

Model Assisted Design of Granular Products

Linking Process and Product Models for Wet Granulation

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Project Brief

Model-Assisted Design of Granular Products

- *Develop multi-dimensional process models of binder agglomeration*
- *Output the appropriate particle properties (likely distributed), linked to associated product models to predict product performance.*



Proposal

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

- *Develop a modeling framework for product performance driven process design*
- *Deployable to industry*
- *Demonstrate the potential of this strategy with two case studies: fluidised bed spray granulation and high shear granulation.*

Project Overview

- Project Commenced in October 2019
- PhD student Peyman Mostafei joined as the primary researcher in November 2019
- IFPRI Liasons:
 - Poul Bach
 - Christophe Grosjean
 - Joris Salari

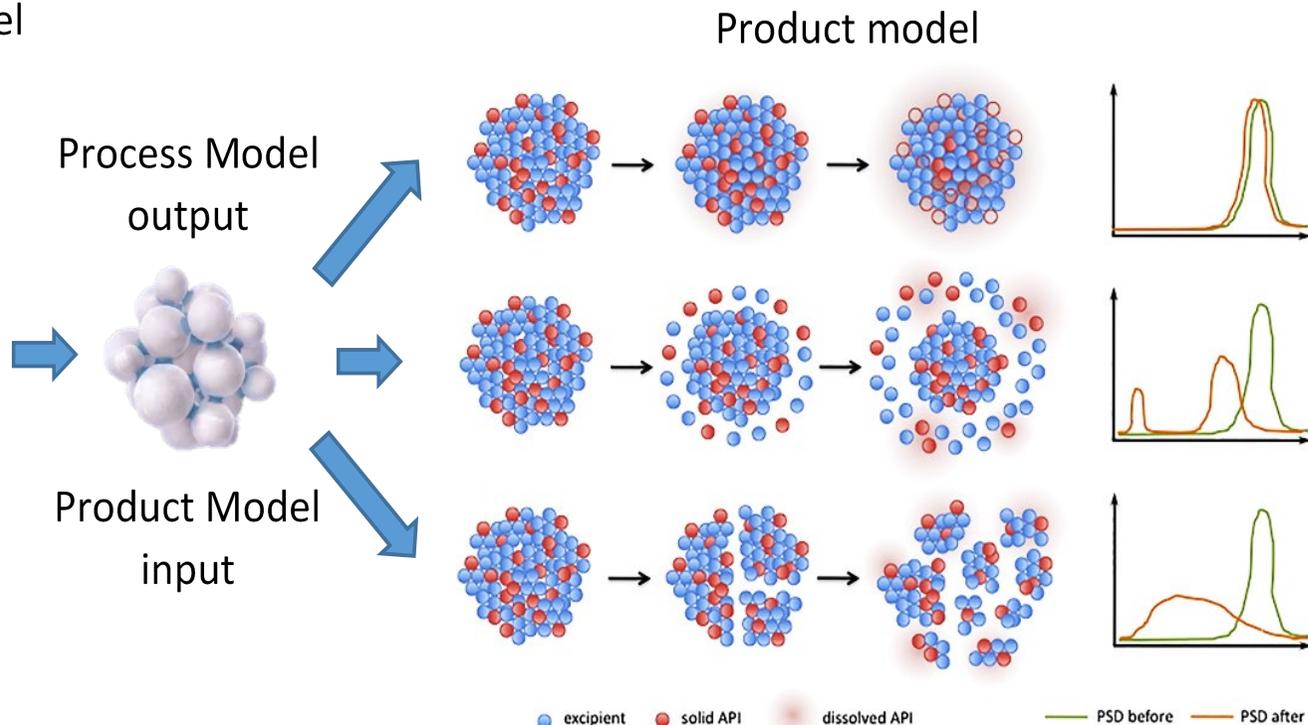


Linking Process and Product Models

Wet granulation model



e.g. fluidised bed [1]

