Feasibility/Collaboration Proposal: Model calibration as a Tool for Material Characterisation

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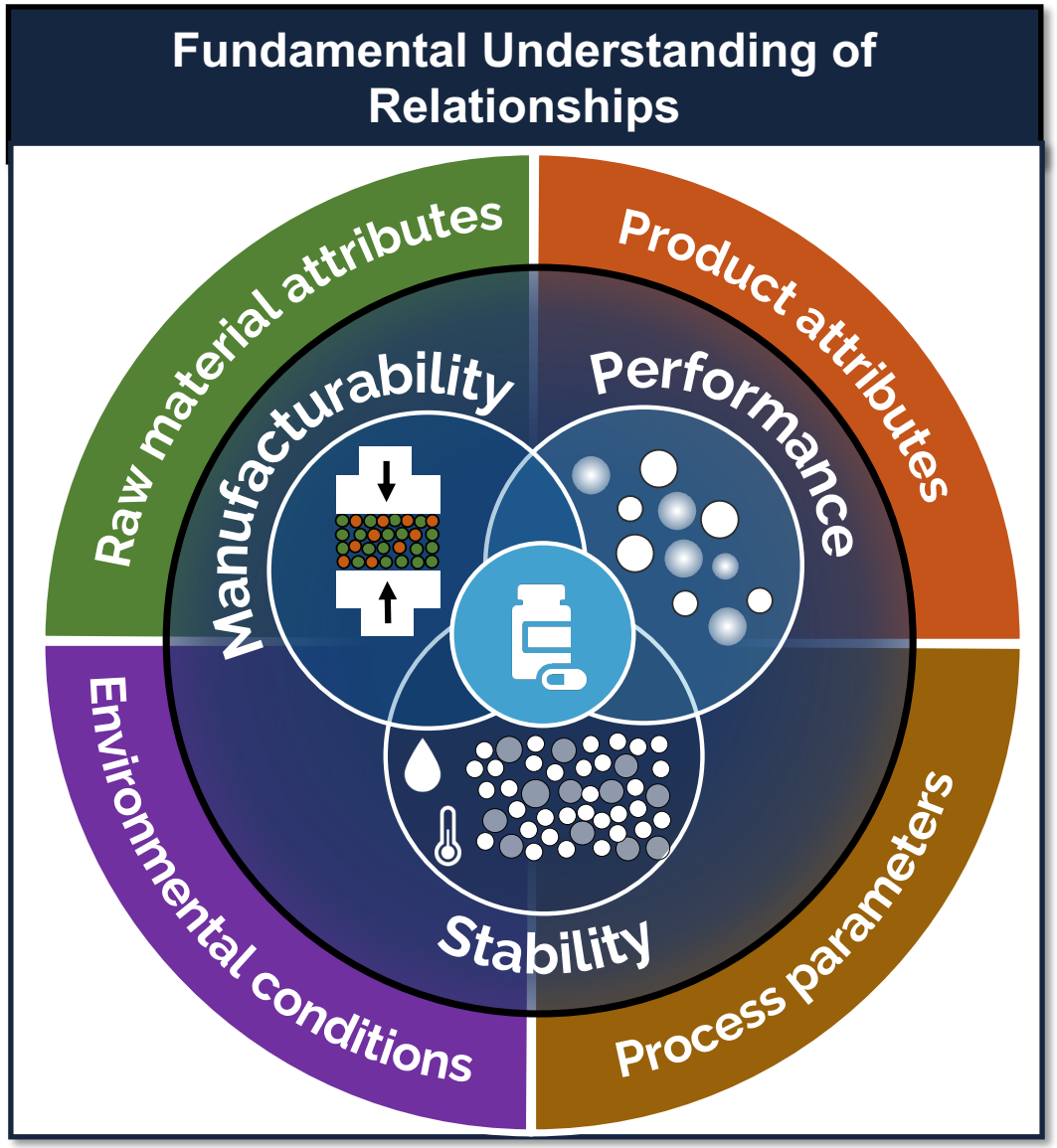
Neeru Bala, Daniel Markl , Rachel Smith

University of Sheffield & University of Strathclyde

CMAC

Agile & Flexible Development & Manufacturing



Agile & Flexible Development & Manufacturing

to reduce speed & cost and increase efficiency of how medicines are developed and manufactured to meet changing demands.

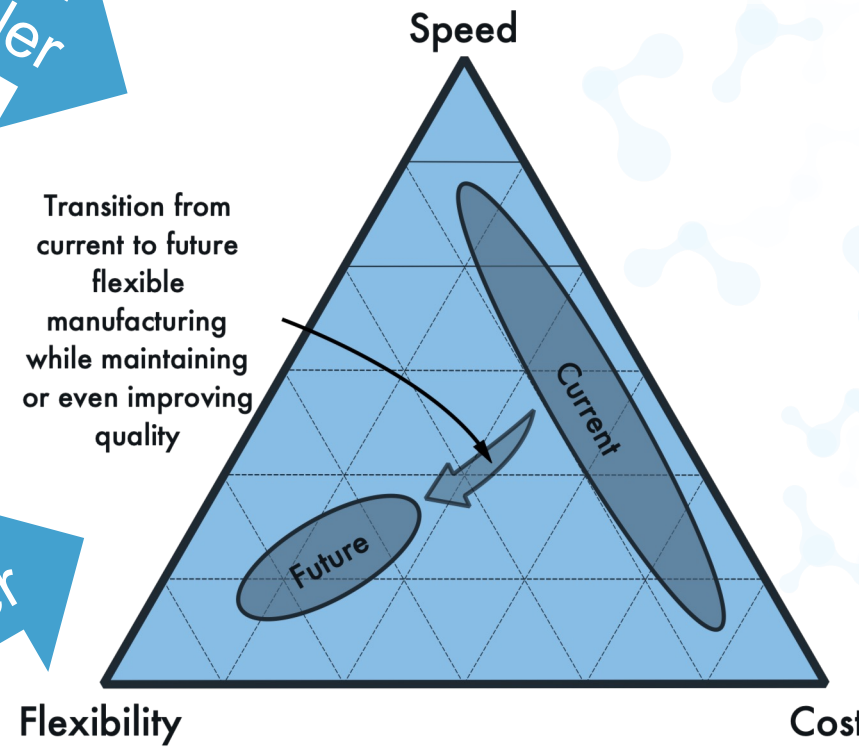
Innovative manufacturing & sensor technologies

