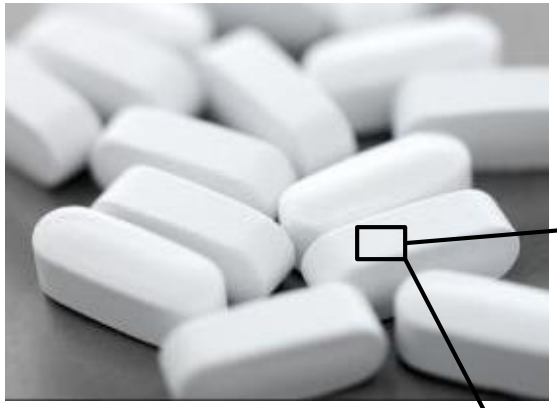
Microstructure-based modelling of tablet disintegration and dissolution

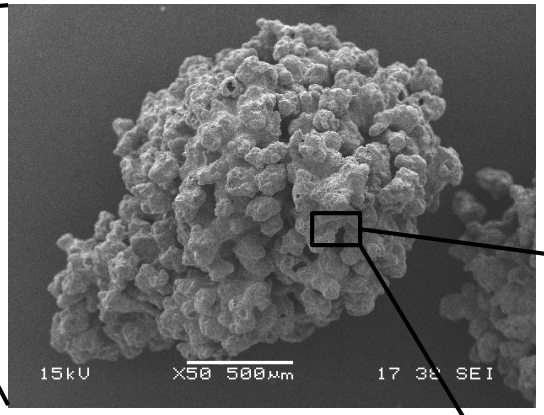
Frantisek Stepanek

Department of Chemical Engineering
University of Chemistry and Technology, Prague

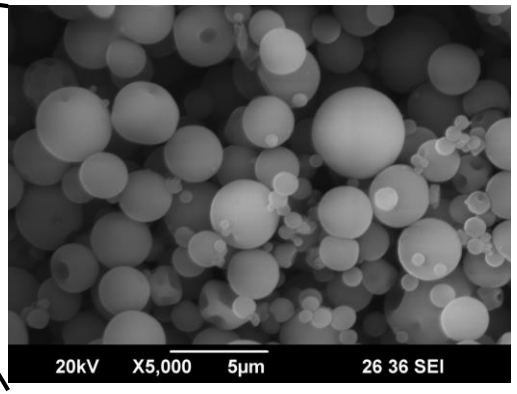
Tablet microstructure



Tablets

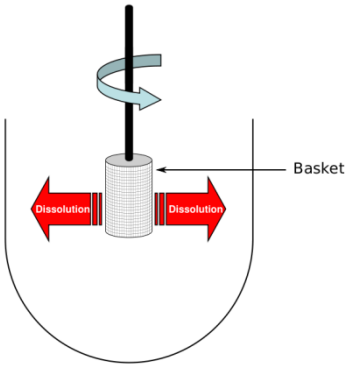


Granules

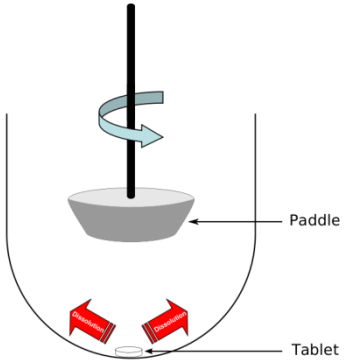


Primary particles

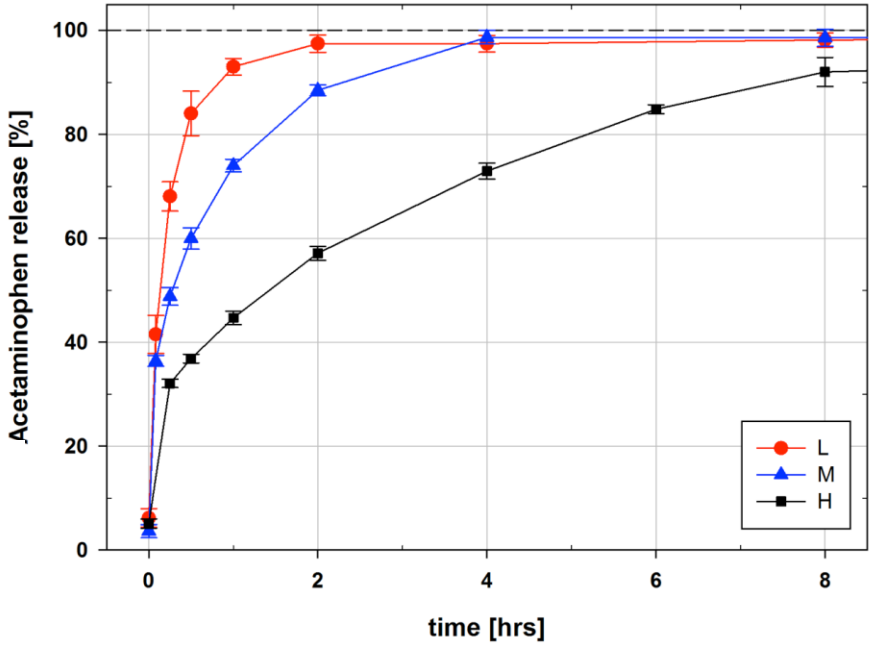
Conventional dissolution tests



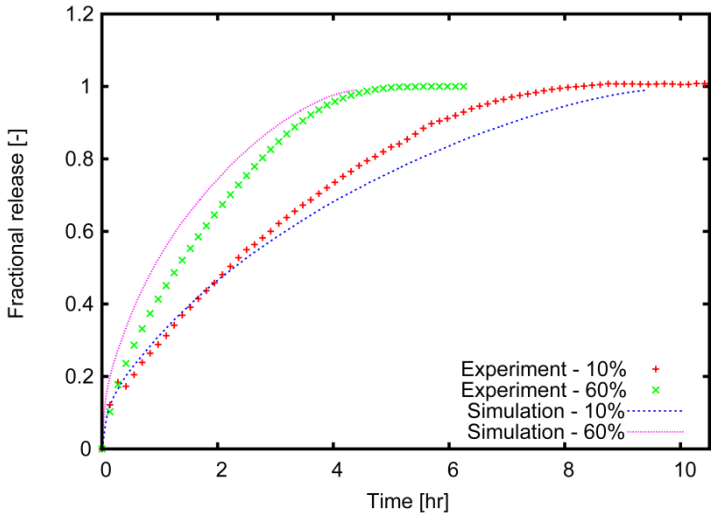
Basket method



Paddle method



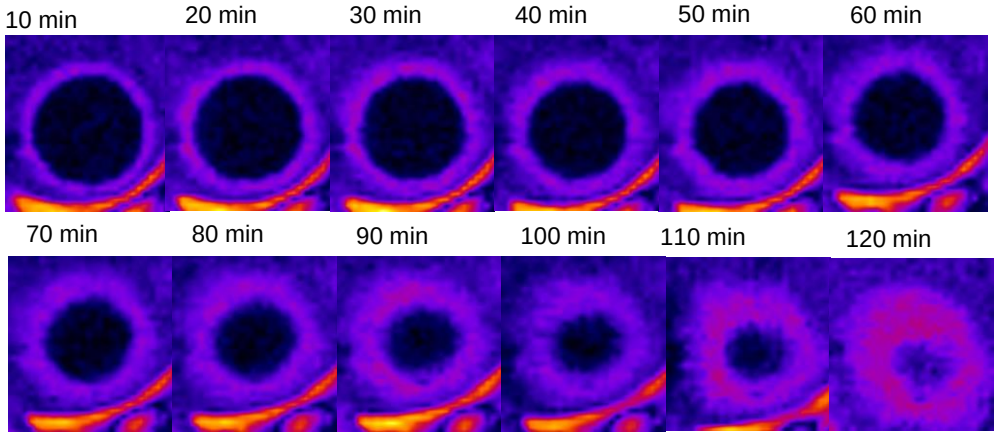
Forward problem (simulation)