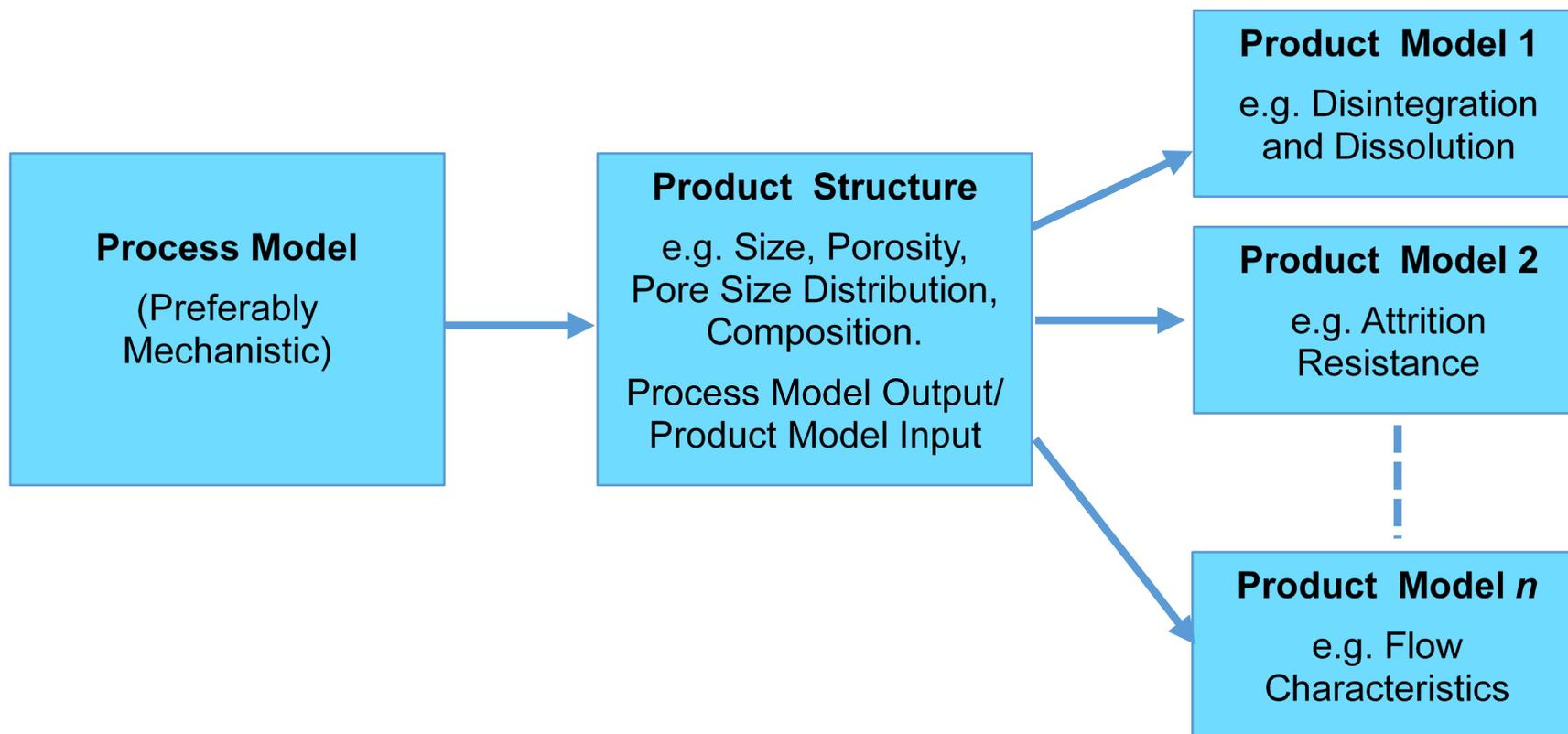


e.g. Dissolution and disintegration model [2]