Enabler

Enabler

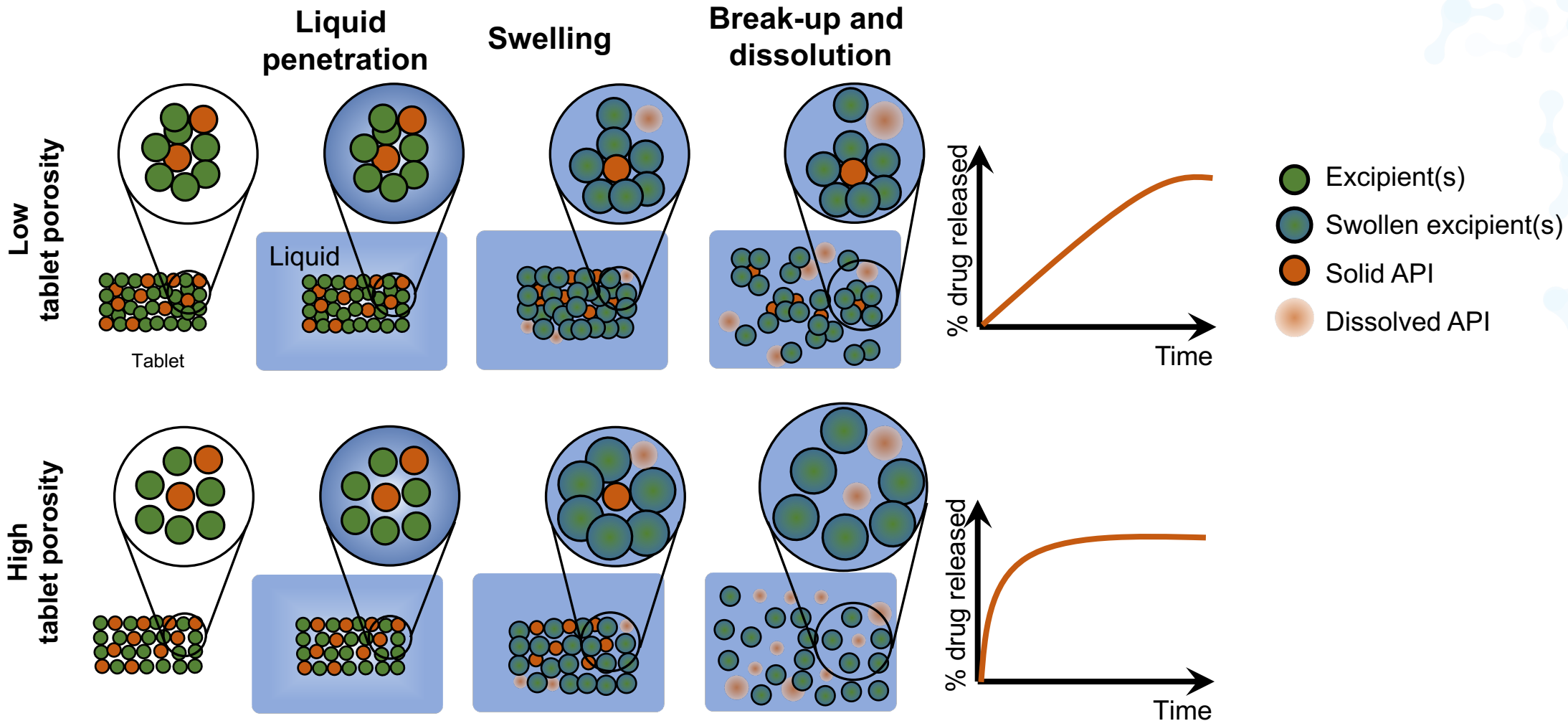
Digital transformation

Enabler



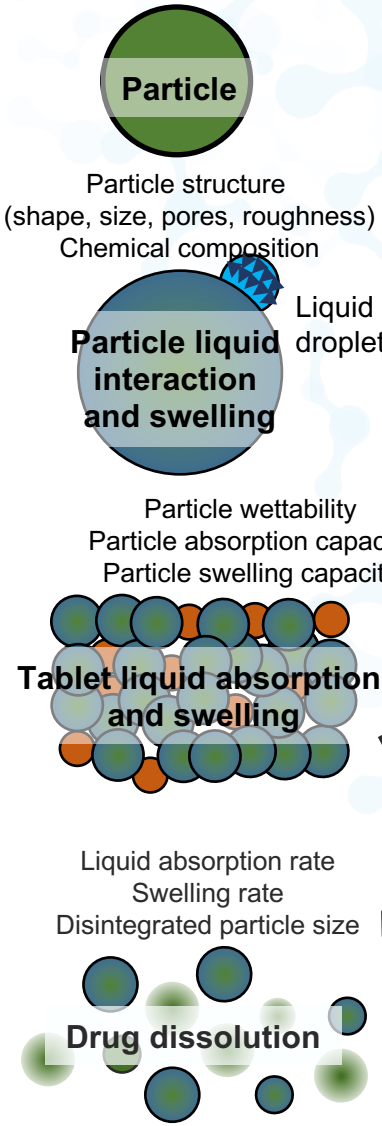
Product Performance

Tablet Disintegration – Dissolution Relationship



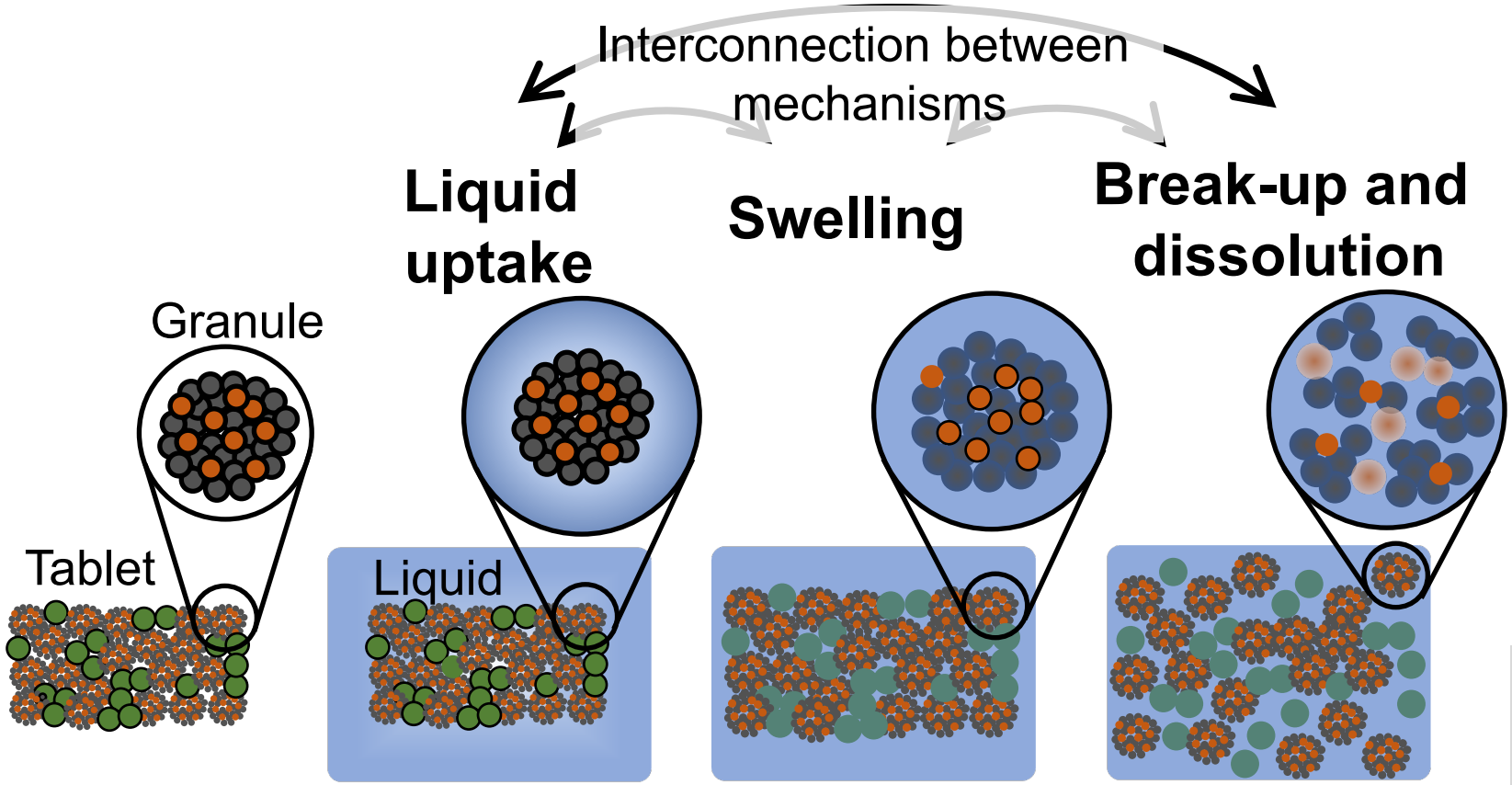
Markl D and Zeitler JA *Pharm Res* **34**(5), 890-917 (2017)

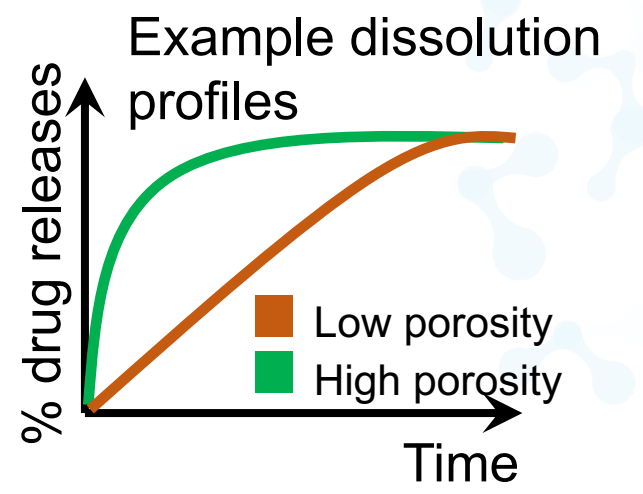
Product Performance
Disintegration and Dissolution



Markl D and Zeitler JA *Pharm Res* **34**(5), 890-917 (2017)
Markl D *et al. Int J Pharm* **538**(1-2), 188-214 (2018)

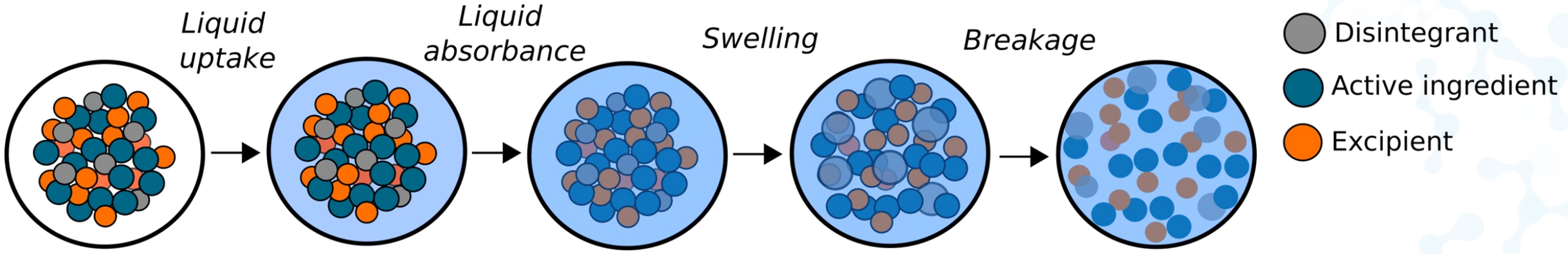
Disintegration of Granulated Tablets



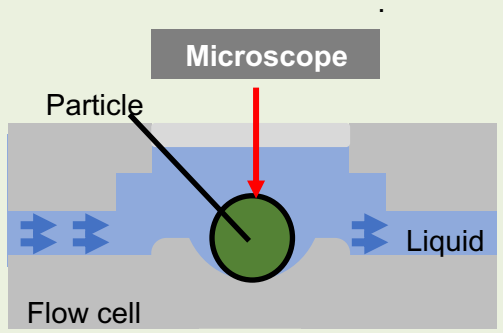


- Tablet excipient(s)
- Swollen tablet excipient(s)
- Granule excipient(s)
- Swollen granule excipient(s)
- Solid API
- Dissolved API

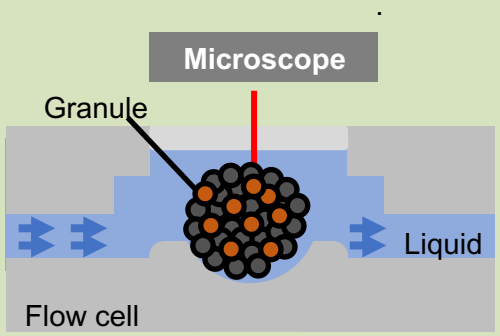
Experimental Investigation



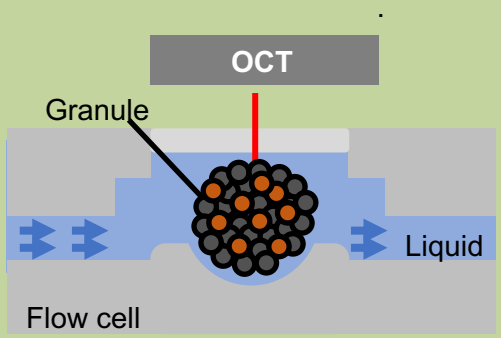
Investigating swelling of single particles particles



Investigating liquid uptake of granules



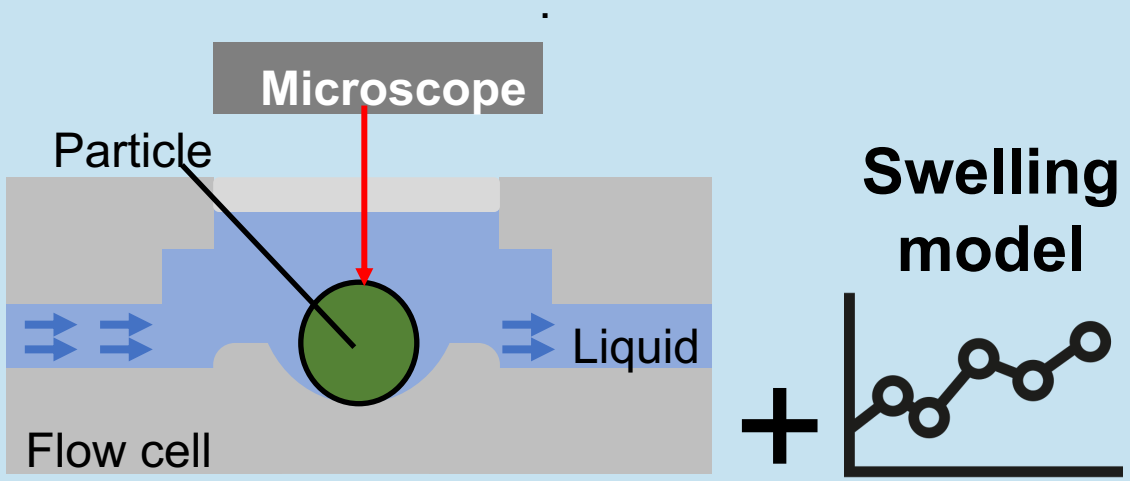
Investigating liquid uptake and swelling of granules



