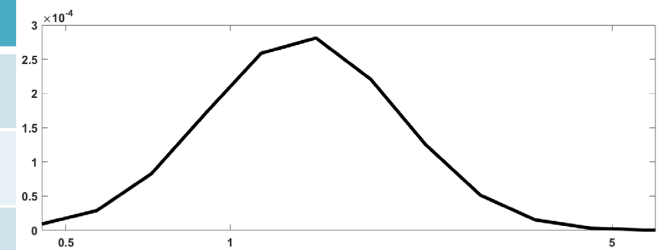


[1]: Hounslow, M. J., J. M. K. Pearson, and T. Instone. 'Tracer Studies of High-Shear Granulation: II. Population Balance Modeling'. AIChE Journal 47, no. 9 (2001): 1984–99

Product Performance Model: Simulation Results

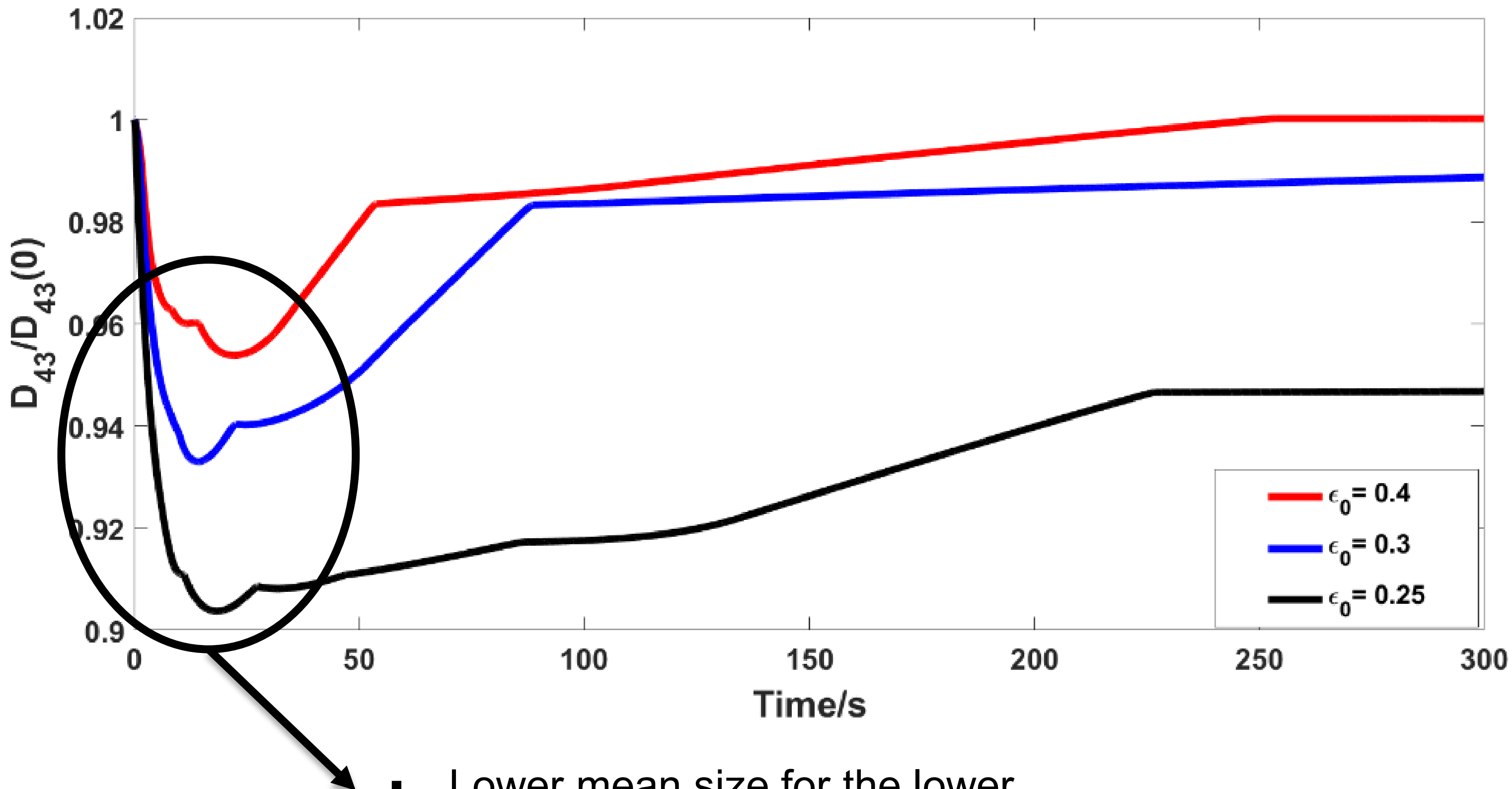
Model parameters

Parameter	Value	Unit	Definition
$d_{4,3}(0)$	$1-4$	mm	Mean size of the granules
σ_{dev}	0.4	$-$	Standard deviation
D	5×10^{-1}	m^2/s	Diffusivity
Q_{max}	$5-15$	g/g	Maximum absorption ratio
ρ_l	1000	kg/m^3	Fluid density
ρ_s	1400	kg/m^3	Dry disintegrant (primary) particles density
ε_0	$0.3-0.9$	$-$	Initial porosity
$R_{p,0}$	$25-50$	μm	Initial primary particle radius
s_0	0.02	$-$	Initial saturation
s_{thr}	0.1	$-$	Threshold saturation
E_0	5×10^4	Pa	Young modulus at zero porosity



