

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 mechanism during the performance of 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.

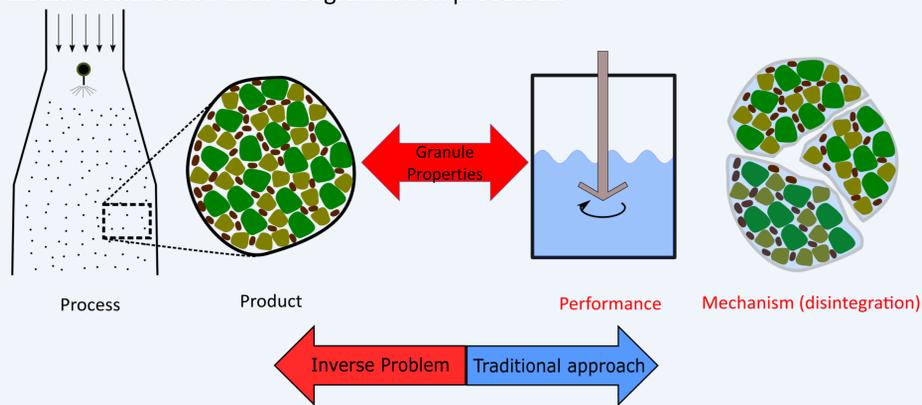


Fig 1. Disintegration Mechanism

2. Single Granule Swelling Model

The **disintegration of single granule via swelling** 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.

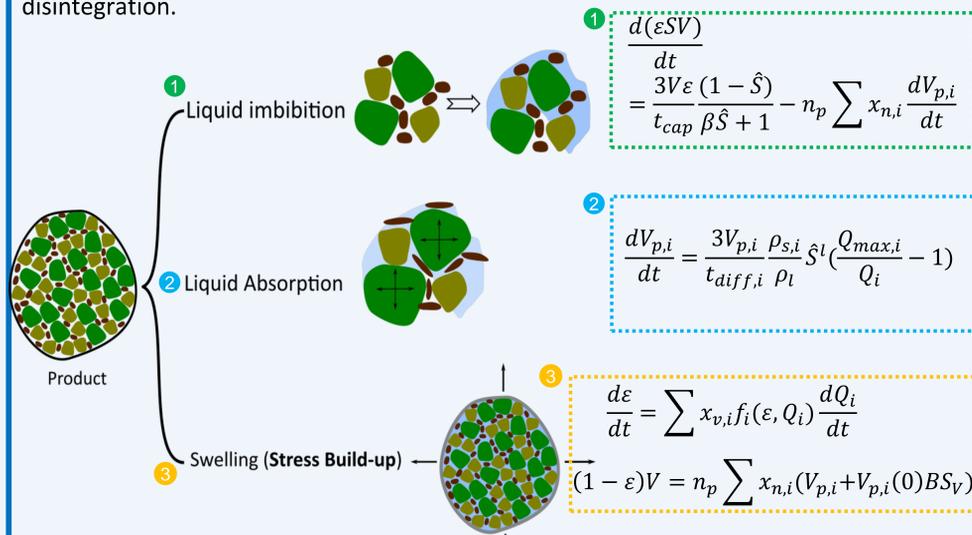


Fig 2. Single granule swelling model

t : time, R : granule radius, ε : porosity, S : saturation, \hat{S} : normalized saturation V : volume, n_p : total number of primary particles in the granule, $x_{n,i}$: number fraction of i^{th} component particle in the solid phase, $x_{v,i}$: volume fraction of i^{th} component particle in the solid phase, $V_{p,i}$: volume of a single i^{th} component particle, t_{cap} : a characteristic capillary time, β : a parameter describing the Sherwood capillary number, Q_i : mass absorption ratio of i^{th} component, $Q_{max,i}$: maximum mass absorption ratio of i^{th} component, $t_{diff,i}$: a diffusion-absorption characteristic time, $\rho_{s,i}$: density of i^{th} component, ρ_l : fluid density, $V_{p,i}(0)$: initial volume of a single i^{th} component particle, BS_V : volumetric ratio of solidified binder in the granule to solid

3. Single Granule Swelling Characterisation

To **monitor the size evolution** of individual granules and calibrate the single granule swelling model, a specially **3D printed flow cell** combined with a digital **optical microscope** was used. The captured images from the microscope, then were analysed in a **designed app** in MATLAB to obtain the size of the granules.

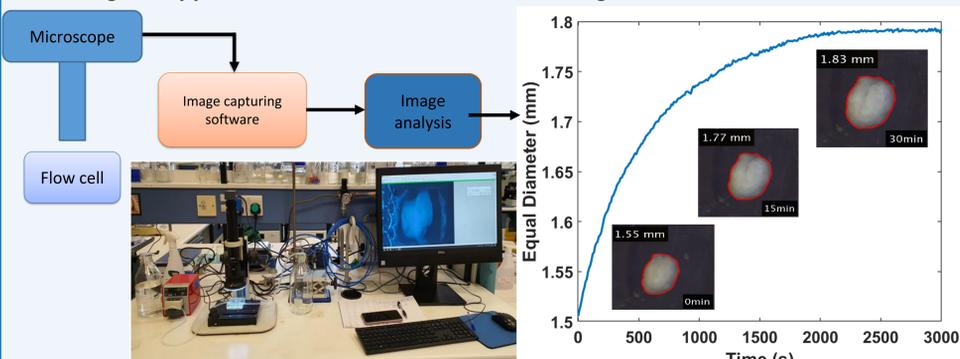


Fig 3. Flow Cell experimental setup

Fig 4. Diameter vs disintegration time

4. Global sensitivity analysis

In order to identify key parameters in single granule disintegrating model, a two stage global sensitivity was performed on the model. The first stage focused on the process parameters while the second analysis studied the impact of superdisintegrant inherent parameters.