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

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

Linking Process and Product Models



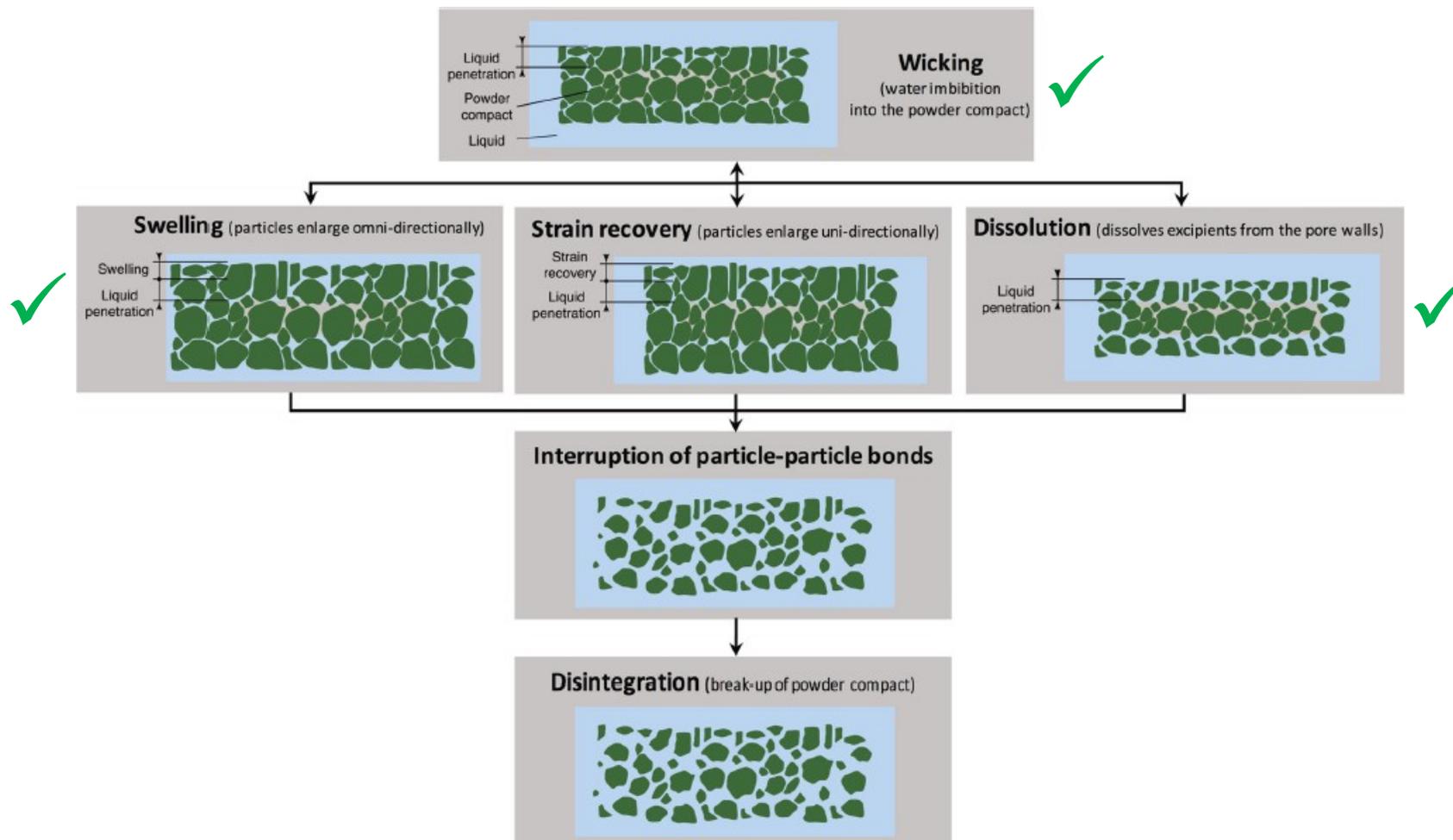
← Inverse Problem



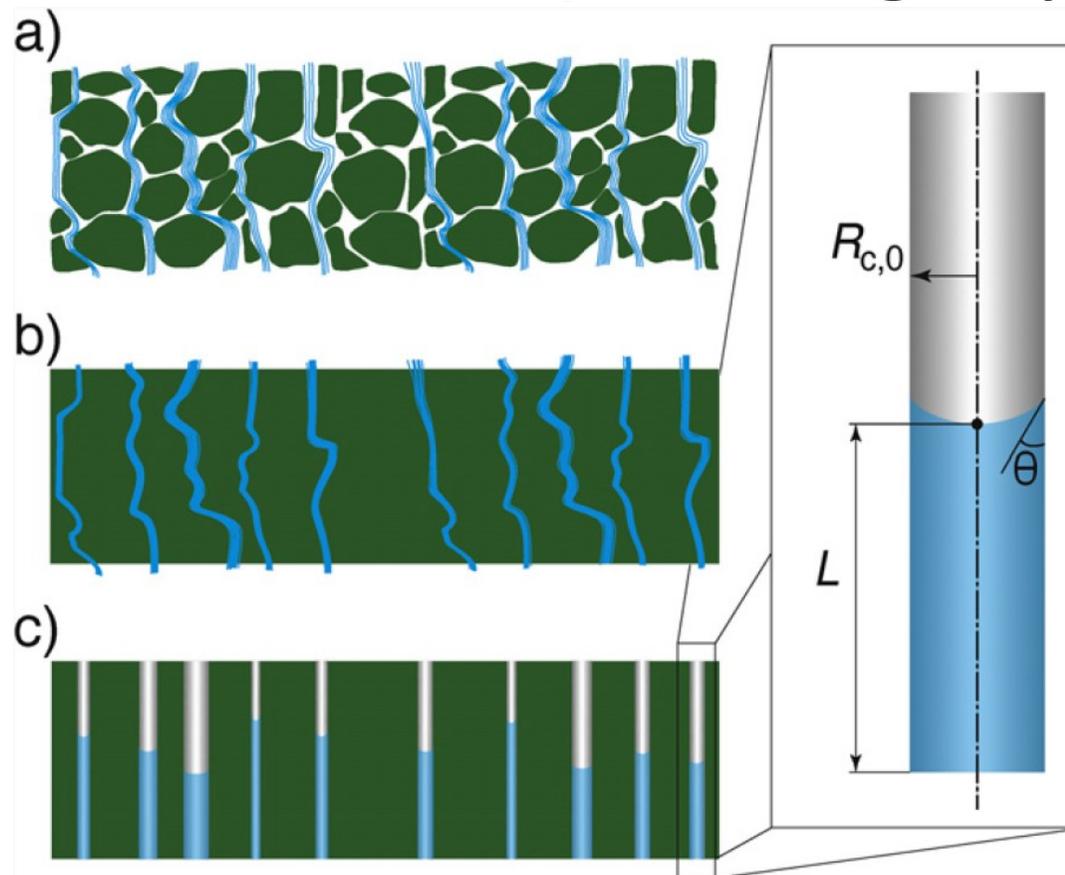
1st Year Objectives

- Complete a comprehensive literature survey of process and product modeling for wet granulation.
- Prepare a review paper based on the literature survey for publication
- Identify exemplar product model/s for development/modification, and commence development of these model/s to work cooperatively with process models. → Chose Disintegration/Dissolution
- Commence development and modification of Sheffield PBM High Shear and Fluidised Bed Granulation Models, to work with identified product models.
- Develop initial framework for co-operative process and product models
- A proposal submitted to the EPSRC for complementary project funding, to leverage this work, and increase project positive outcomes.

Creating a Product Model (PBM): Granule Dissolution and Disintegration



Liquid Penetration (Wicking/Hydration)



- Very fast in immediate release formulations
- Can affect other variables such as porosity and permeability

