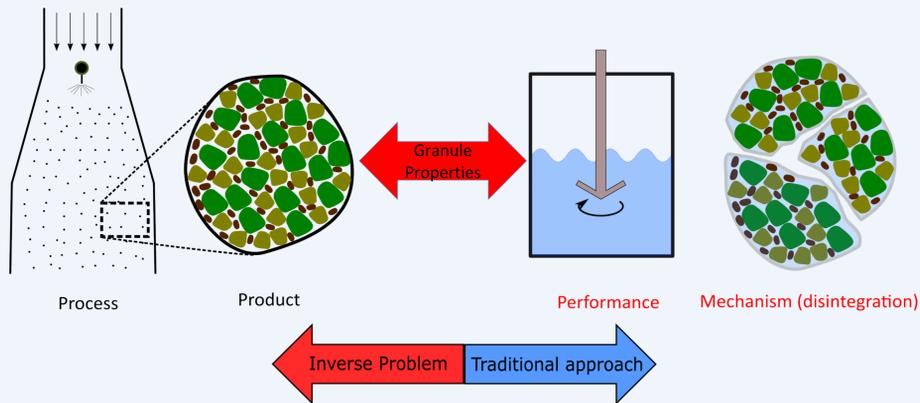


Model Assisted Design of Granular Products: Linking Process and Product Models for Wet Granulation

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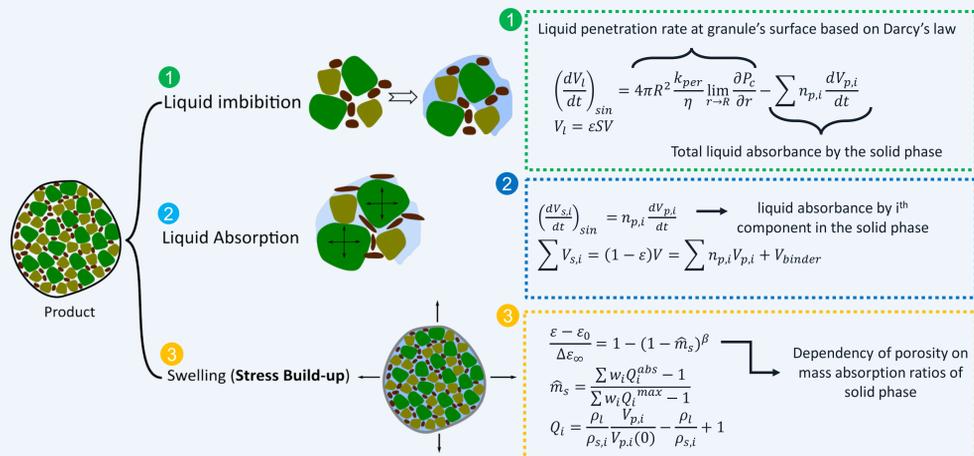
1. Introduction and Aims

Disintegration is an important performance characteristic of many pharmaceutical, agricultural and food products, which involves the break-up of granules to smaller particles. This leads to an augmented surface-to-volume ratio, enabling the rapid release of a significant quantity of desired active pharmaceutical ingredients (APIs) within the desired environment. The objective of this work is to create a model for product performance that can accurately predict the disintegration behavior of granules and establish a connection with wet granulation processes.



2. Single Granule Swelling Model

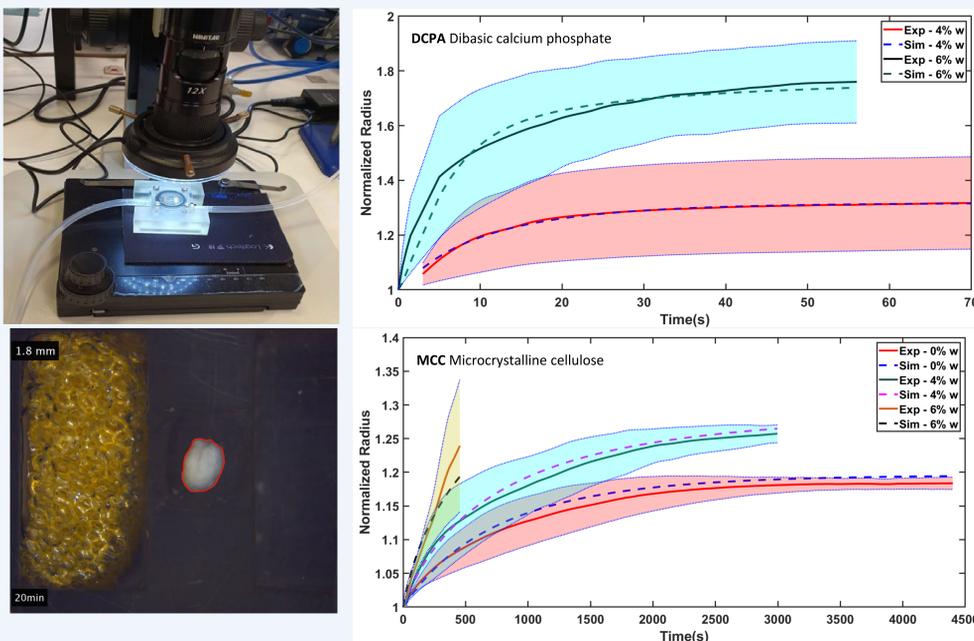
A two-step approach was chosen to model the disintegration of granules due to swelling driven breakup is modelled using two step approach. In the first step the granule properties such as porosity, saturation, and the size of primary particles is modelled. In the second step, these variables are fed into the population balance disintegration model to predict the particle size distribution during disintegration.