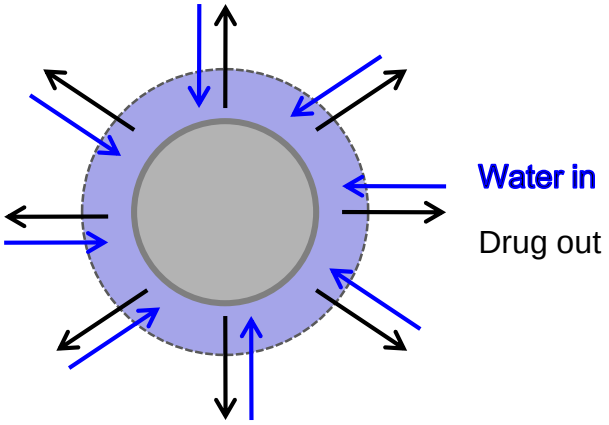


Inverse problem (design)

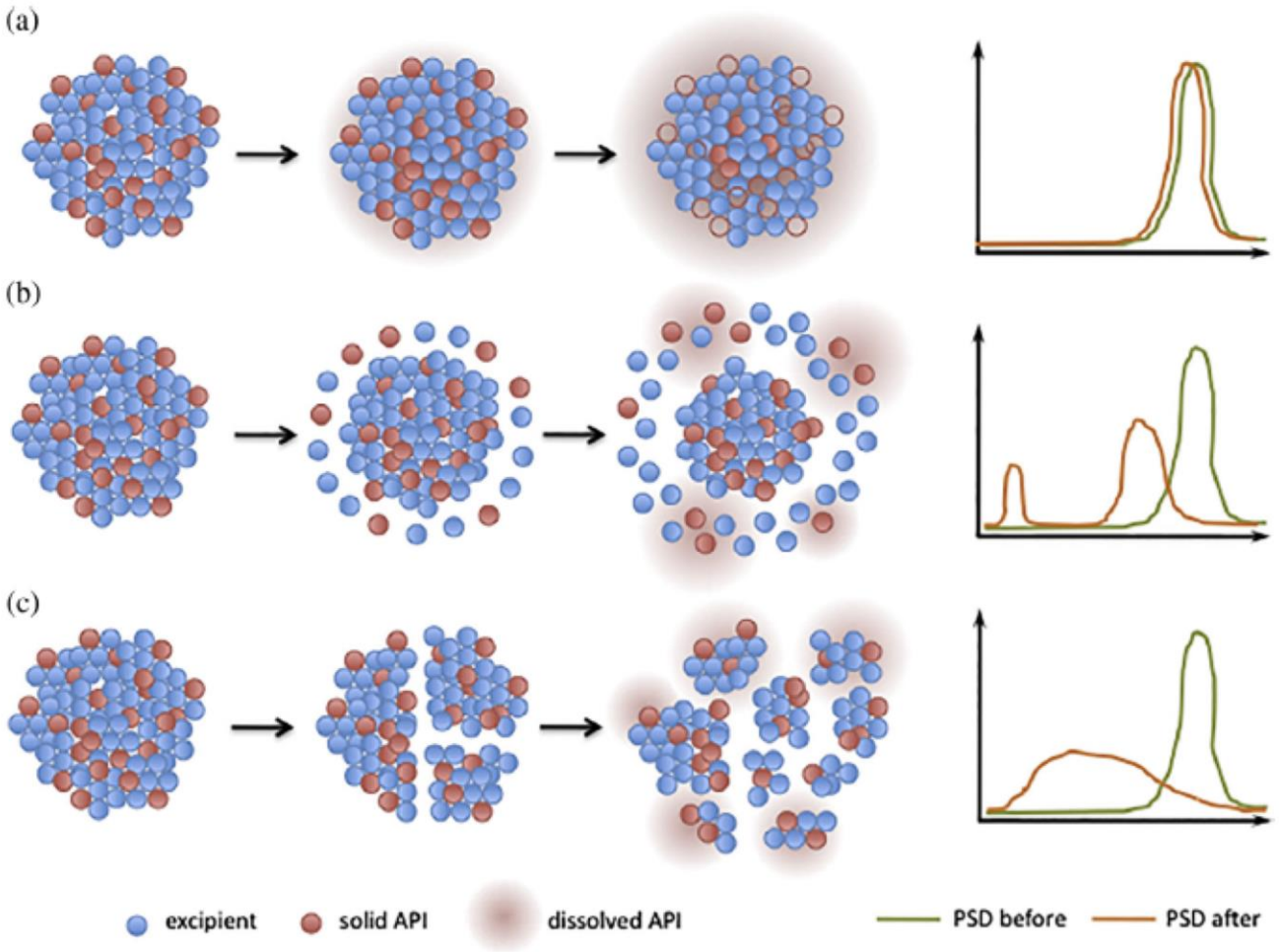
Elementary rate processes

- Ingress of dissolution medium
- Intrinsic dissolution
- Internal mass transfer (diffusion)
- External mass transfer (diffusion/convection)
- Swelling
- Disintegration





Disintegration



“leaching”

“erosion”

“break-up”