Useful Hydration Models/Descriptors

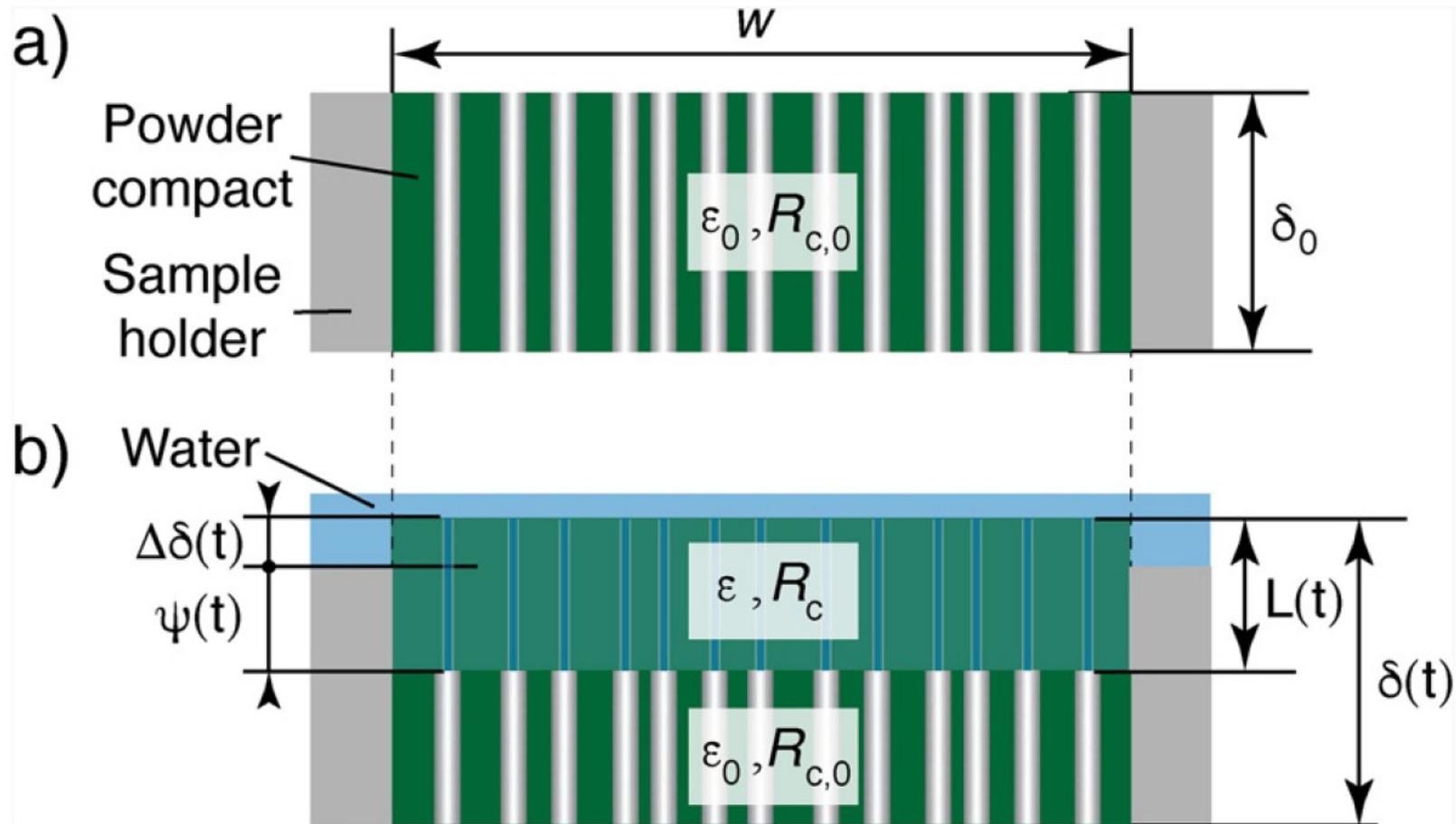
Darcy's Law:
$$q = -\frac{K \Delta P}{\mu L(t)}$$

Depth of Liquid Penetration:
(adapted from [5])
$$L(t) = 2 \sqrt{\frac{\gamma \cos(\theta)}{\varepsilon_{f0} \mu} \int_0^t K(t') / R_c(t') dt'}$$

Pressure difference [5]:
$$\Delta P = \frac{2\gamma \cos(\theta)}{R_c}$$

q is flow rate; K is the permeability; μ is the viscosity; ΔP is the pressure difference; $L(t)$ is the depth of liquid penetration at time t ; γ is the surface tension; θ is the solid-liquid contact angle; ε_{f0} is the initial porosity; R_c is the capillary radius.