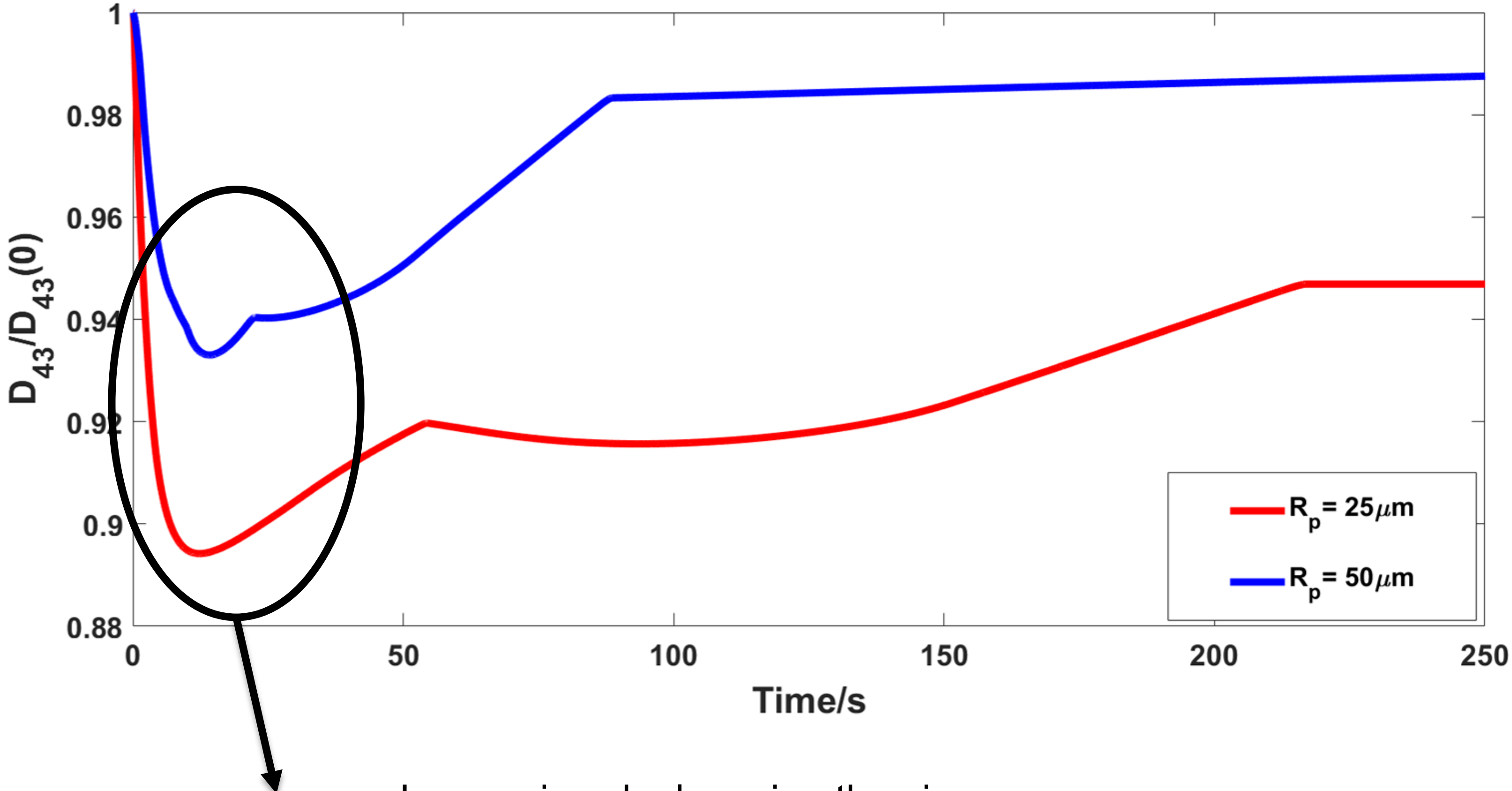
Log-normal initial distribution

Effect of initial porosity on granule size distribution



- Lower mean size for the lower porosity (higher stress experienced)
- Different humps are due to different disintegration time of granules

Effect of dry disintegrant size on granule size distribution