Smrcka et al. / Eur. J. Pharm. Biopharm. ***106*** *(2016) 107–116*

Overall methodology / workflow

1) Create the starting microstructure

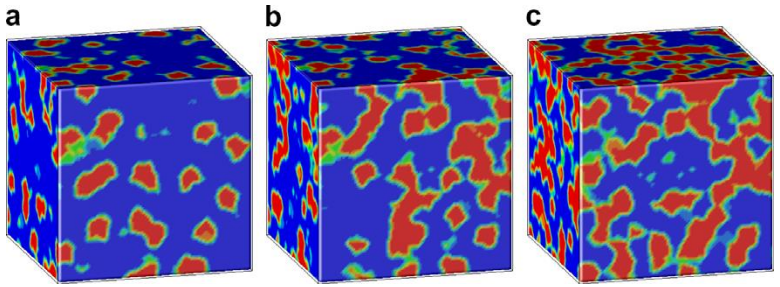
   - physically

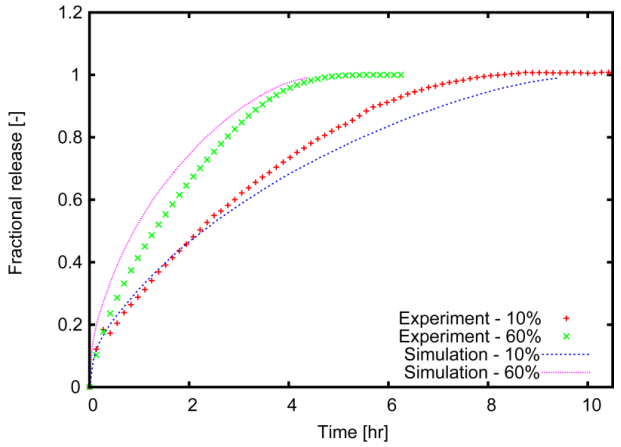
   - computationally

2) Use experimental data for model validation and parameter calibration

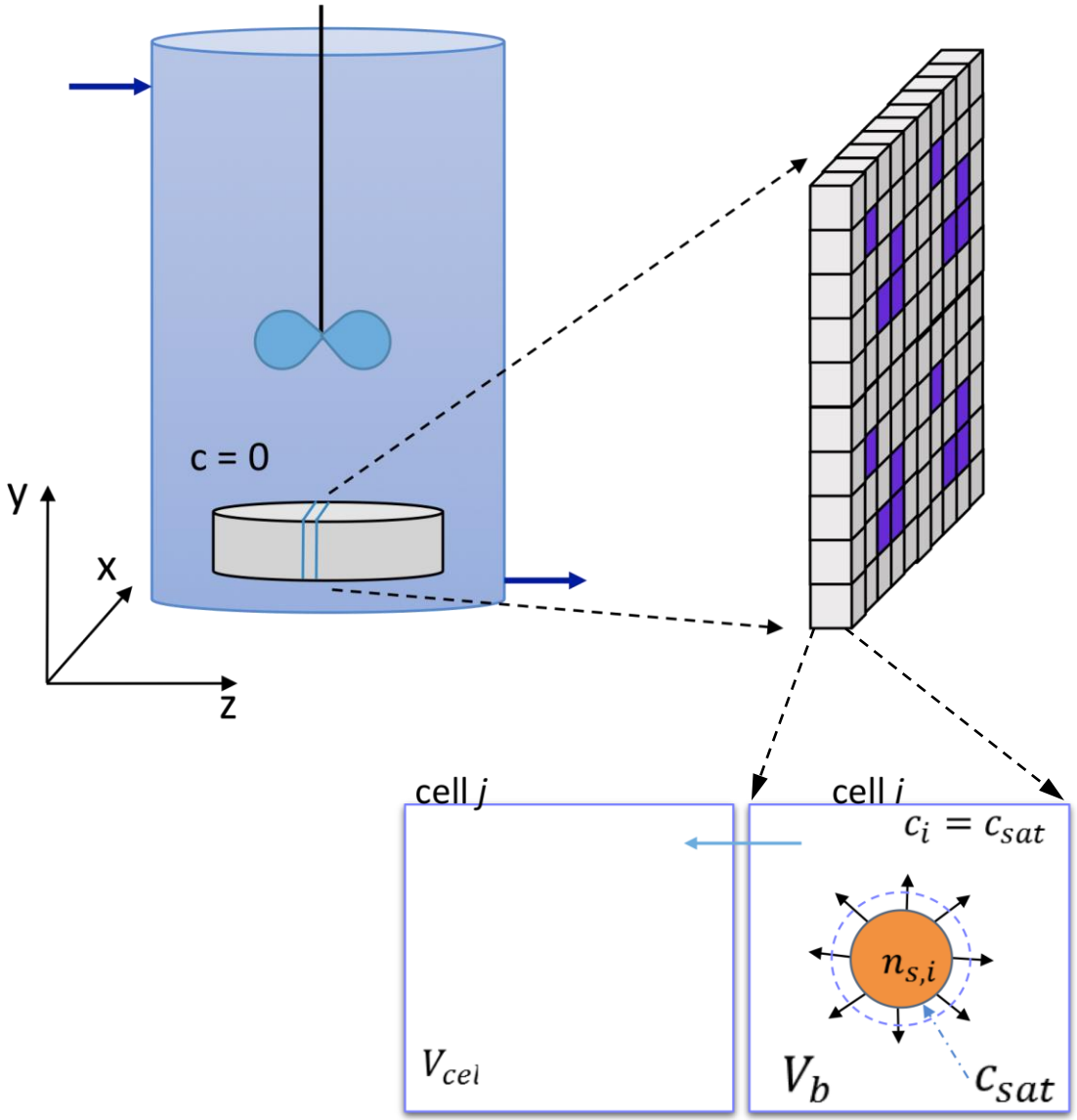
3) Run the model to perform parametric studies

   => structure-property relationships





Model set-up



Components:

- API
- Excipient(s)
- Solvent

Phenomena:

- Mass balance in bulk
- Local dissolution
- Mass transfer

(diffusion, convection)

$$\frac{dn_{s,i}}{dt} = -\sum_j \frac{D}{\delta}(c_i - c_j)A_{ij}$$

$$\frac{dc_j}{dt} = \sum_j \frac{D}{\delta}(c_i - c_j)\frac{A_{ij}}{V_{cell}}$$

Progress of a simulation

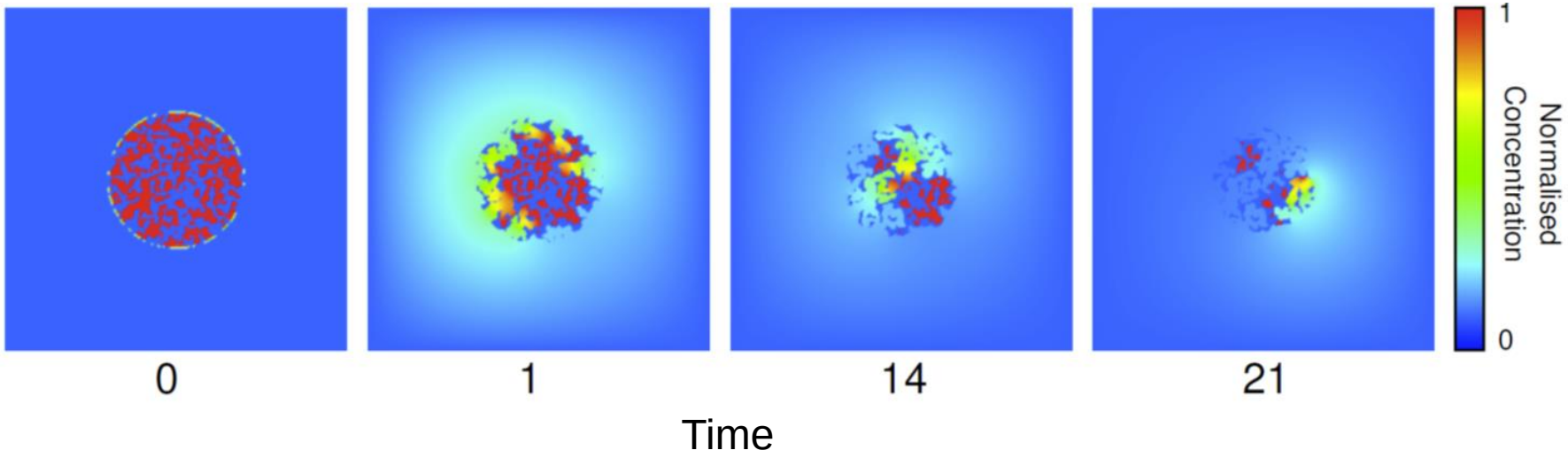
Diffusion equation in the liquid phase

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot (-D_i \nabla c_i) + s_i \quad i = A, B$$

$$s_i(\mathbf{x}) = \begin{cases} k_i(c_i^{sat} - c_i(\mathbf{x})) & \forall \mathbf{x}: \phi_i(\mathbf{x}) > 0 \\ 0 & \text{otherwise} \end{cases}$$