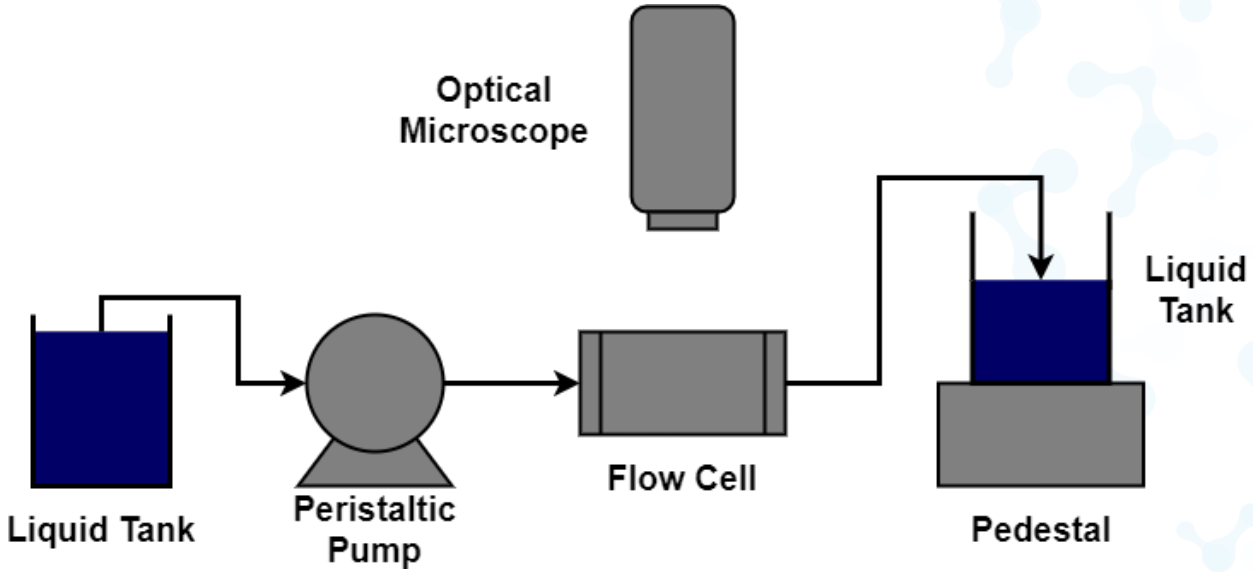
OCT: optical coherence tomography

Single Particle Swelling Characterisation

In-situ monitoring and modelling of single particle swelling

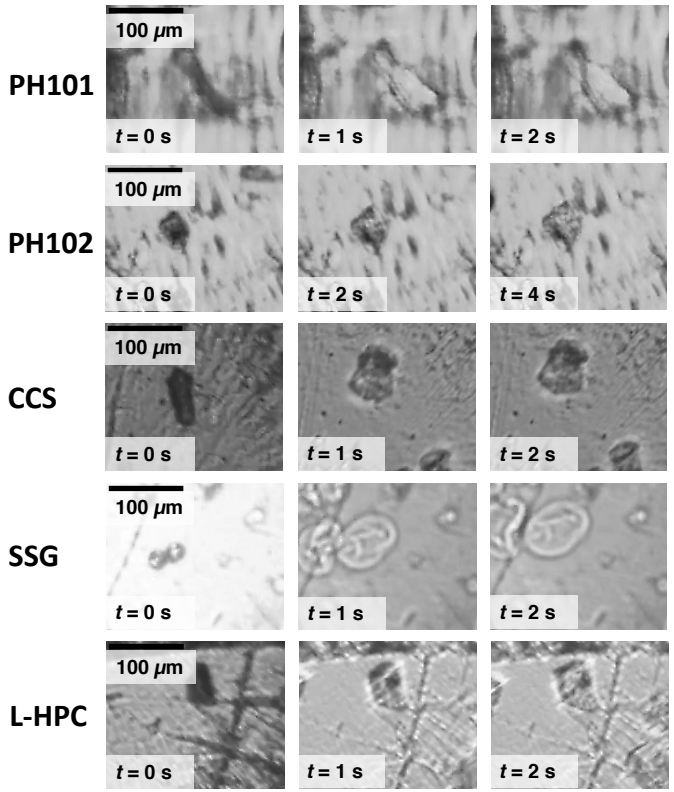


Extraction of characteristic swelling properties and swelling-limiting mechanisms

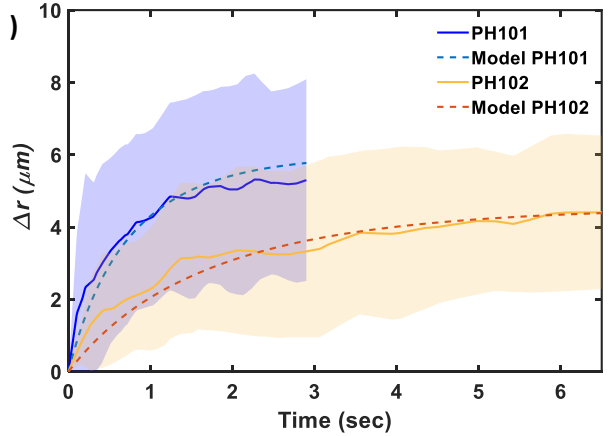


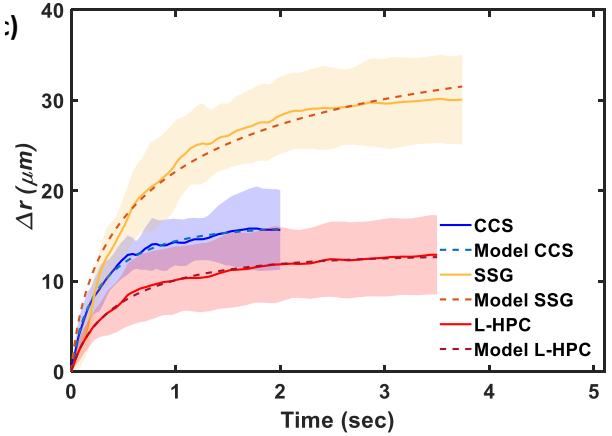
Single Particle Swelling Characterisation

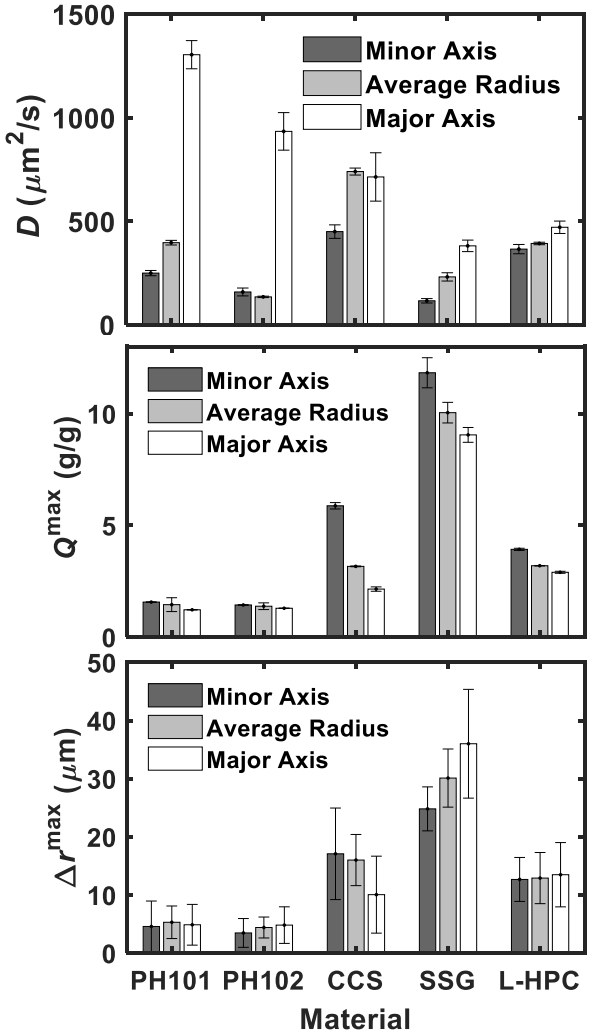
1 *In-situ* images of single particle swelling

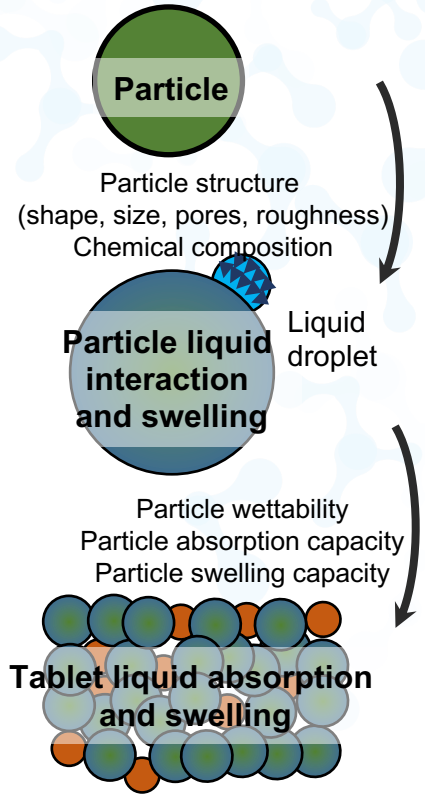


2 Single particle swelling modelling and parameter estimation





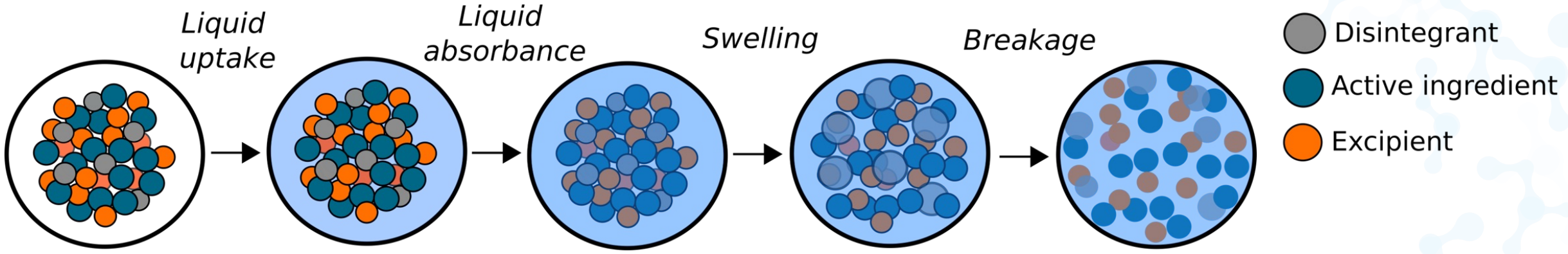




PH101/102: microcrystalline cellulose grades
CCS: croscarmelose sodium
SSG: sodium starch glycolate
L-HPC: hydroxypropyl cellulose