- Lower sizes by lowering the size of dry disintegrant size (higher liquid absorbance rate leading to a higher growth rate hence faster swelling)

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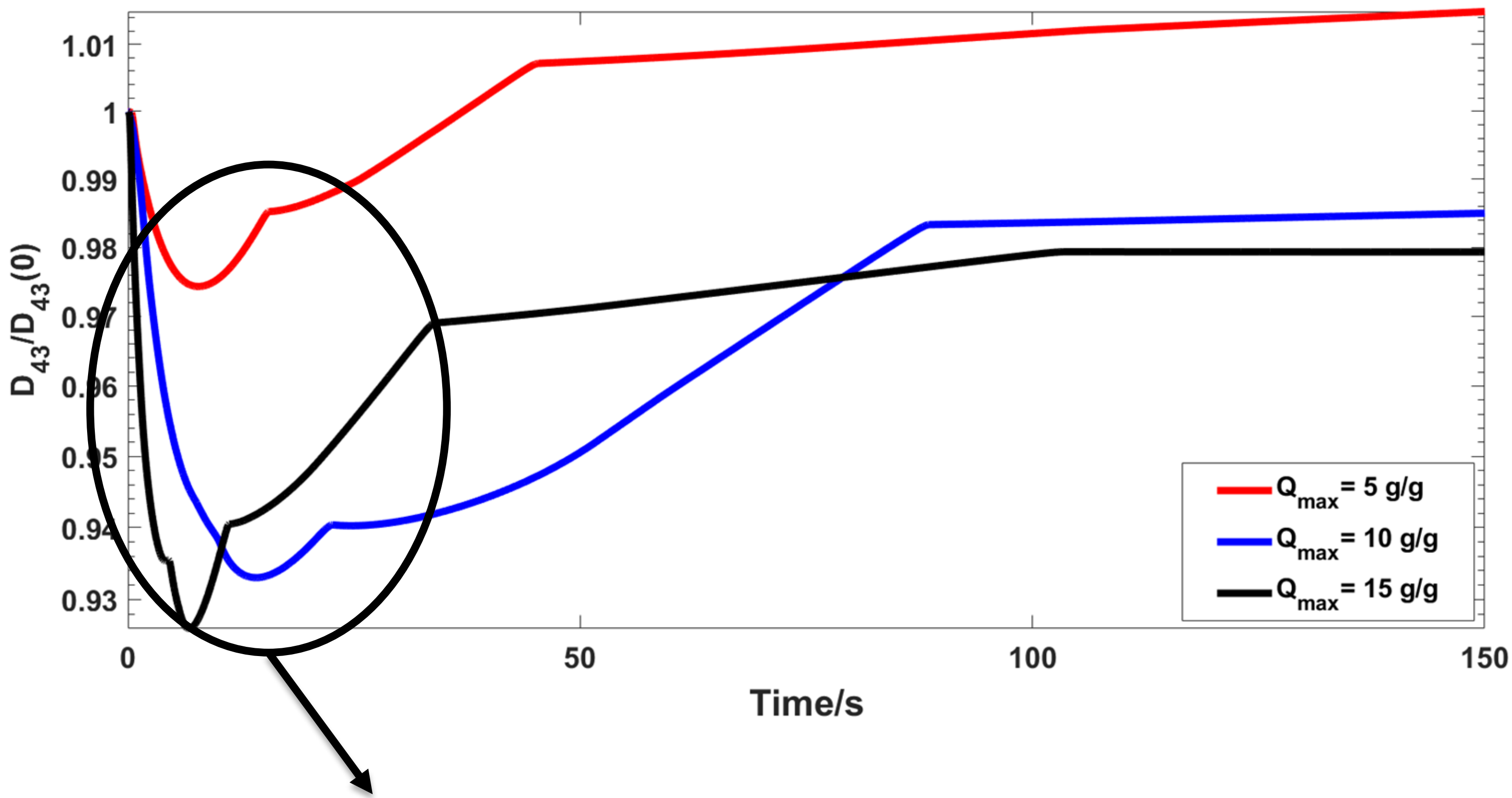
Effect of maximum absorption ratio on granule size distribution