Evolution equation for the solid phase

$$\frac{\partial \phi_i}{\partial t} = -\frac{s_i}{\rho_i}$$



Progress of a simulation

Diffusion equation in the liquid phase

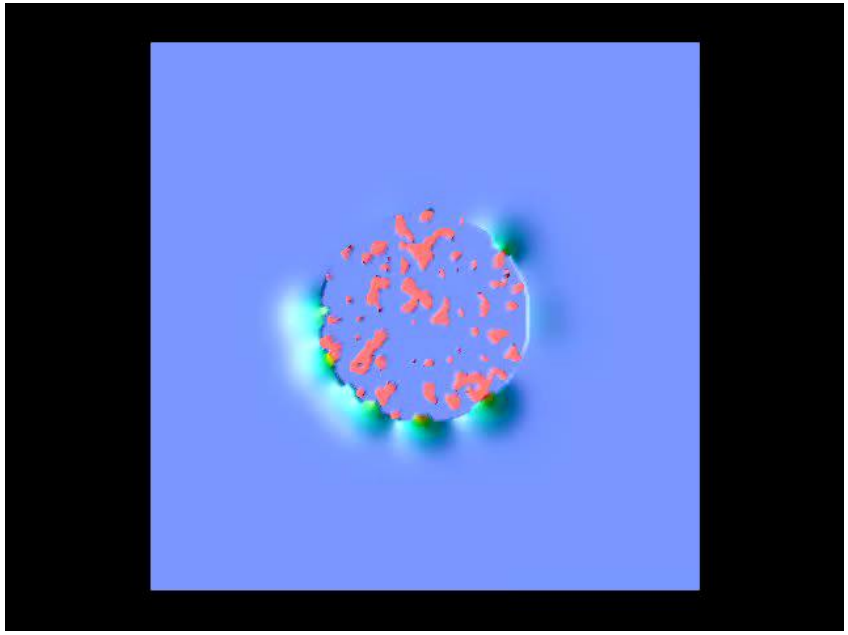
$$\frac{\partial c_i}{\partial t} = -\nabla \cdot (-D_i \nabla c_i) + s_i \quad i = A, B$$

$$s_i(\mathbf{x}) = \begin{cases} k_i(c_i^{sat} - c_i(\mathbf{x})) & \forall \mathbf{x}: \phi_i(\mathbf{x}) > 0 \\ 0 & \text{otherwise} \end{cases}$$

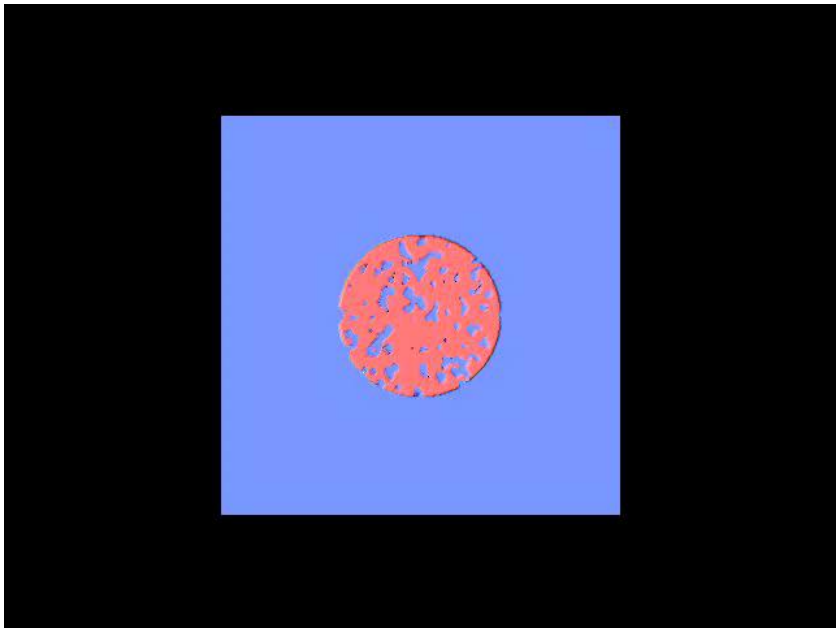
Evolution equation for the solid phase

$$\frac{\partial \phi_i}{\partial t} = -\frac{s_i}{\rho_i}$$

Component A (fast)

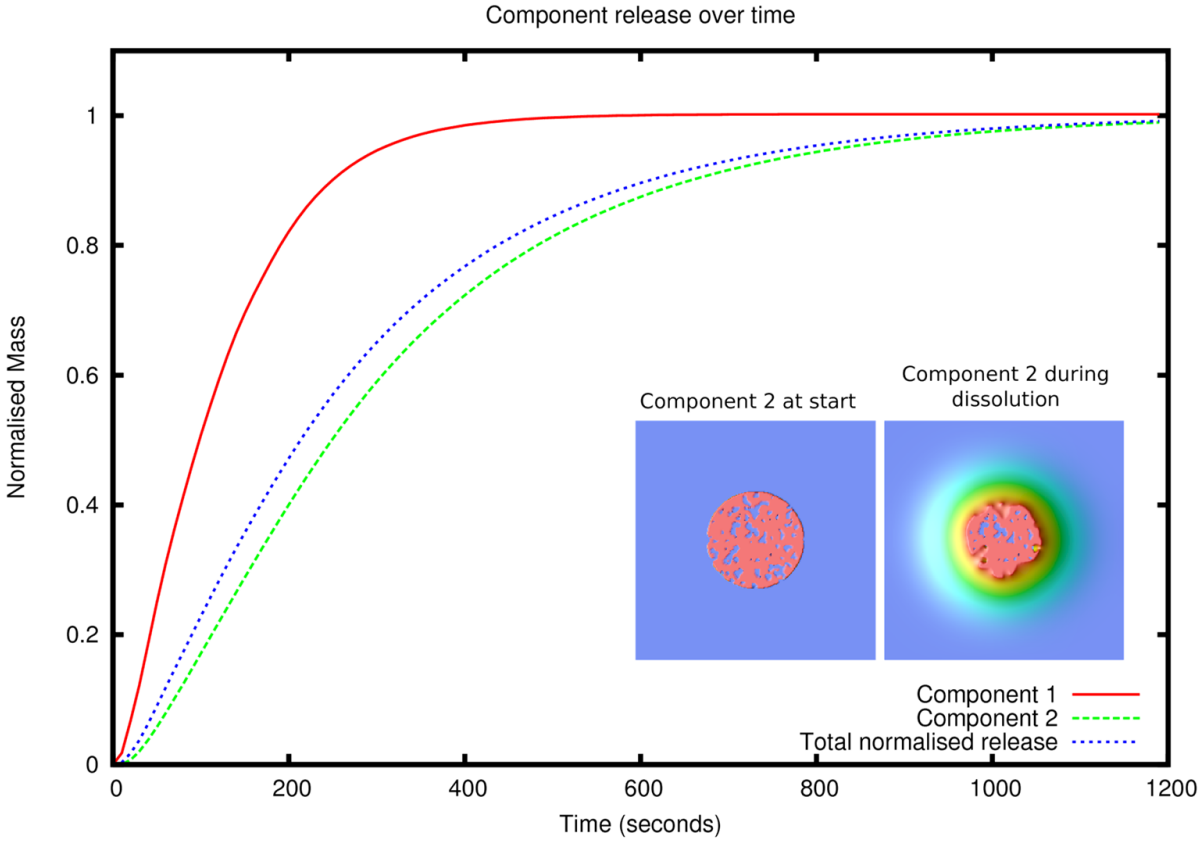


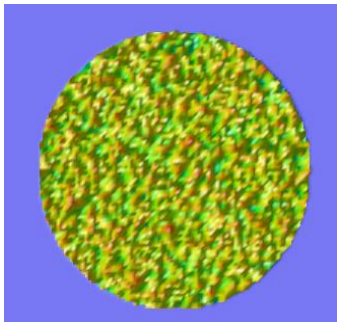
Component B (slow)

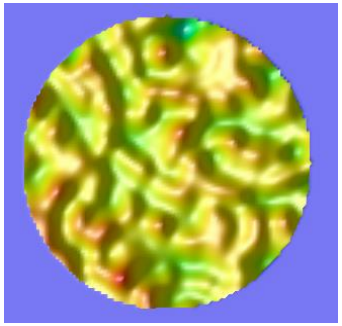


Outputs

- Concentration of each species in bulk $c_i(t)$
- Size distribution and composition of tablet residua