D: Diffusion coefficient
$Q^{\max}$: maximum absorption ratio
$\Delta r^{\max}$: swelling capacity

Experimental Investigation



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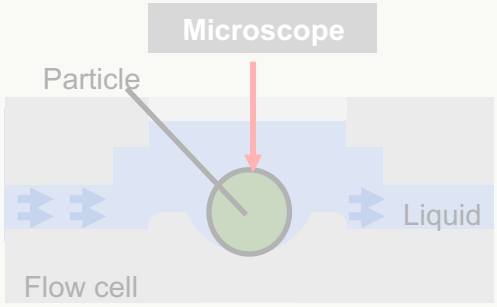
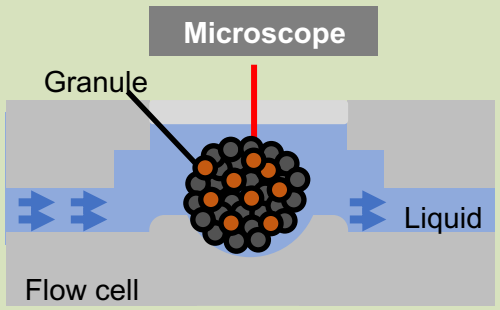
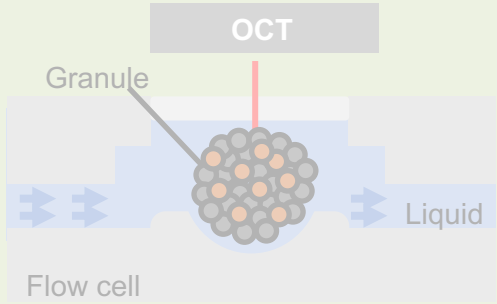


Investigating liquid uptake of granules



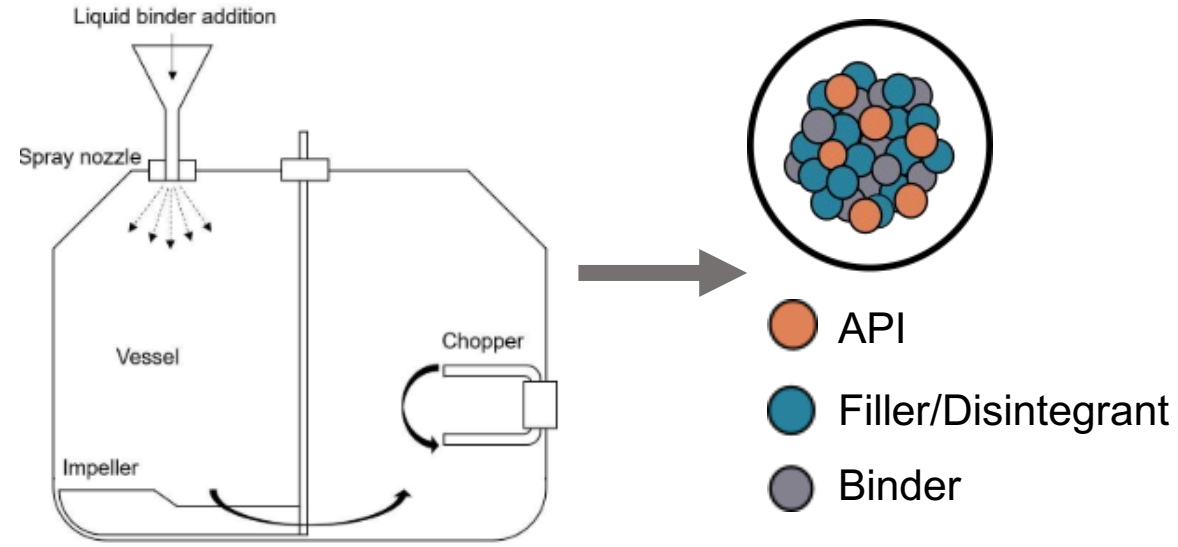
Investigating liquid uptake and swelling of granules



OCT: optical coherence tomography

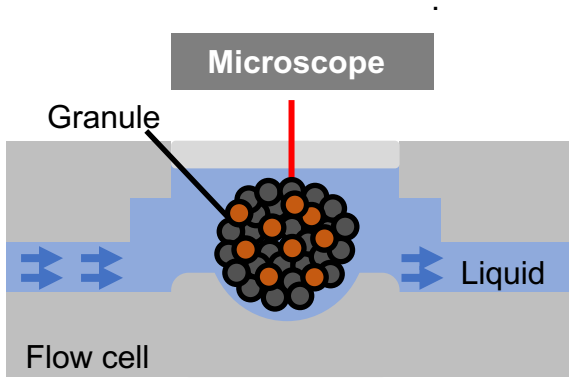
Granule Swelling Characterisation

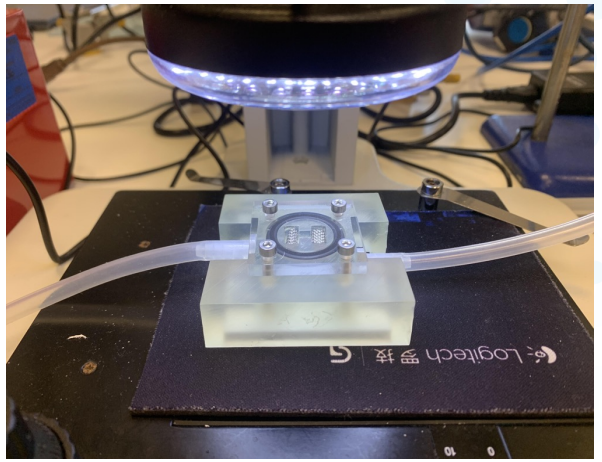
1 Granule generation via high shear wet granulator



Material	Function	%
Aspirin	API	10
Microcrystalline cellulose	Filler, partial lubricant & disintegrant	80-90
Sodium Starch Glycolate (SSG)	Superdisintegrant	2-7%
Water/PEG	Liquid binder	-

2 Granule swelling performance assessment



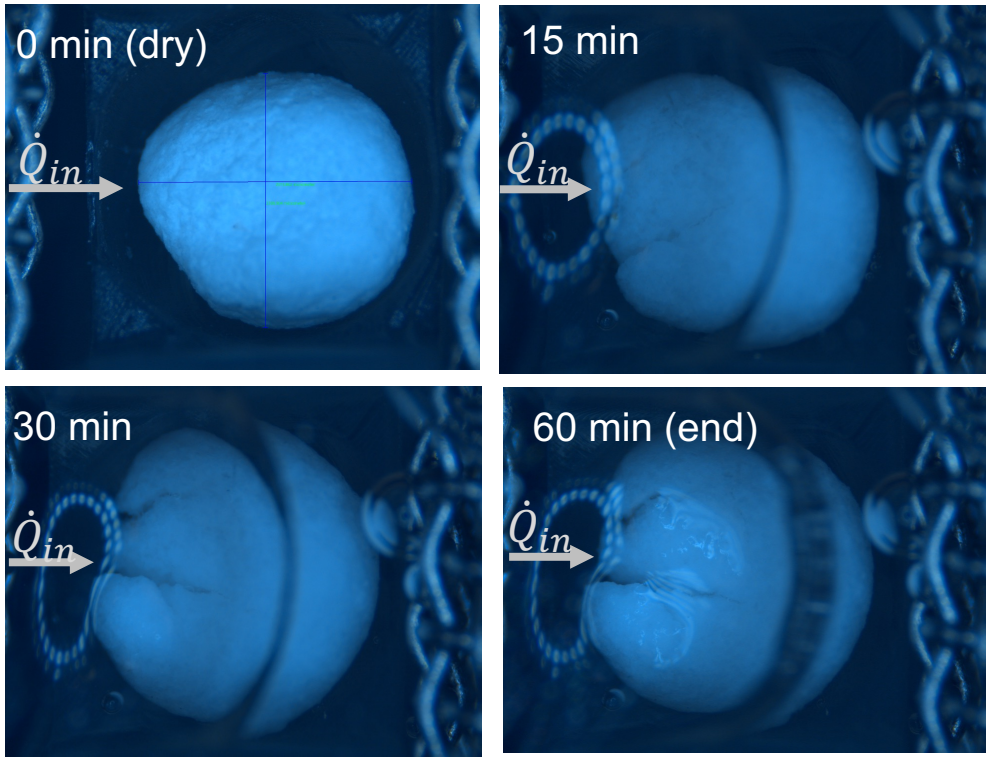


Material	Size, x (mm)	Porosity, ε (%)	L/S	Flow rate, $\dot{Q}$ (mL/min)
MCC	1.9-2.5	47	1	10
MCC+SSG	1.8-1.9	25	1	10
Aspirin+MCC	1.9-2.5	30-62	0.8-1.2	10
Aspirin+MCC +SSG	1.9-2.5	35-52	1	10

Granule Swelling Characterisation

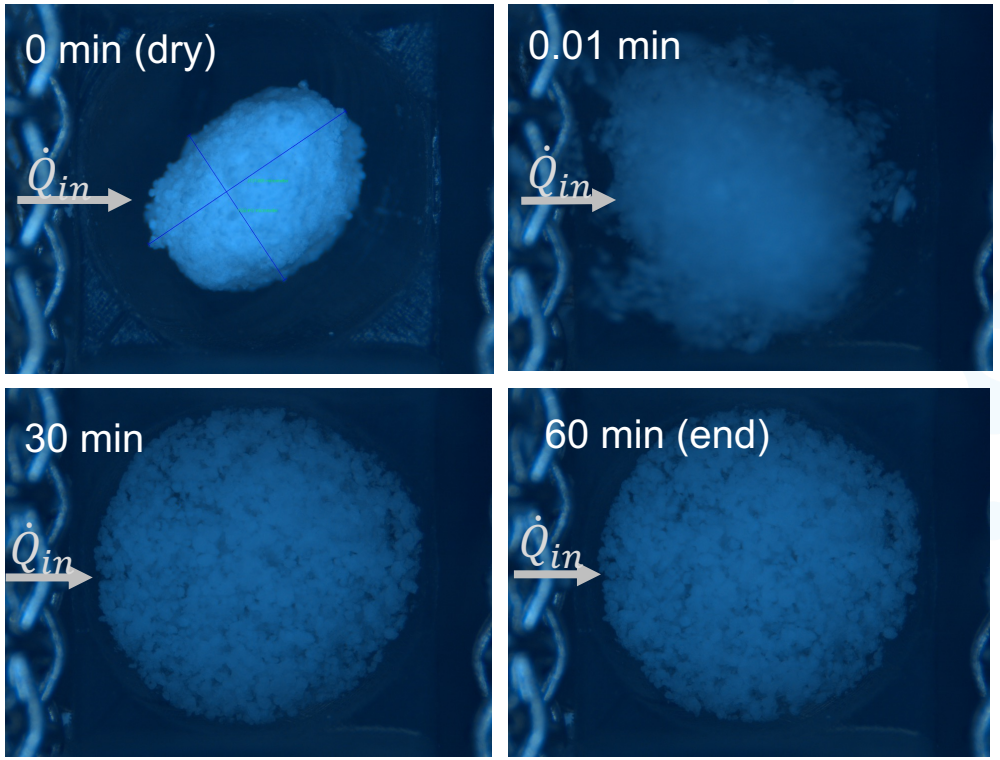
Microcrystalline Cellulose

MCC



- Surface erosion and slow crack propagation observed over time
- No excessive granule movement, challenges with bubble formation

