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

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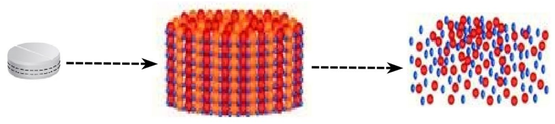
1. Introduction

Disintegration is an important mechanism during the performance of pharmaceutical, agricultural and food products, which involves the break-up of granules to smaller particles. This produces an increase of surface to volume ratio whereby, a considerable amount of desired APIs can be released in a short period of time within the targeted environment.

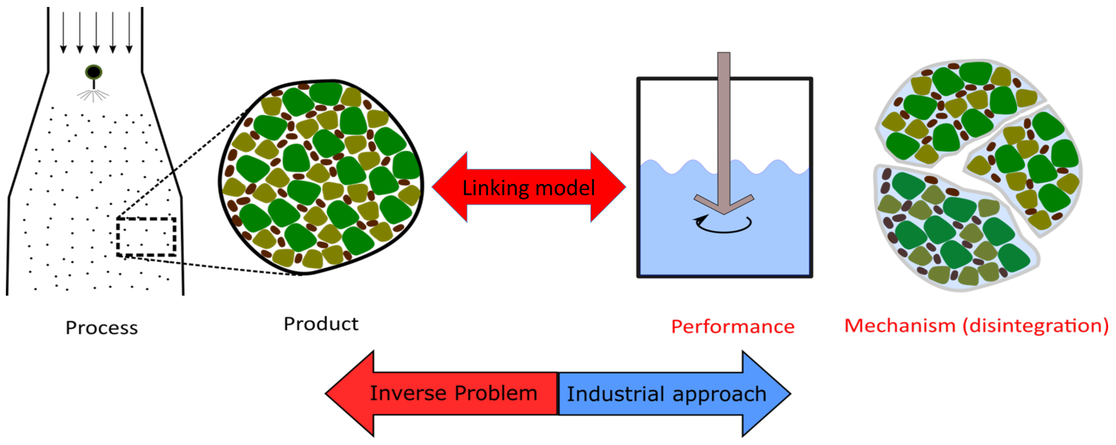


There is a great need for mechanistic understanding of disintegration processes. This is owed to the complex interplay of different mechanisms such as **liquid imbibition**, **liquid absorbance** and **deformation**.

2. Project Aims

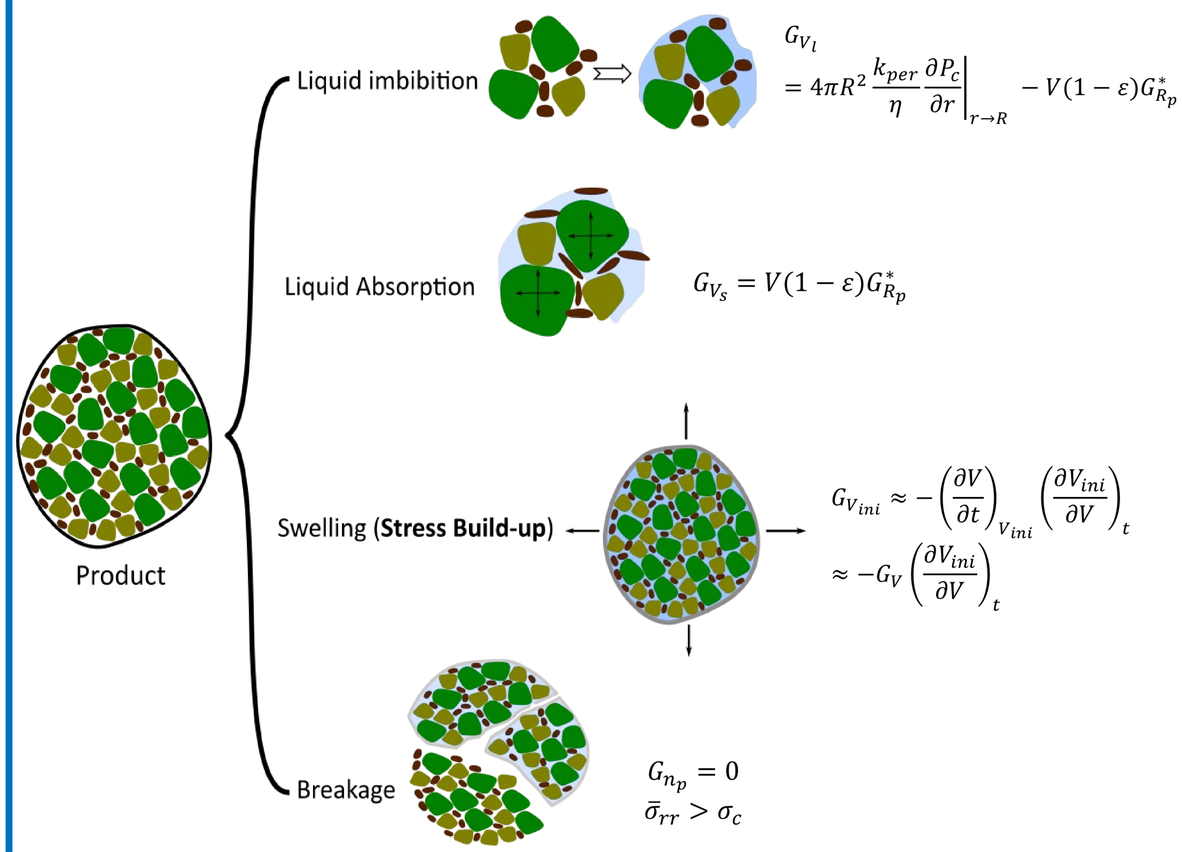
The aim of this project is to develop a product performance model which is capable to predict the disintegration behaviour of granules and can be linked with wet granulation processes. However, the **challenges** are:

1. There is **no mechanistic product model** for predicting the granule size distribution during the disintegration process.
2. There is a **gap** that can **link** the post-process variables to product performance parameters.
3. To achieve product-process linking, an **inverse problem** is required in order to optimize the controllable granulation process parameters for a desired product attribute.



3. Single Granule Disintegration Model

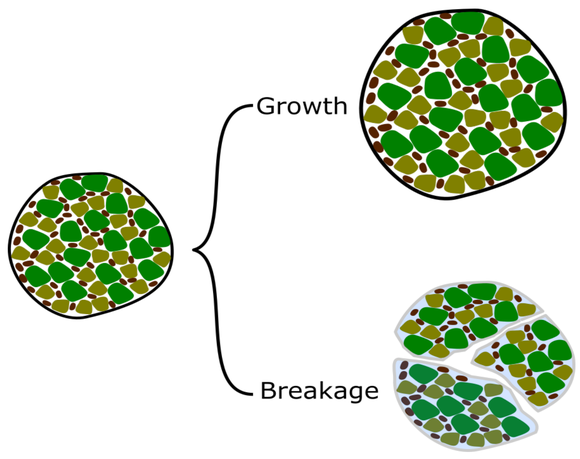
The purpose of a single granule disintegration model is to describe the **key rate processes** which is then **coupled** to a population balance model to account for granule breakage events. This model has four steps:



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

4. Population Balance Model Framework

The mechanisms involved within the population balance model for disintegration are:



The PBM is a **1D+4L** model with following variables:

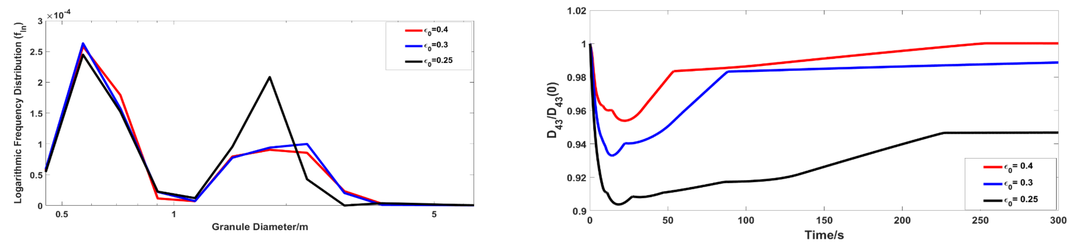
$$\frac{\partial n(V,\boldsymbol{M},t)}{\partial t} = -\frac{\partial}{\partial V}\left(G_V n(V,\boldsymbol{M},t)\right) - S(V,\boldsymbol{M},t)n(V,\boldsymbol{M},t) + \int_V^{V_{max}} S(U,\boldsymbol{M},t)b(V|U)\,n(U,\boldsymbol{M},t)dU$$