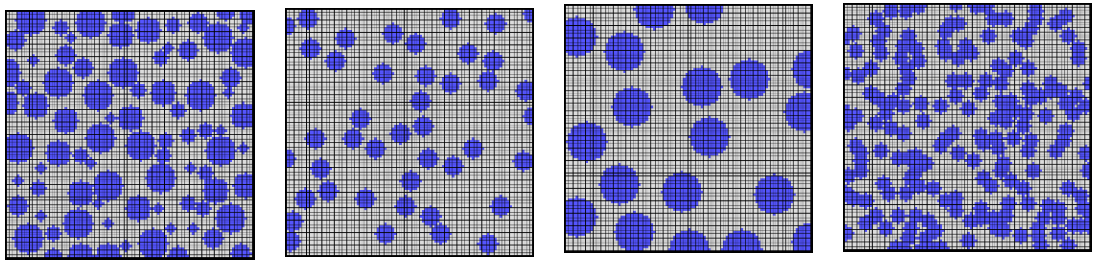




Kimber et al. / Comput. Chem. Eng. **35**, 1328–1339 (2011)

Input microstructures

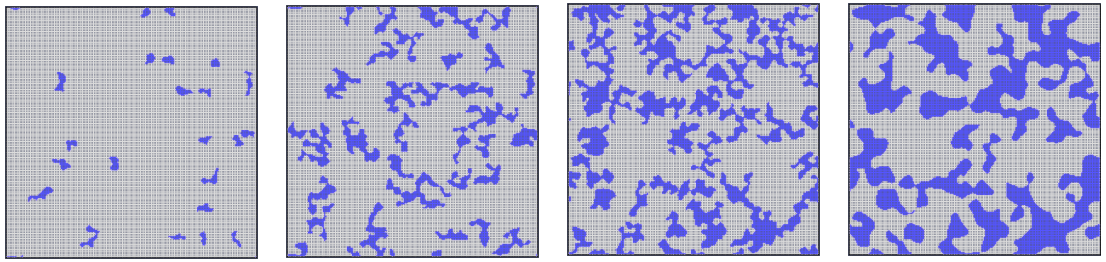
1) Computer-generated hypothetical structures



We can vary:

- Mass fraction of components
- Particle size distributions
- Choice of geometrical primitives

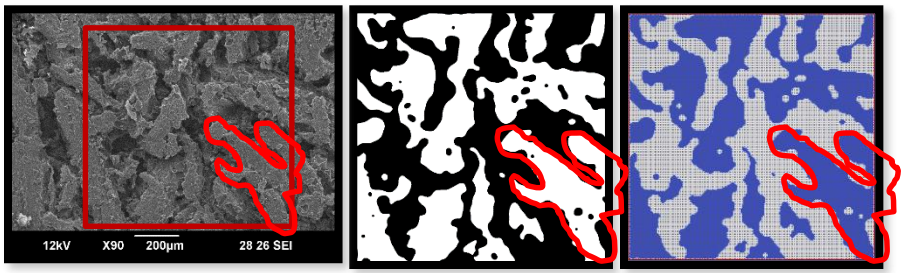
2) Computer-generated structures based on process simulation



For example:

DEM simulation of blending and direct compression

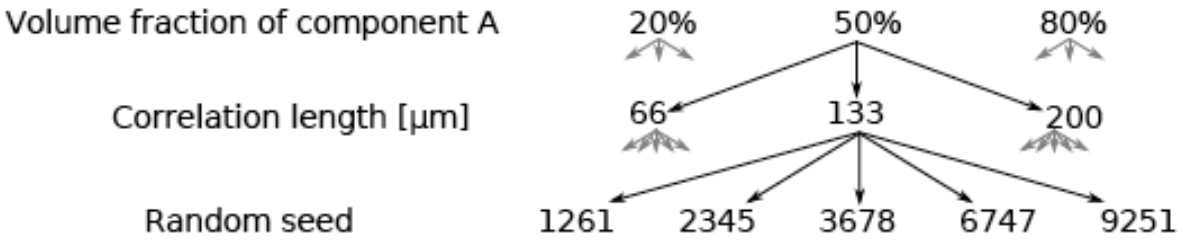
3) Real structures from experimental data