Swelling



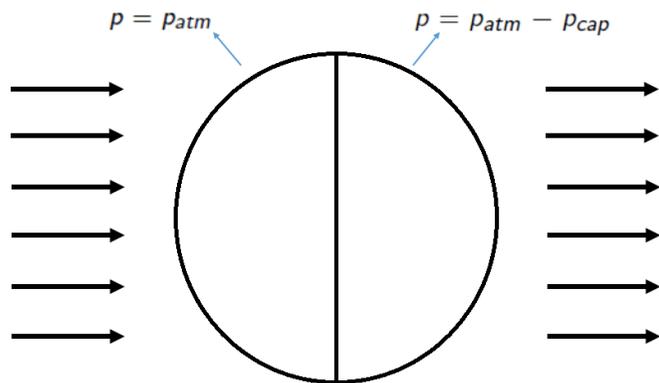
Swelling

- Very quick in formulations which incorporate disintegrants
- There are competing actions which can both aid and hinder release of components
 - Swelling creates pressure in the granule/tablet, which can promote breakup (links to agglomerate strength)
 - Swelling reduce capillary size, and can hinder liquid penetration and dissolution
- Need to consider the competing mechanisms of component swelling and agglomerate strength

Preliminary Model for Swelling

Model developed from work of Masoodi and Pillai [5]

Boundary Conditions:

$$\begin{cases} \frac{\partial p}{\partial r} = 0, & r = 0 \\ p = p_{atm}, & r = R, \quad 0 < \phi < \frac{\pi}{2} \\ p = p_{atm} - p_{cap}, & r = R, \quad \frac{\pi}{2} < \phi < \pi \end{cases}$$


Solution:

$$p(r, \phi) = p_{atm} - \frac{p_{cap}}{2} + \frac{\mu}{6K} (1 - b) \frac{d\varepsilon}{dt} (r^2 - R^2) + p_{cap} \sum_{n=0}^{\infty} A_n \left(\frac{r}{R}\right)^{2n+1} P_{2n+1}(\cos \phi)$$

Preliminary Model for Swelling

Relationship with agglomerate's radius:

$$\frac{dR}{dt} = \int_0^{\pi/2} \frac{K}{\mu \varepsilon_{sur}} \frac{\partial p}{\partial r} \Big|_{r=R} \sin \phi d\phi = \frac{R(1-b)}{3\varepsilon_{sur}} \frac{d\varepsilon}{dt} + \frac{K p_{cap}}{\mu R \varepsilon_{sur}} \sum_{n=0}^{\infty} (2n+1) A_n^2$$

Solution of Radius:

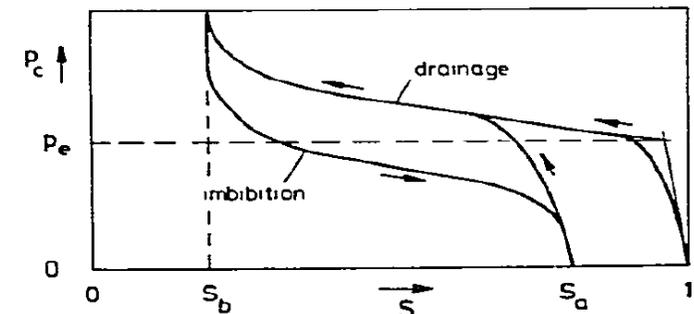
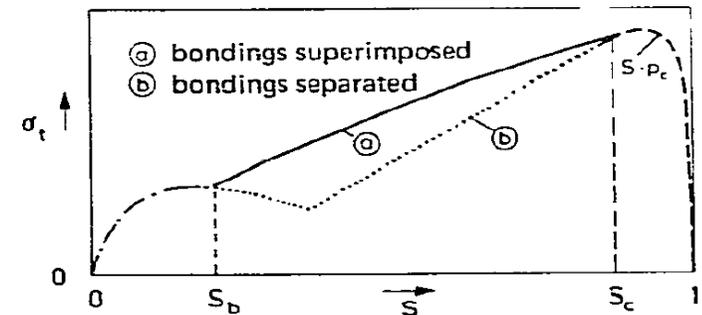
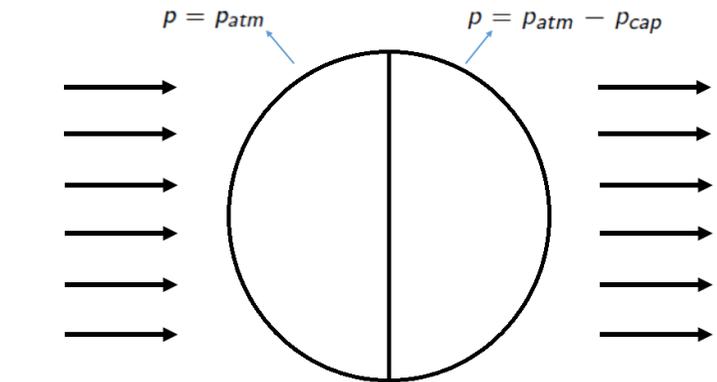
$$R^2 = R_0^2 \varepsilon^{\frac{2}{3}(1-b)} + \frac{\sum_{n=0}^{\infty} (2n+1) A_n^2}{\mu} \int_0^t \left(\frac{\varepsilon(t)}{\varepsilon(t')} \right)^{\frac{2}{3}(1-b)} \frac{K(t') p_{cap}(t')}{\varepsilon(t')} dt$$