- Lower granule mean size for a higher maximum absorption ratio due to a higher liquid absorbance

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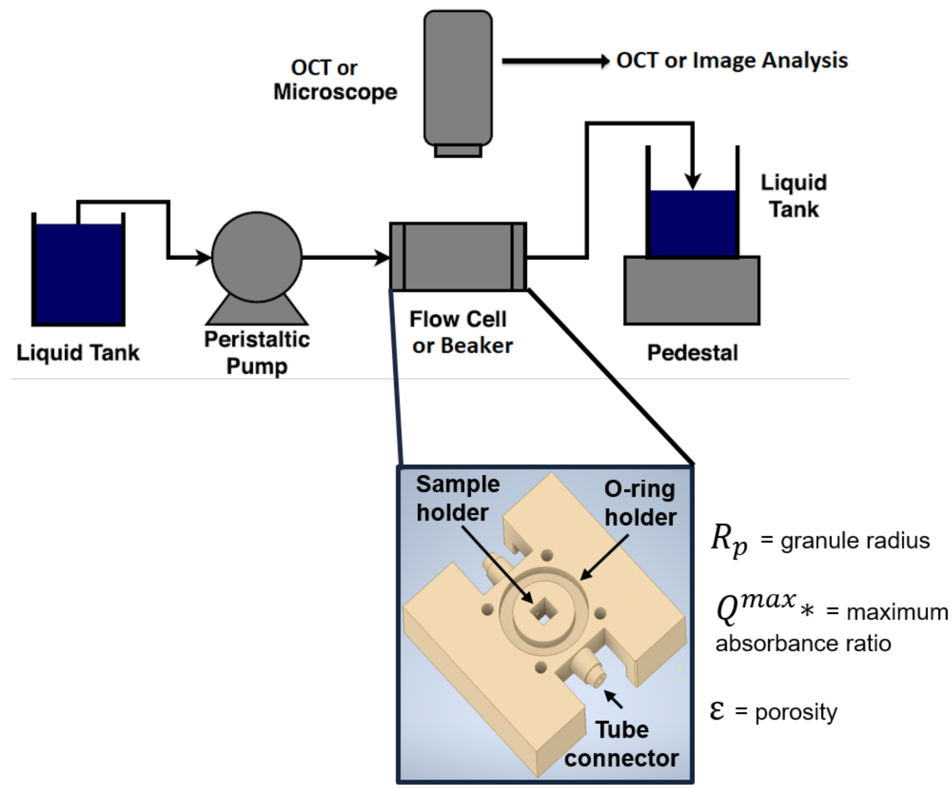
Experimental planning for validation