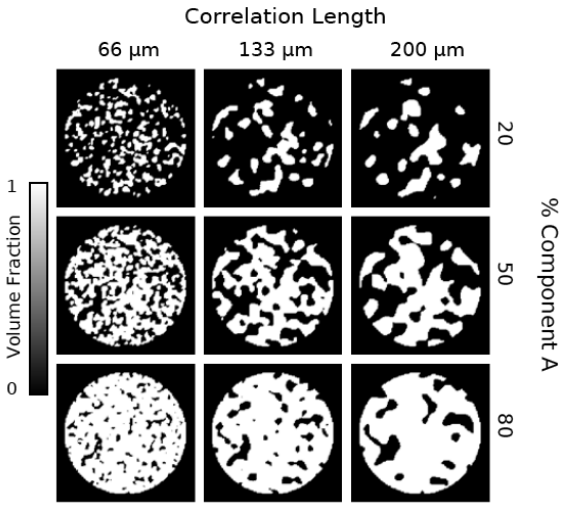


- X-ray micro CT
- SEM
- FTIR / Raman mapping

Parametric studies for inverse problem

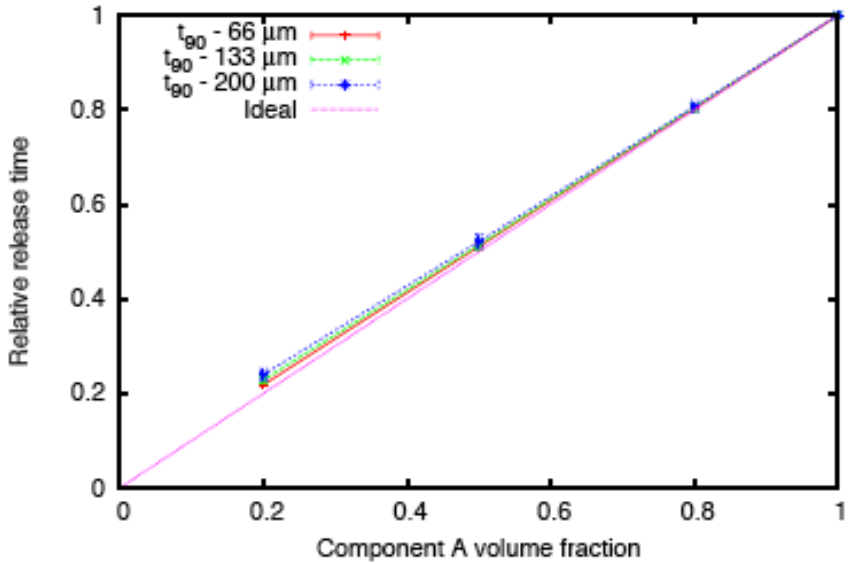
Study 1: microstructure & heterogeneity



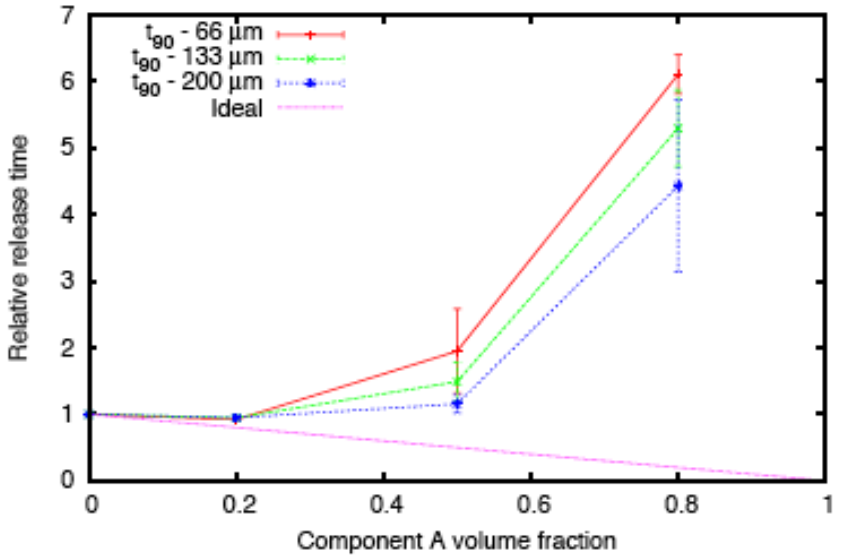


Physical properties kept constant: $D_A = D_B$, $c_A^* = 0.1\ c_B^*$

Relative release time of A

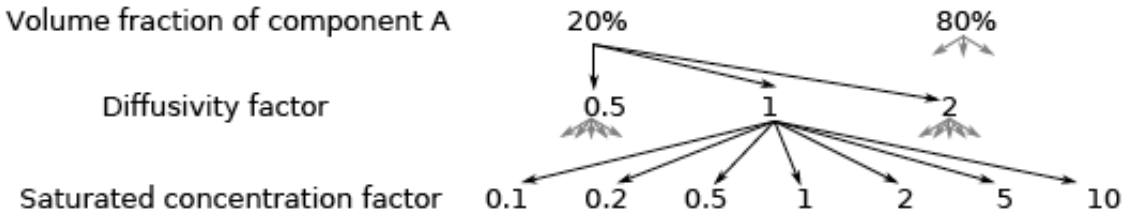


Relative release time of B



Parametric studies for inverse problem

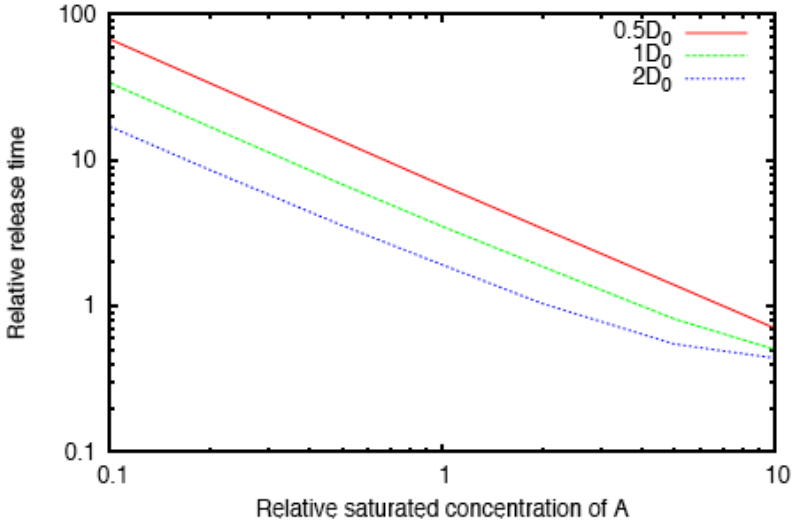
Study 2: material properties



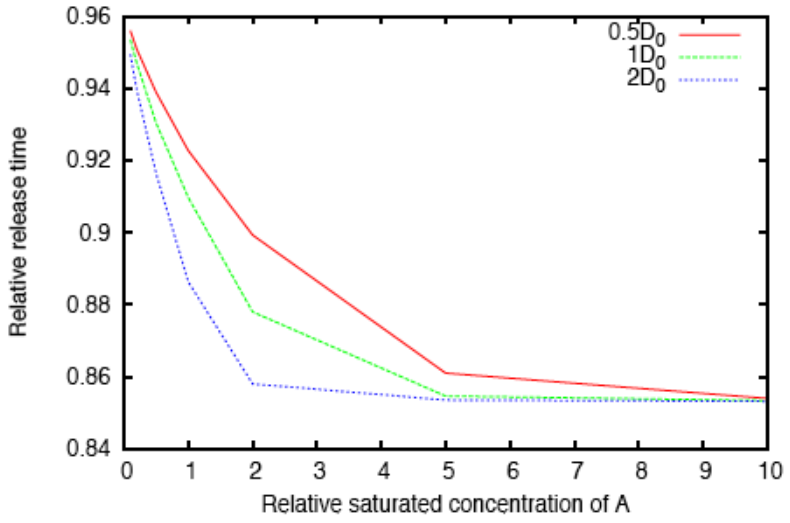
Relative release time of pure A

c_A^{sat*}	D_A^*		
	0.5	1	2
0.1	19.70	9.85	4.93
0.2	9.87	4.93	2.47
0.5	3.97	1.98	0.99
1	2.00	1.00	0.50
2	1.02	0.51	0.25
5	0.43	0.21	0.11
10	0.24	0.12	0.06