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, $x_{p,i}$: 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_0 : initial porosity, $\Delta \epsilon_{\infty}$: porosity difference at infinite, $\rho_{s,i}$: density of i^{th} component, \hat{m}_s : normalized liquid uptake, w_i : mass fraction of components, ρ_l : fluid density, $V_{p,i}(0)$: initial volume of a single i^{th} component particle.

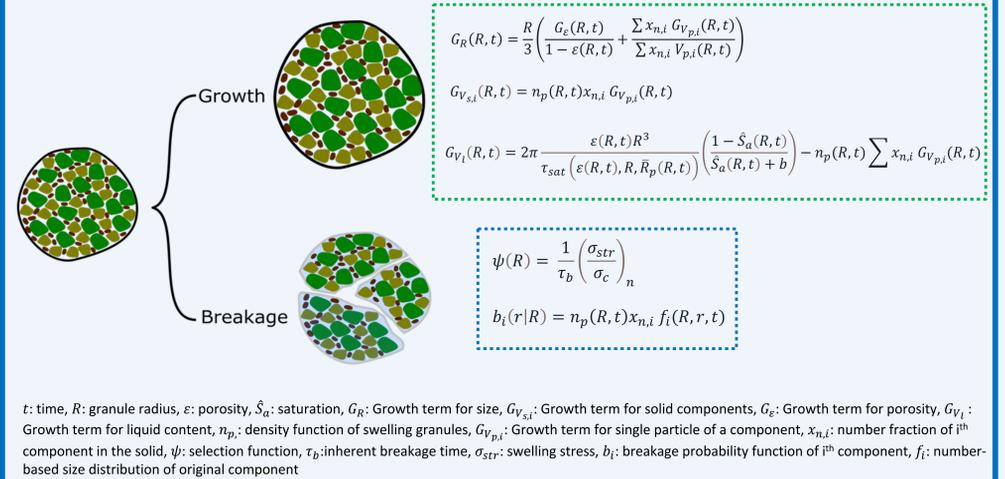
3. Single Granule Swelling Validation

To validate and complete parameter estimation, granules were produced using a high shear granulator. Individual granules were then placed in a 3D printed flow cell combined with a digital optical microscope. Captured images then analysed in an app designed in MATLAB to obtain the evolving granule size. Amount of SSG was varied to modify swelling behaviour.



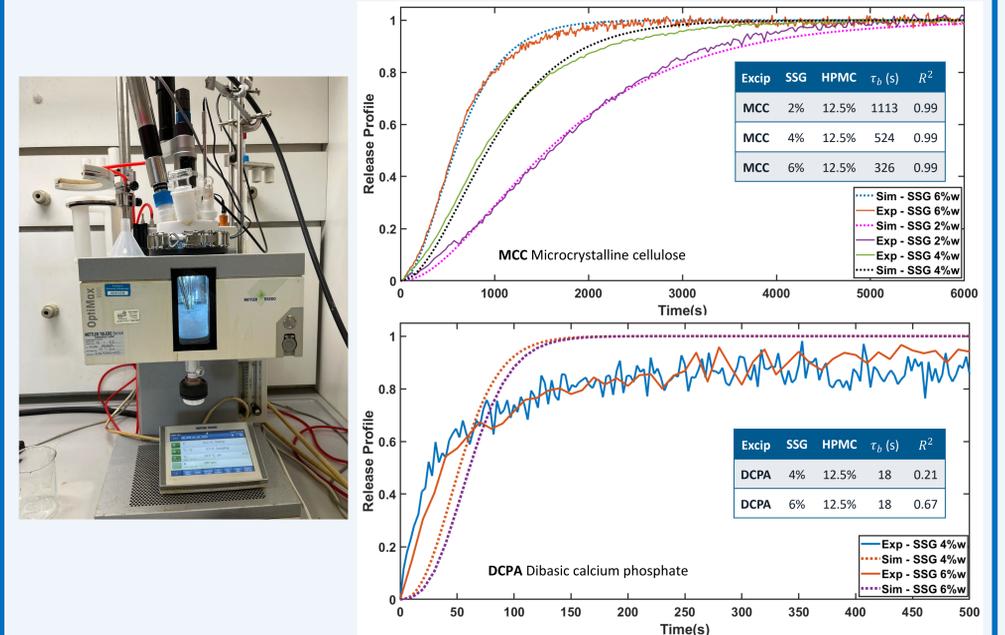
4. Population Balance Model

A population balance approach has been used to predict the evolving particle size distribution, coupled with a single particle swelling model. This has been implemented in Siemens PSE gPROMS.



5. PBM Validation

To measure the particle size distribution (PSD) during disintegration, G400 Focused Beam Reflectance Method (FBRM) was used to monitor granule dispersion with time. Model validation and parameter estimation was then performed in gPROMS.



6. Conclusions

- A mechanistic model for swelling driven granule disintegration and dispersion has been developed and implemented.
- Novel experimental validation methods for model validation and parameterization have been developed, for both early-stage granule swelling and bulk granule disintegration and dispersion.
- The ability of the model to predict granule swelling and the evolving granule disintegration has been demonstrated.

7. Planned Further Work

- Validate and Parameterize the Population Balance Model for High Shear Wet Granulation.
- Develop a surrogate model for the Granule Disintegration Model and link the wet granulation model with the granule disintegration model.
- Apply inverse problem techniques to provide model driven design of granulation.

8. Acknowledgments

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