MCC + SSG



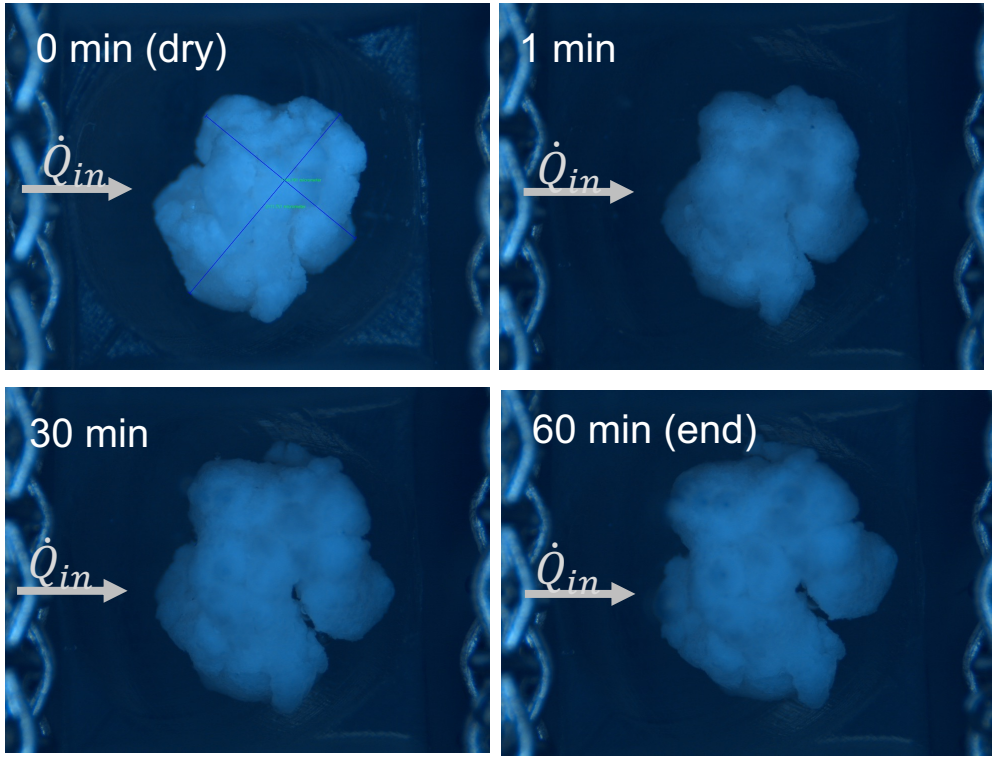
- Adding superdisintegrant caused sudden expansion and swelling over time
- Slow loosening of microstructure and strain recovery observed

SSG: Sodium Starch Glycolate

Granule Swelling Characterisation

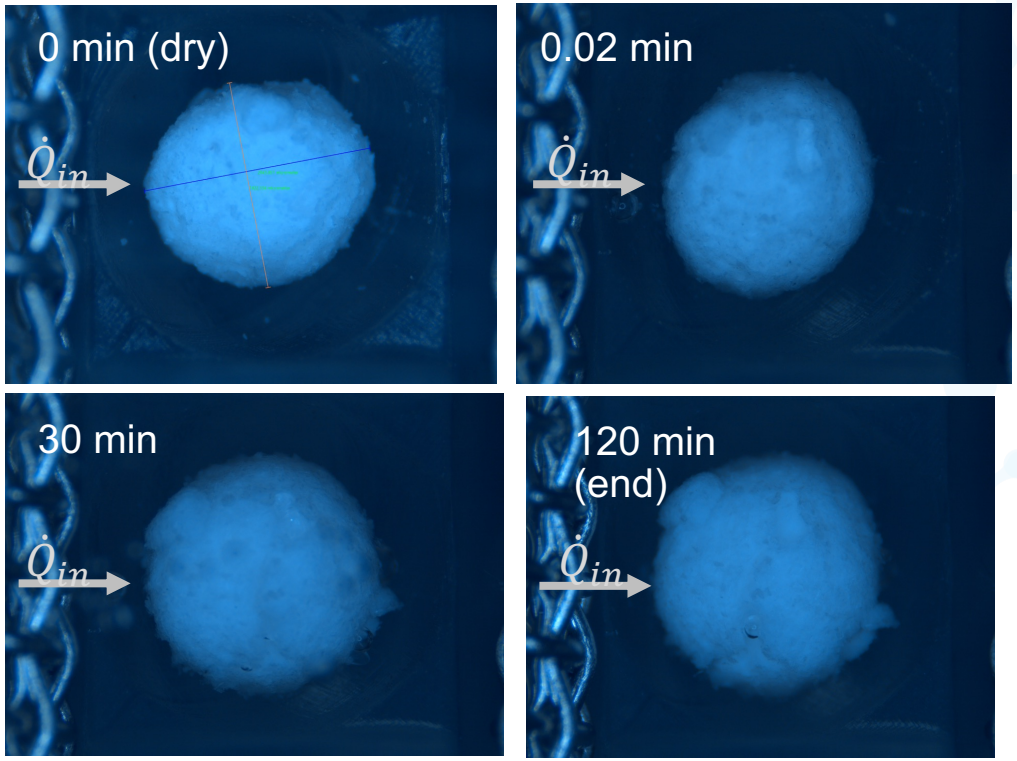
Aspirin and Excipients

Aspirin + MCC



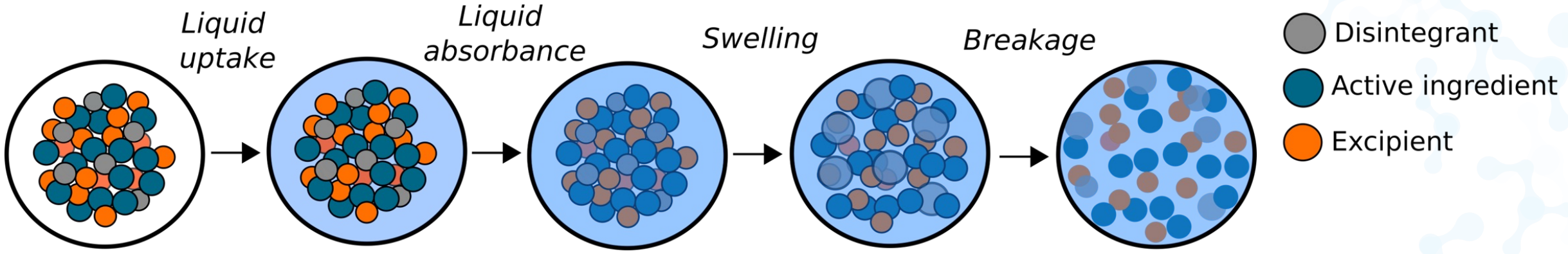
- Aspirin added to MCC (no superdisintegrant)
- Erosion and crack propagation observed with slow swelling

Aspirin + MCC + SSG



- All components included within granule
- Controlled crack propagation and erosion occurs. Gradual swelling

Experimental Investigation



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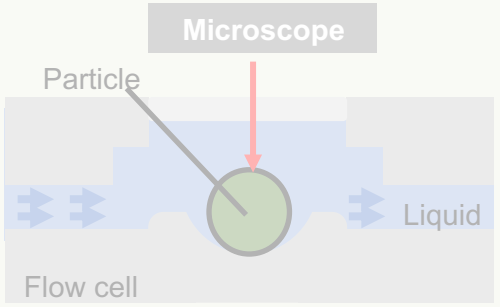
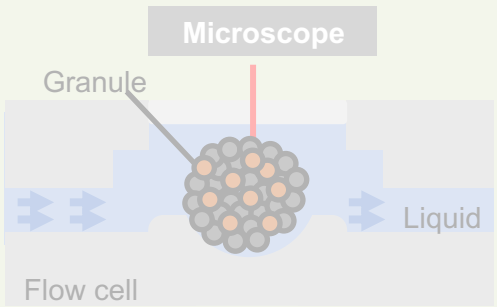
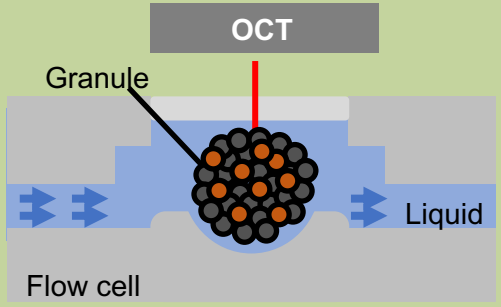


Investigating liquid uptake of granules



Investigating liquid uptake and swelling of granules



OCT: optical coherence tomography

Granule Liquid Absorption and Swelling Characterisation

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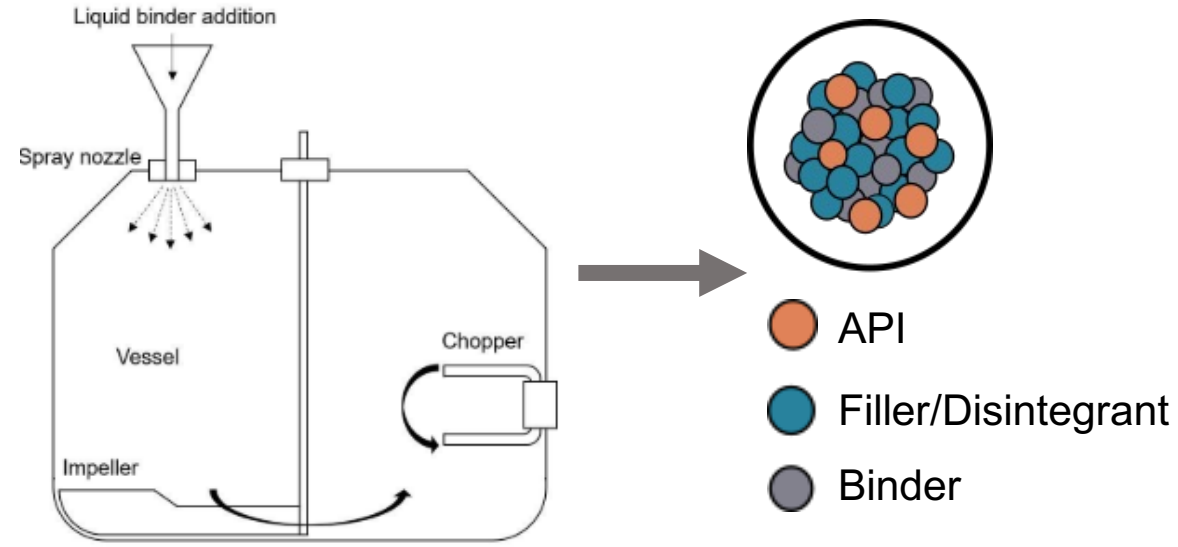