Swelling vs Strength

Challenge: agglomerate strength changes with liquid imbibition

- Wet agglomerate strength has proven difficult to model
- Changing agglomerate strength is also difficult to measure experimentally

Challenge: what measure of agglomerate strength do we use?

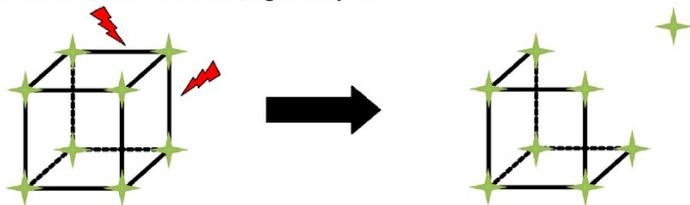


Dissolution

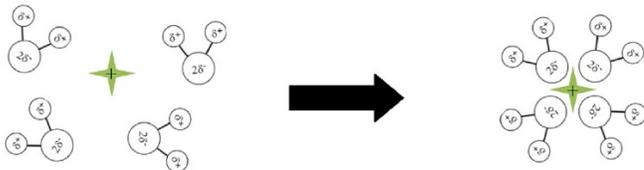
a) Wetting of the particle's surface with water



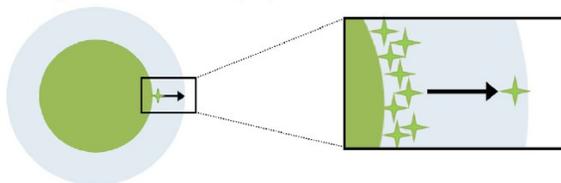
b) Breakdown of solid state bonds, e.g. in a crystal



c) Solvation of the individualized species, e.g. ions



d) Diffusion through the liquid unstirred boundary layer



e) Convection within the well-stirred bulk fluid



- Many approaches available in the literature
 - Noyes–Whitney equation
 - Nernst–Brunner equation
 - Hixson–Crowell equation

Dissolution and Disintegration Model Development

- Complex problem
- Will require extensive experimental validation
- Propose to use simplified systems
 - 3 components maximum
 - Reduce the number of “significant” mechanisms (e.g. eliminate non-swelling components, or non-dissolving components)
 - Include non-mechanistic elements where necessary

Key Progress 2020

1. Recruited PhD student Peyman Mostafei
2. Made significant progress in reviewing the literature
3. Dissolution/Disintegration chosen as the case study product model, and key mechanisms identified
4. Progress towards identifying and modifying mechanistic expressions for hydration, swelling dissolution

Looking Forward 2020

1. Complete a comprehensive literature survey of process and product modeling for wet granulation
2. Make decisions on mechanism inclusion and complementary experimental systems for disintegration model (effectively eliminate mechanisms)
3. Develop a granule disintegration/dissolution model designed to work cooperatively with process models (intermediate structure link).
4. Develop initial product model validation methodology
5. Initiate process model modification
6. Develop initial framework for co-operative process and product models



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your questions 😊

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