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, n: number density function, $\boldsymbol{M}$: lumped parameters, G_V: Growth term related to the size

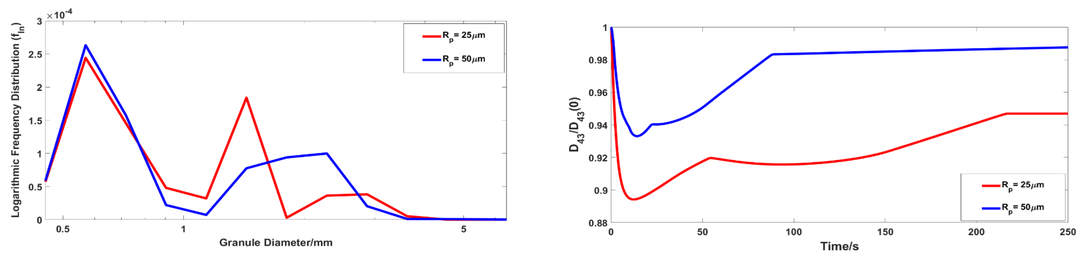
5. Simulation Results

A parameter sensitivity analysis for four different model variables was investigated:

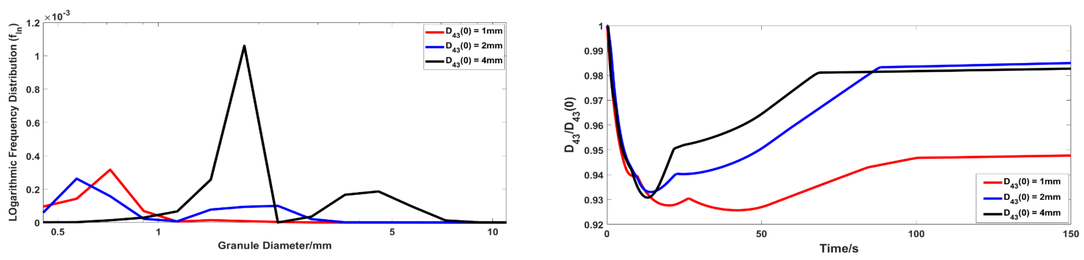
1. Initial porosity



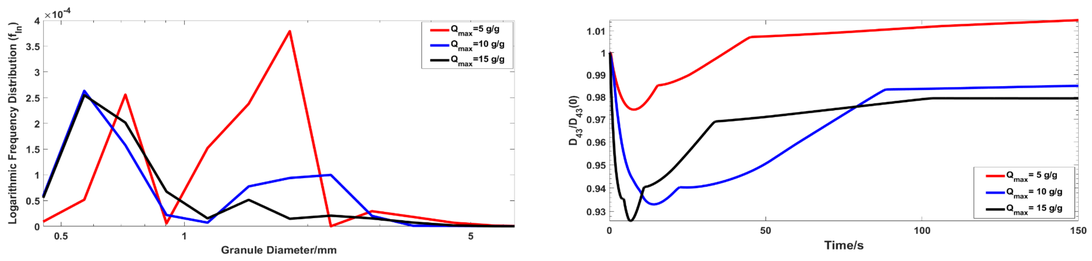
2. Dry disintegrant particle radius



3. Initial granule mean size $d_{4,3}(0)$



4. Maximum absorption ratio



6. Conclusion

- A **new mechanistic population balance model** has been developed to investigate the **disintegration of granules** during product performance.
- **Five key rate processes** were considered: *capillary induced liquid penetration & absorbance*, *swelling, stress build-up and breakage*.
- Two coupled models: a **single granule** model alongside a **1D+4L** PBM model has been **developed** for the disintegration of a distribution of granules.
- A **new way** to **monitor the growth** of a single granule has been proposed[1].

References:

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