Process Parameters	Parameter	Porosity		Normalized diameter	
		First Effect	Total Effect	First Effect	Total Effect
Global Sensitivity Analysis	Initial porosity	0.303	0.483	0.146	0.306
	Initial radius of superdisintegrant (μm)	0.270	0.566	0.364	0.726
	Initial radius of excipient (μm)	0.074	0.255	0.0912	0.322427
	SSG mass percentage	0.021	0.099	0.046	0.124
	Liquid to solid ratio	0	0	0	0

Superdisintegrant inherent parameters	Parameter	Porosity		Normalized diameter		Mass absorption ratio	
		First Effect	Total Effect	First Effect	Total Effect	First Effect	Total Effect
Global Sensitivity Analysis	Superdisintegrant's porosity factor (Γ_{sup})	0.713	0.794	0.666	0.744	-0.003	0
	Diffusivity of the disintegrant (D_{sup})	0.063	0.100	0.076	0.114	0.242	0.303
	Maximum absorption ratio of the disintegrant (Q_{max}^{sup})	0.132	0.195	0.166	0.230	0.698	0.760

5. Validation

A series of granules were made in a **high shear granulator** that consisted of **Microcrystalline cellulose (MCC)**, **Sodium starch glycolate (SSG)** and 12.5% aqueous solution of **Hydroxypropyl methyl cellulose (HPMC)** with different concentration of SSG.

Parameter	D (μm^2)	Q_{max} ($\frac{g}{g}$)	Γ
Component			
MCC	0.35	1.5	0.2
SSG (%4)	1.76	9.29	2.35
SSG (%6)	2.33	9.89	5.71

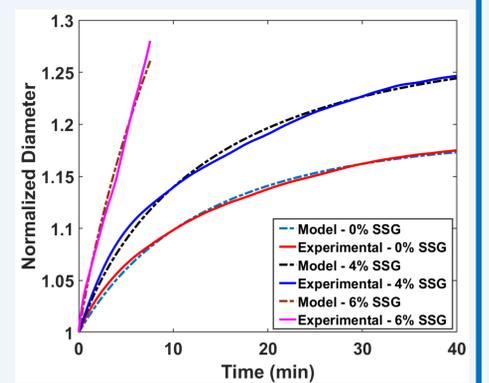


Fig 5. Single Granule Swelling Model validation

6. PSD measurement

To **measure the particle size distribution (PSD)** during disintegration, Optimax setup is used with **G400 Focused Beam Reflectance Method (FBRM)**. Granule size range of 1- 1.4 mm is investigated with concentration of 1.5% (mg/ml) in 400 ml water at 300 RPM.

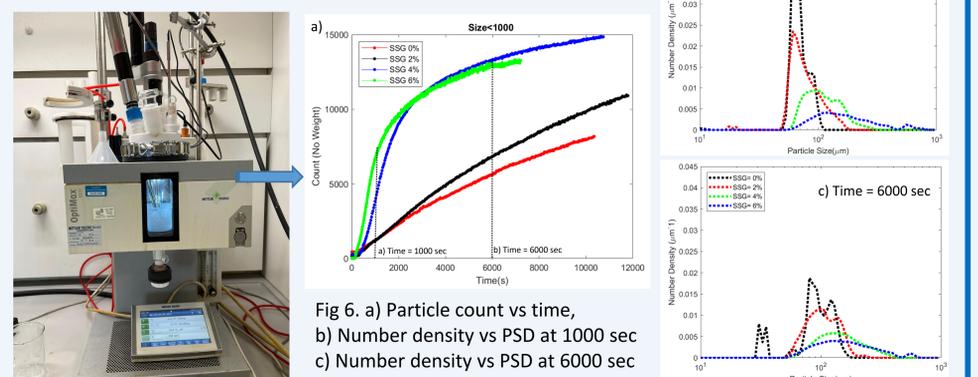


Fig 6. a) Particle count vs time, b) Number density vs PSD at 1000 sec c) Number density vs PSD at 6000 sec

7. Conclusion

- A new mechanistic single granule swelling model has been developed to predict the swelling of granules during disintegration.
- A new way to monitor the size of individual granules using a 3D designed flow cell, optical microscopy and image analysis has been proposed.
- The model was tested on a specific formulation with emphasis on swelling behaviour was tested. The results showed good agreement with the experimental data.
- A new setup has been proposed involving FBRM technique has been proposed to measure PSD during disintegration

8. Acknowledgment

We would like to specially thank Daniel Markl and his group from the University of Strathclyde, Poul Bach from Novozymes, Christophe Grosjean and Michael Brozio from Syngenta, Joris Salari from Corbion, Sri Sharath Kulkarni and Daniel Sieber from DFE Pharma, Tristan Hessberger and Tobias Heß from Budenheim, Vanessa Havenith from Setylose, Bindhu Gururajan from Novartis, Stefan Bellinghausen from PSE Enterprise and IFPRI for funding this research project.