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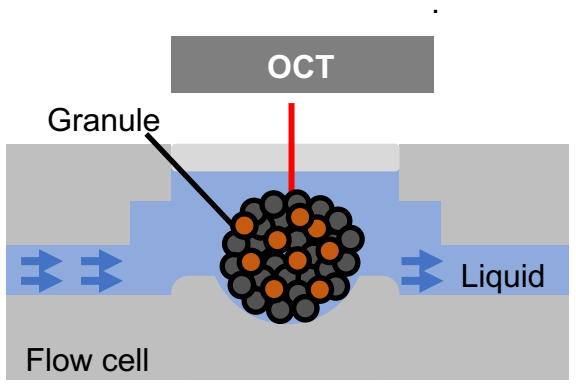

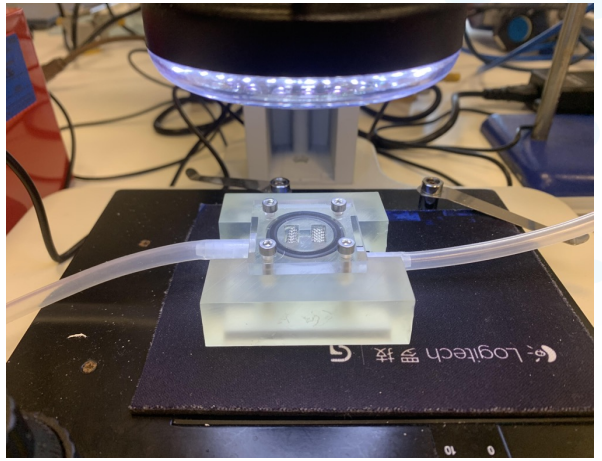

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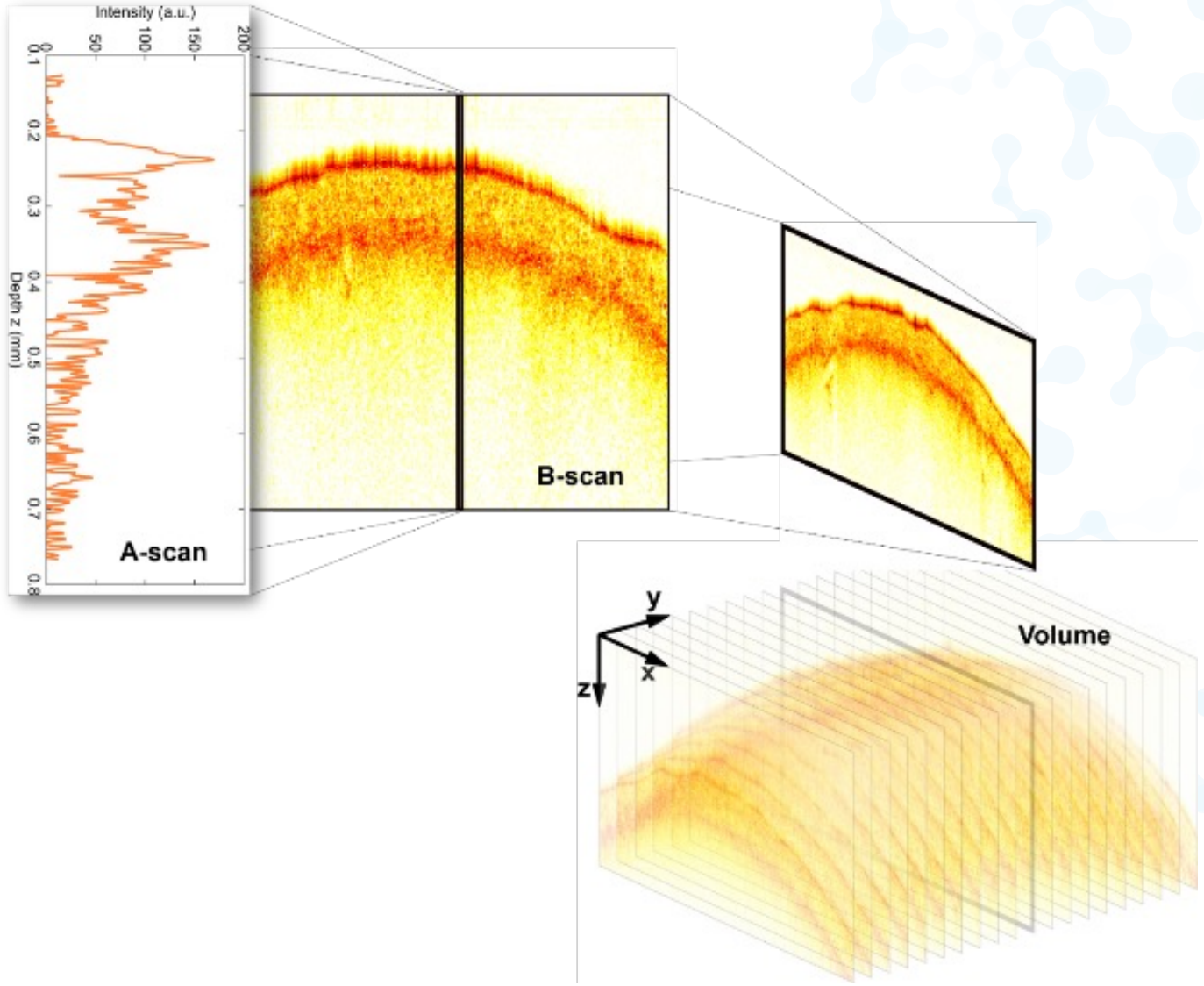
Aspirin+MCC +SSG	1.9-2.5	-	1	10

Optical Coherence Tomography for Material Characterisation

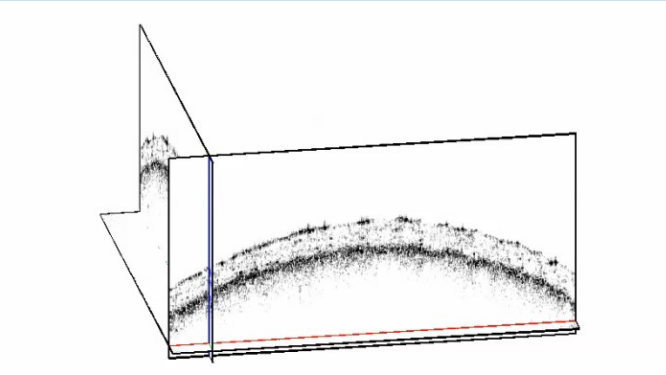
- Optical coherence tomography is a non-destructive, contactless and fast method to resolve sub-surface structures.
- It generates 1D, 2D and 3D depth profiles within seconds.
- Acquisition rate of 1D profiles can be as high as 230 kHz (→ 230 cross-sectional images per second)