Parameter	Definition	Techniques	Model
D	Liquid diffusivity	Flow Cell + Optical Microscopy designed by [7]	Diffusion model
Q_{max}	Maximum absorption ratio		
E_o	Young's modulus at zero porosity	Nano-Indentation Technique [8]	Constitutive law
$[E]$	Intrinsic tensile modulus		
ν	Poisson's ratio		
σ_c	Strength of the binder	The setup designed by [9]	Strength model
p	Average number of smaller granules created from a granule	Optical Microscopy	Population balance model



→ Collaboration with Dr Daniel Markl group (University of Strathclyde, UK) for real-time granule disintegration monitoring using process analytical technology

University of Strathclyde Glasgow

The Markl Group
Pharmaceutical Manufacturing, Process Analytics and Digital Product Design

1. Soundaranathan, et al. Int. J. Pharm. 590 (2020)

Summary

1. Development of a new mechanistic population balance model for the disintegration of granules

2. Five key steps considered: capillary induced liquid penetration, non-linear Fickian liquid absorbance model, non-linear swelling model, stress build-up and breakage

3. Two coupled models to describe the processes occurring within a single granule and population of granules

4. Parameter sensitivity analysis was undertaken on the influence of the initial means radius of the granule, initial disintegrant particles radius, initial porosity and maximum absorption ratio

Next steps

1. Perform a global sensitivity analysis on the model (2-3 months)
2. Validate the product model (3-5 months)
3. Modify the existing process model (high shear granulation) (5-6 months)
4. Link the pre-product variables in the product model to post-process variables (5-6 months)
5. Perform a global sensitivity analysis and validation from the pre-process step to post-product one (12-18 months)
6. Solve the inverse problem, i.e. optimize processing parameters based on chosen post-product performance (12-18 months)

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I look forward to your questions ☺

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Appendix

Liquid absorbance model (single granule model)

Diffusion model:
The liquid absorbance of disintegrants is a non-Fickian Diffusion with constant diffusivity containing a parameter known as maximum absorption ratio

$$G^*_{R_p} = 3\frac{G_{R_p}}{R_p} = \frac{\rho_s}{\rho_l}\frac{D}{R_p^2}\left(\frac{s - s_{thr}}{s_{max} - s_{thr}}\right)^{\lambda}\left(\frac{Q_{max}}{Q(R_p)} - 1\right), Q(R_p) = \frac{\rho_l}{\rho_s}\left(\frac{{R_p}^3}{{R_{p,0}}^3} - 1\right)^3 + 1, s > s_{thr}$$

$$G_{V_s} = V(1-\varepsilon)G^*_{R_p}$$

$$V(1-\varepsilon) = n_p V_p$$

Conditions: $\begin{cases} R_p(t=0,R) = R_{p,0} \\ \varepsilon(t=0,R) = \varepsilon_0 \end{cases}$

t: time, R: size, R_p: primary particle's radius, $R_{p,0}$: initial primary particle's radius, D: diffusivity, Q: absorption ratio
Q_{max}: maximum absorption ratio, s : saturation, λ: exponent, s_{thr}, s_{max}: threshold and maximum saturation

Liquid uptake

Brooks-Corey model for the relationship between capillary pressure and saturation [3,4]

$$P_c = \frac{\kappa_g \gamma}{R_p} \sqrt[3]{\frac{1-\varepsilon}{\varepsilon}} \left(\frac{s - s_r}{s_{max} - s_r}\right)^{-M}$$

Modified Carman-Kozney equation to include the impact of saturation [3,5]

$$k_{per} = c_K \zeta^2 \frac{\varepsilon^3}{(1-\varepsilon)^2} R_p^2 \left(\frac{s - s_r}{s_{max} - s_r}\right)^{\beta}$$

P_c: capillary pressure, κ_g: geometric constant, γ: surface tension, s:normalized saturation, ε: porosity
s_{max}, s_r: maximum and residual saturation, M, β: exponents, c_K: constant, ζ: tortuosity, R_p: primary particle radius

Liquid uptake

Saturation model:
In this model, it is assumed the saturation is uniform through the granule but changes with time and size, The changes are due to liquid absorbance and liquid uptake at the surface of the granule.

$$G_{V_l} = 4\pi R^2 \frac{k_{per}}{\eta} \frac{\partial P_c}{\partial r}\bigg|_{r\to R} - V(1-\varepsilon)G^*_{R_p}$$

$$\frac{k_{per}}{\eta} \frac{\partial P_l}{\partial r}\bigg|_{r\to R} = \frac{a_{cap}}{R}\left(\frac{k_{per}}{\eta}\frac{\partial P_c}{\partial s}\right)(s_{max} - s)$$

Conditions: $s(t=0,R) = s_0$

R: granule radius, V: granule volume, ε: porosity, k_{per}: permeability, η: fluid viscosity, P_c: capillary pressure
a_{cap}: a constant parameter, s: saturation, s_{max}, s_0: maximum and initial saturation

Model for the growth term of the volume of granule at zero stress V_{ini} and the number of primary particle for a granule n_p

$$G_{V_{ini}} \approx -\left(\frac{\partial V}{\partial t}\right)_{V_{ini}} \left(\frac{\partial V_{ini}}{\partial V}\right)_t \approx -G_V \left(\frac{\partial V_{ini}}{\partial V}\right)_t$$

$$\left(\frac{\partial V_{ini}}{\partial V}\right)_t = K_{ini} V (\alpha_{ini} V - V_{ini})$$

$$G_{n_p} = 0$$

$$\text{Conditions:} \begin{cases} V_{ini}(t=0,R) = V \\ n_p(t=0,R) = V(1-\varepsilon_0)/V_{p,0} \end{cases}$$

Solid body constitutive law

Assumption: The solid acts likes a **semi-linear elastic body** [6]

Stress

$$\begin{cases} \bar{\sigma}_{rr} = E_0(1-\varepsilon)^{-[E]}\left(1-\sqrt[3]{\frac{V_{ini}(t,R)}{V}}\right)/(1-2v(\varepsilon)) \\ v(\varepsilon) = v_0 - \alpha_v^{\varepsilon}\varepsilon \end{cases}$$

Tensile strength

$$\begin{cases} F_{tot} = F_{waal} + F_{cap} + F_{bind} \\ \sigma_c = \frac{9}{32}\left(\frac{1-\varepsilon}{\varepsilon}\right)\frac{F_{tot}}{R_p^2} \end{cases}$$

E_0: Young modulus at zero porosity, ν: Poisson's ratio, ε: porosity, $[E]$: intrinsic modulus, α_v^{ε}: proportionality constant
v_0: Poisson's ratio at zero porosity, V_{ini}: volume of the granule at zero stress, $\bar{\sigma}_{rr}$: uniform radial stress in the granule
σ_c: tensile strength, $F_{tot}, F_{waal}, F_{cap}, F_{bind}$: total, van der Waals, capillary, binder forces respectively

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Breakage mechanisms

$$S(V,t) = K_b\left(\frac{\bar{\sigma}_{rr}}{\sigma_c} - 1\right)^{n_b} H(\bar{\sigma}_{rr} - \sigma_c)$$

$$b\left(V = \frac{4}{3}\pi R^3 \middle| U = \frac{4}{3}\pi R_m^3\right) = \frac{p}{U}\frac{\Gamma\big((c+1)p\big)}{\Gamma(c+1)\Gamma\big((c+1)(p-1)\big)}(1 - \frac{V}{U})^{(c+1)(p-1)-1}(\frac{V}{U})^c$$

S: selection function, $\bar{\sigma}_{rr}$: granule radial stress, H: step function, K_b, n_b: selection function parameters, σ_c: tensile strength
b: probability distribution function, V, u: volume of daughter and mother granules, p, c: probability distribution function parameters