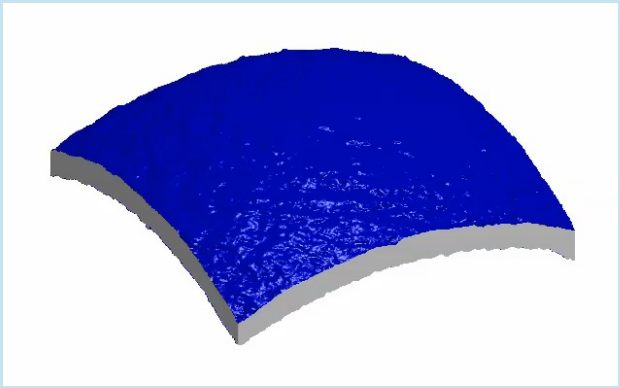


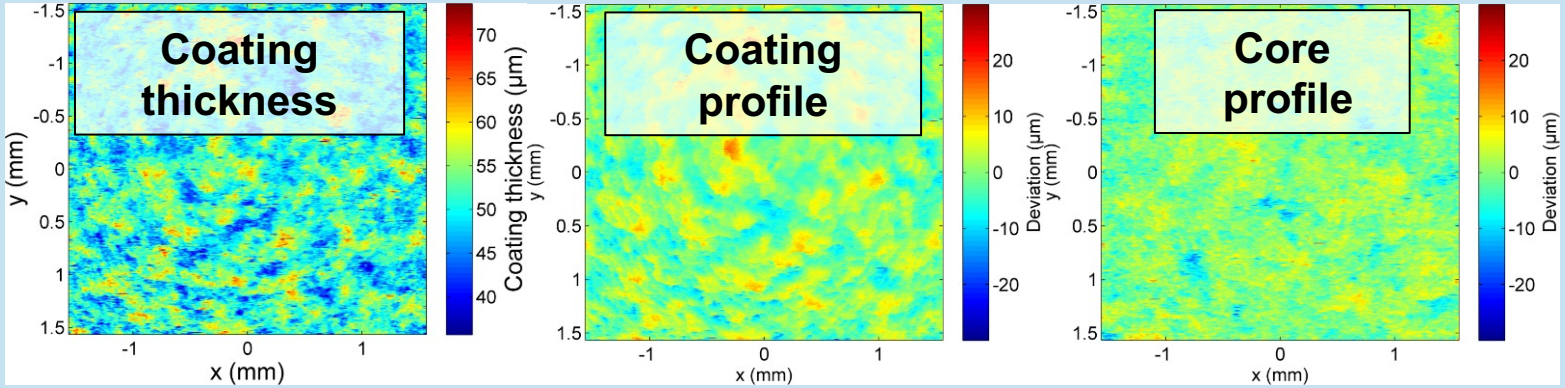
Selected Application of OCT

Tablet Coating Thickness Characterisation

Tablet Coating Characterisation

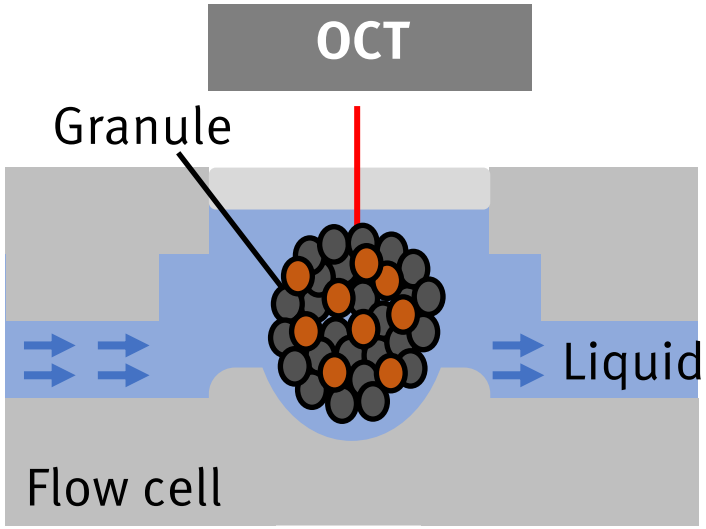


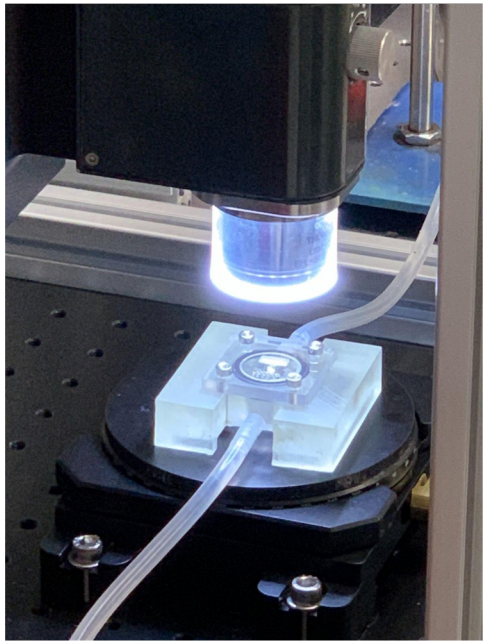


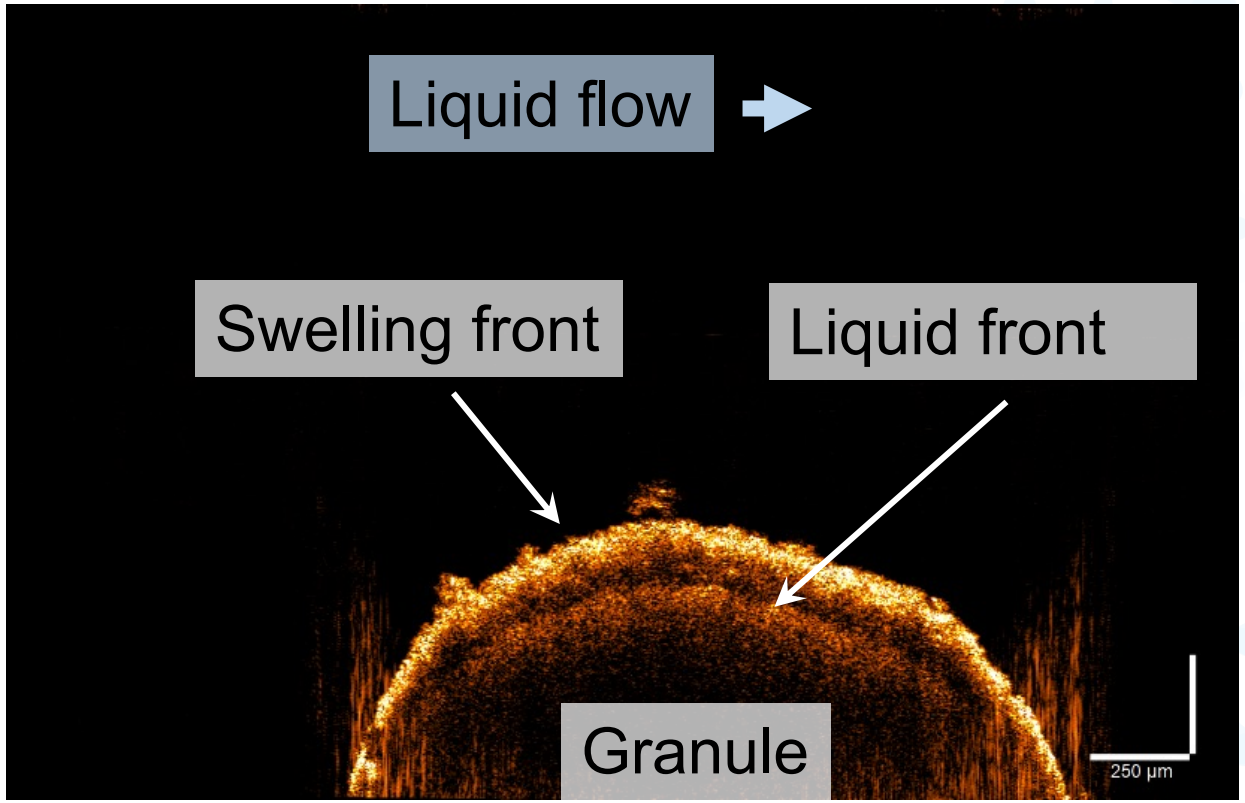


Pellet Coating Characterisation

Disintegration Analysis using Optical Coherence Tomography





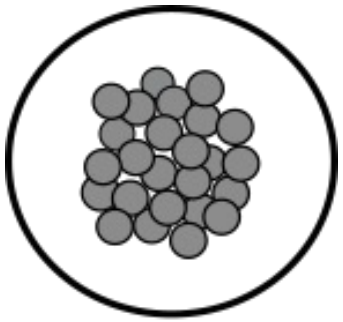


OCT conditions:

- Lens: 18 mm focal length
- Burst of images collected upon liquid addition and granule events
- Only 2D images analysed

Disintegration Analysis
Microcrystalline Cellulose

Product Structure

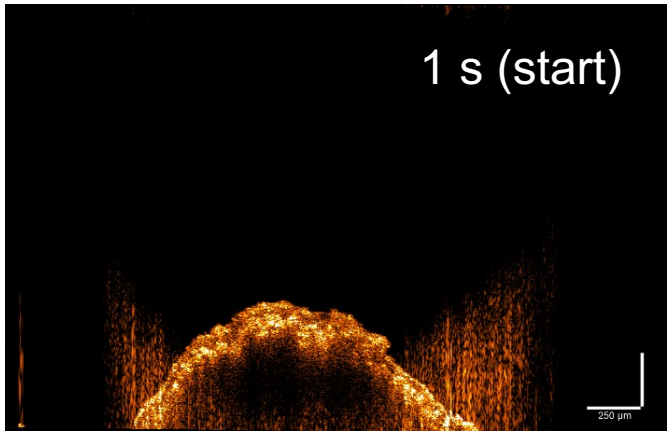


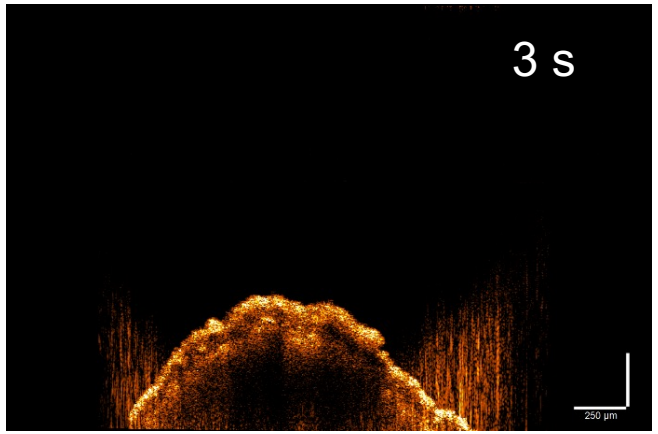
D_p (mm) = 2.3

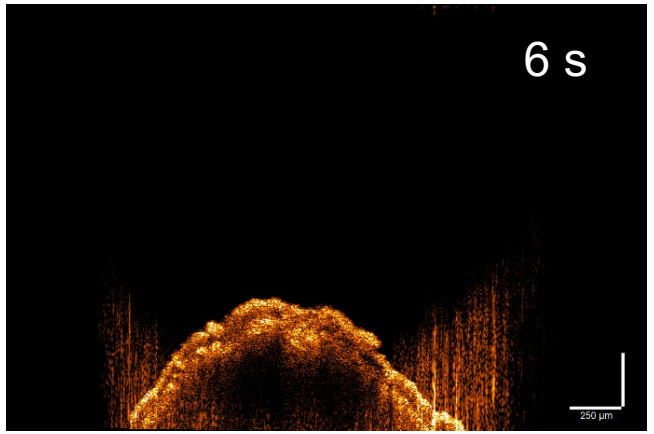
ε (%) = 47

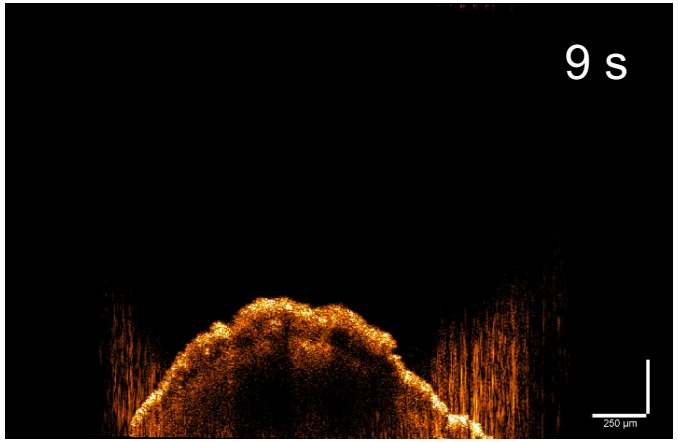
MCC

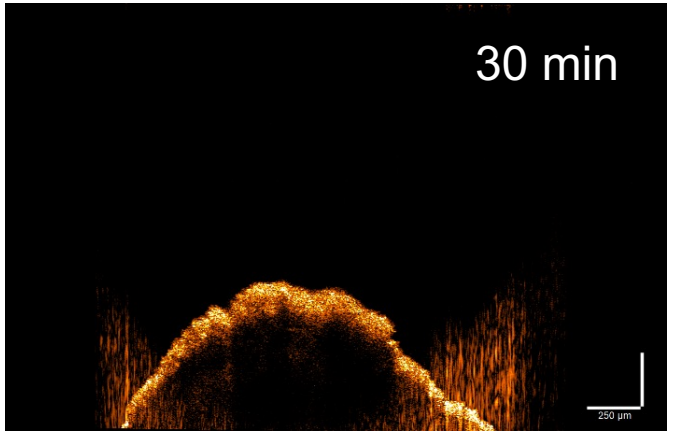
Surface Imaging

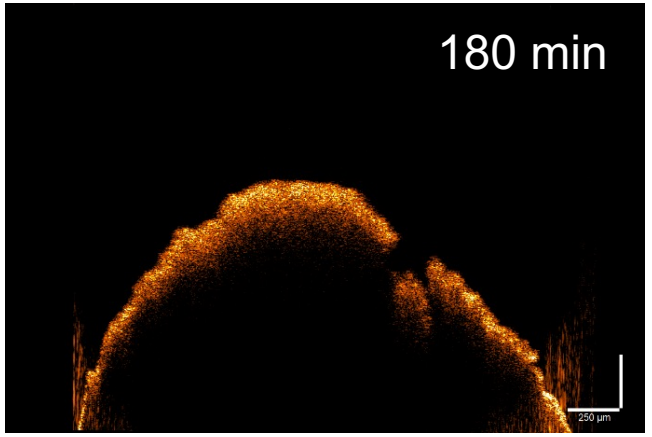






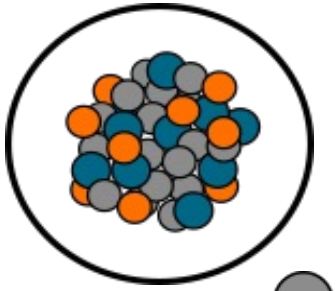
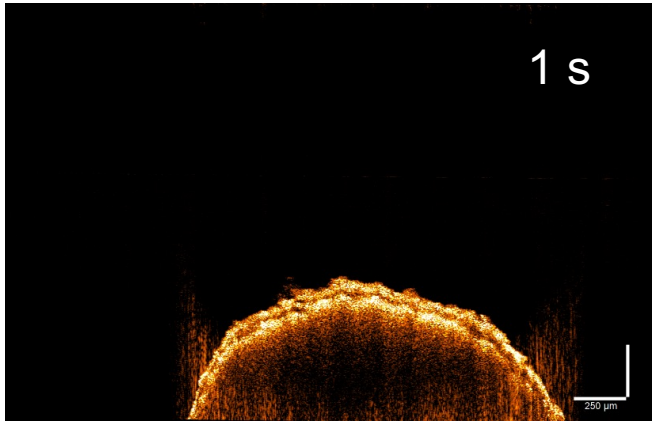
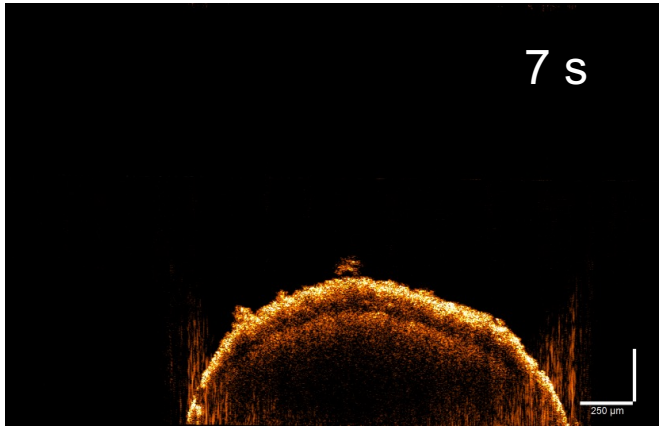
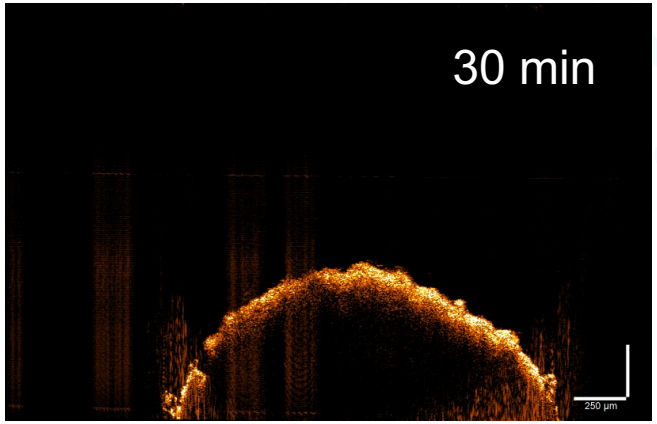
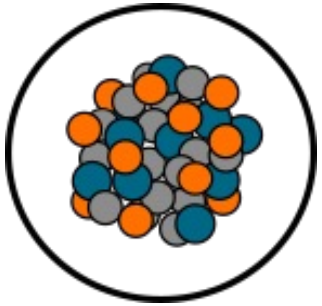
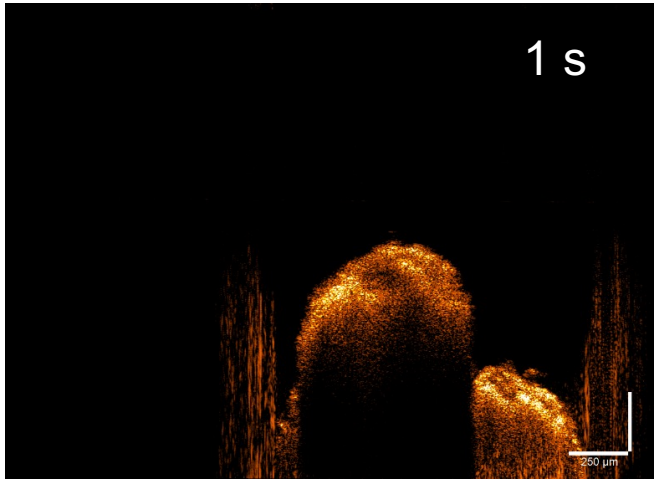
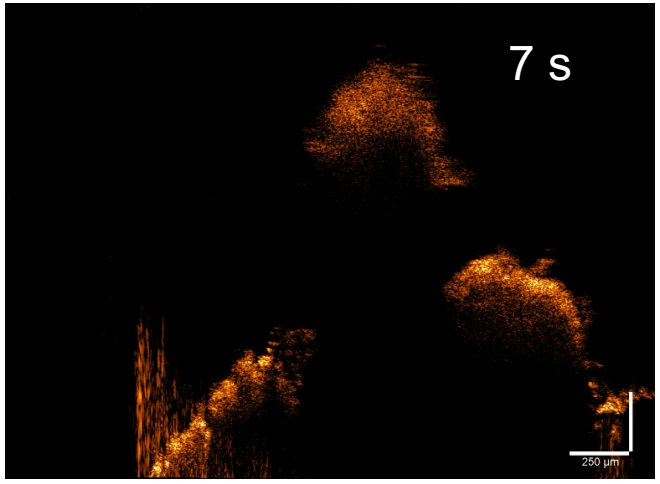
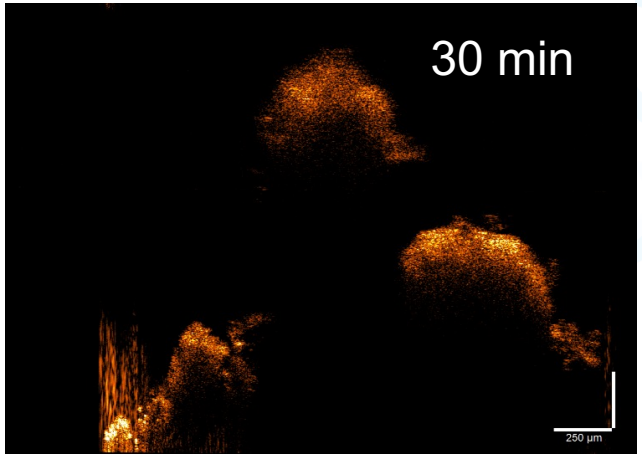






Disintegration Analysis

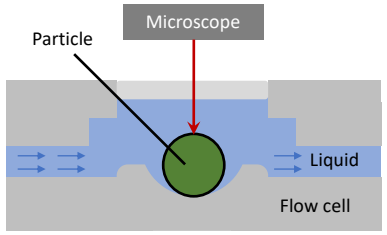
Apsirin and Excipients

Product Structure	Surface Imaging		
 D_p (*mm*) = 2.5 ε (%) = 35			
 D_p (*mm*) = 2.5 ε (%) = 52			

Conclusions

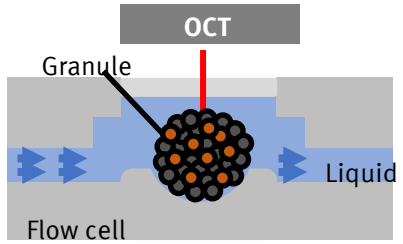
Advanced performance tests

Single particle swelling

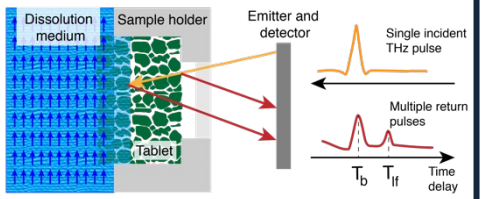


Microscope coupled to a custom-built flow cell

Granule liquid absorption and swelling



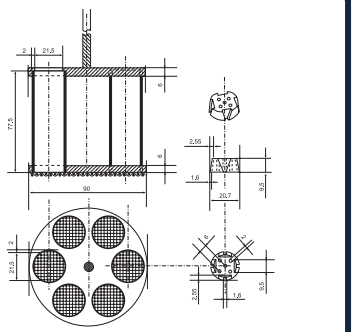
Compact liquid absorption and swelling



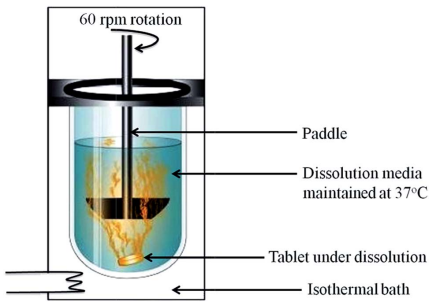
Multimodal dissolution testing system

1 Identify performance-controlling mechanisms

2 Develop data-driven, mechanistic and/or semi-mechanistic models



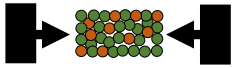
Disintegration testing



Dissolution testing

Traditional performance tests

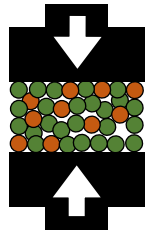
Raw material characterization (e.g. particle size/shape, flow coefficient)



Drug product properties (e.g. breaking force)

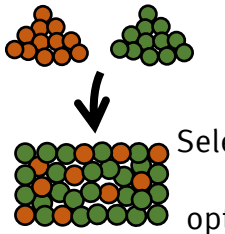
Material and product data

Digitally-enabled Process and Formulation Design



Process design

Selection of process settings to optimise performance



Formulation design

Selection of excipients / concentrations to optimise performance

Performance and stability predictor

Prediction of performance and stability