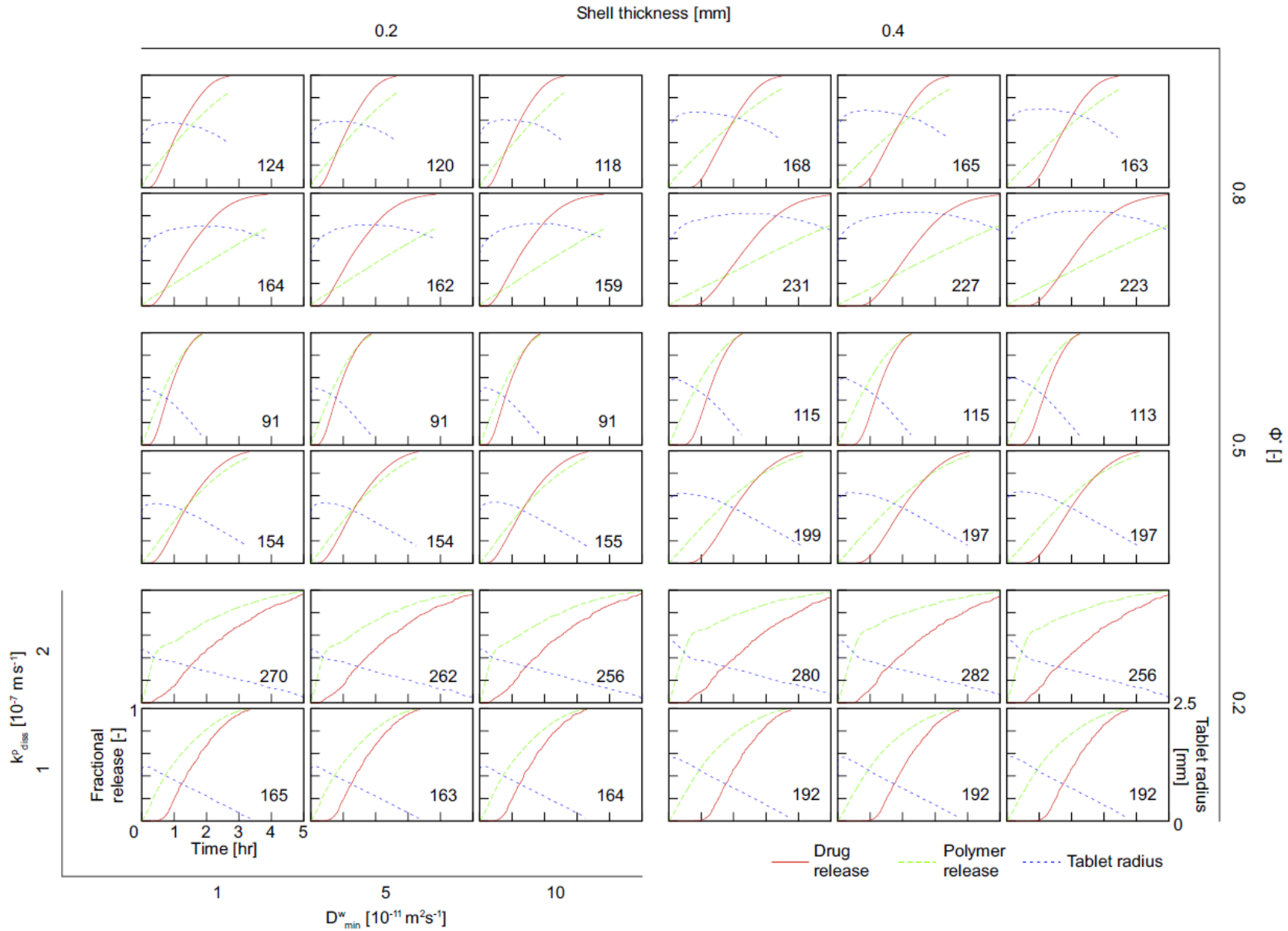
Relative release time of B from 80% A



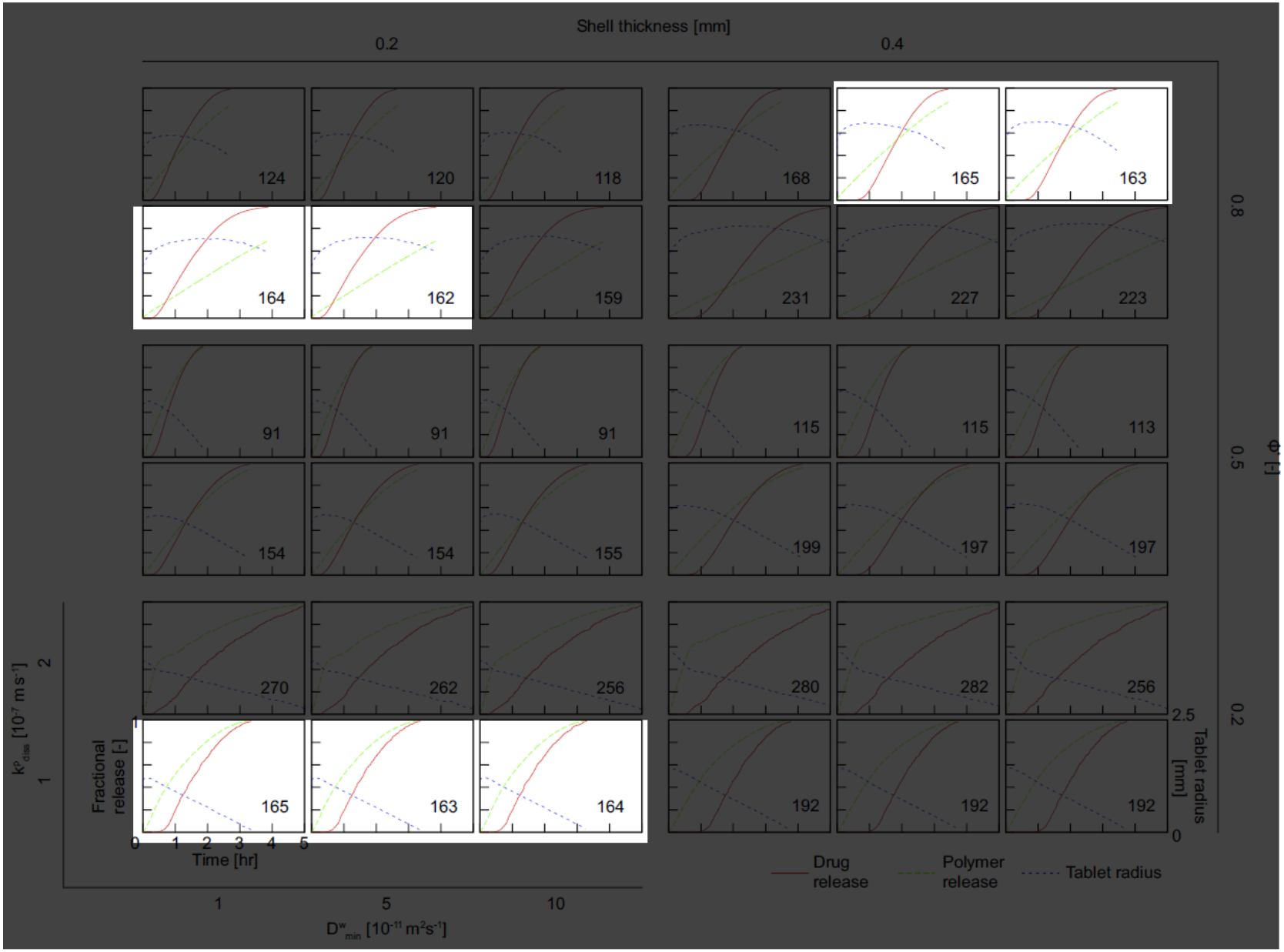
Relative release time of B from 20% A



Parametric studies for inverse problem



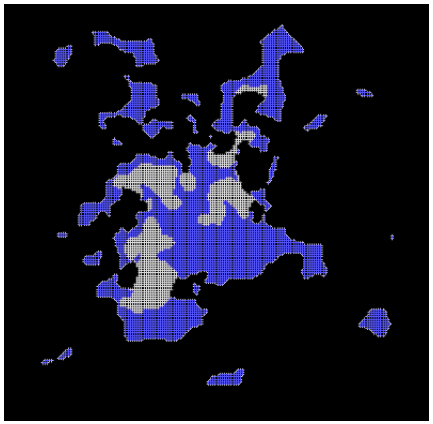
Parametric studies for inverse problem

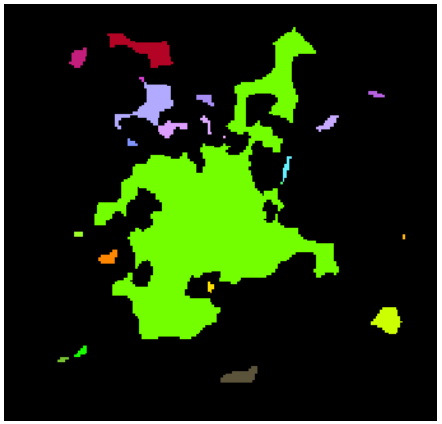


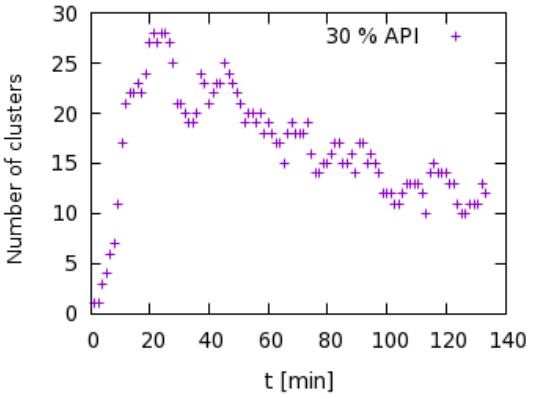
Analysis of disintegration residua

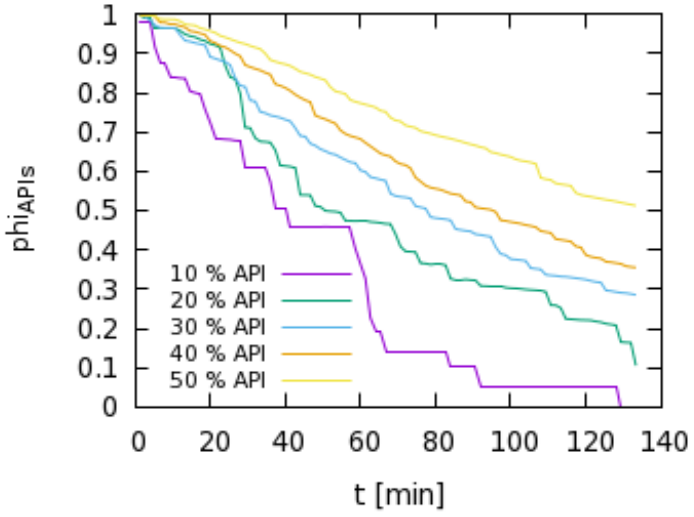
During dissolution:

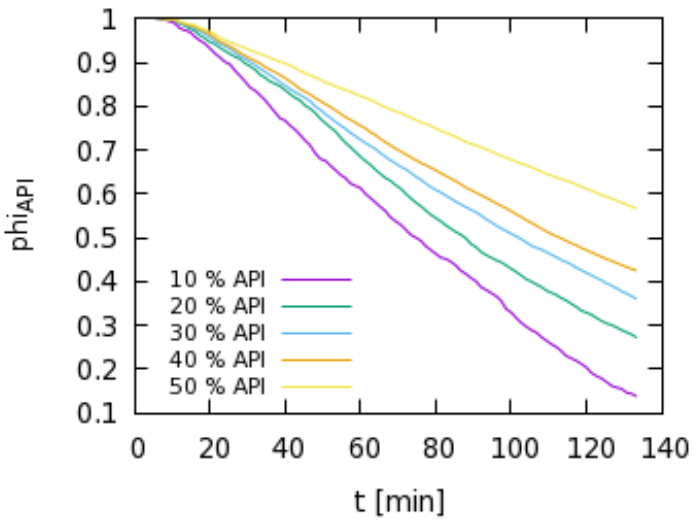
- Test of connectivity (percolation)
- Remove disconnected solid clusters and dissolve them separately











Dissolution and disintegration of tablet residua

Inputs:

- structure
- flowrate, viscosity
- solubilities and Diff coefficients

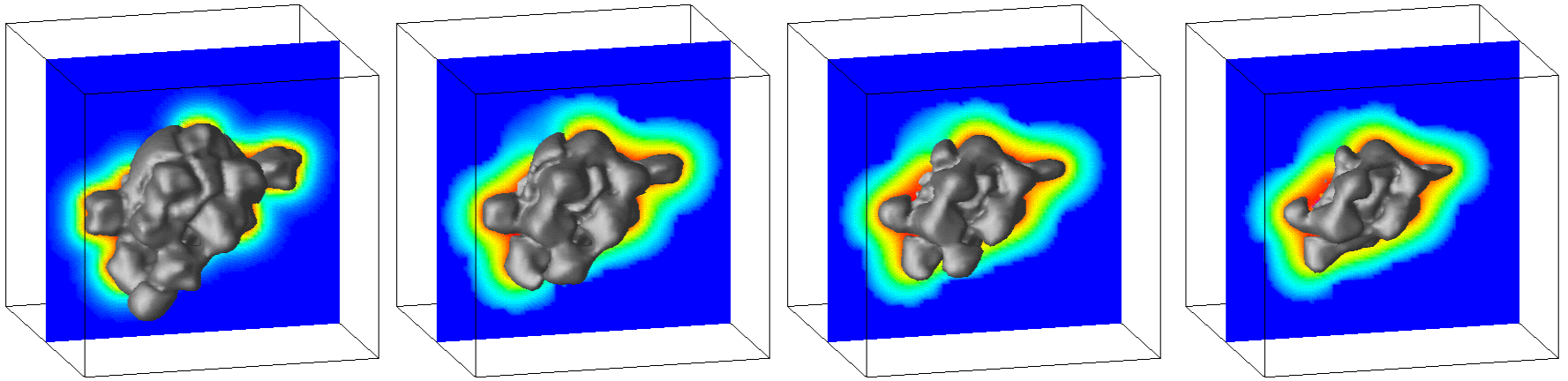
Output:

- dissolution rate and mechanism

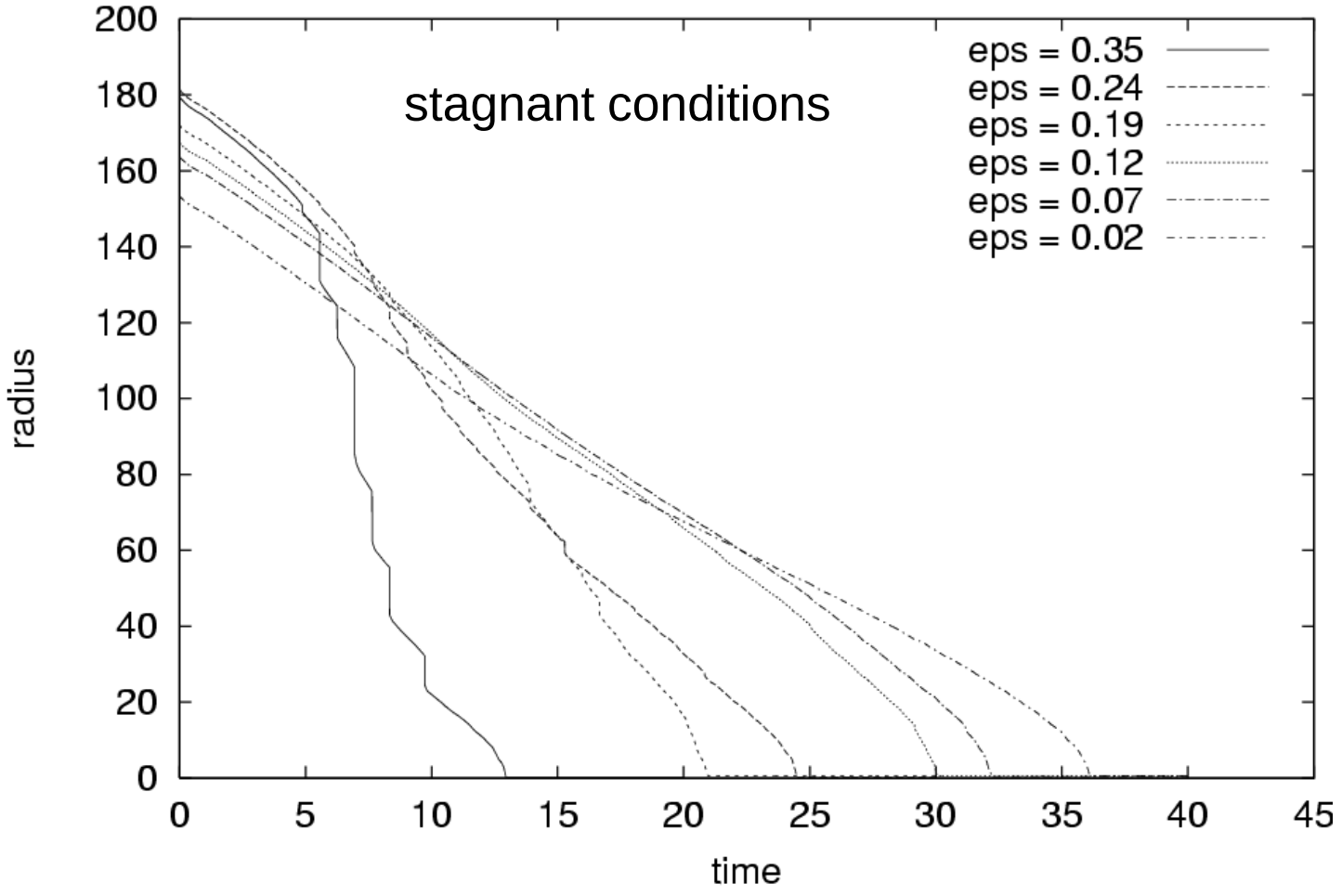
$$\frac{\partial c_i}{\partial t} = -\mathbf{v}\nabla c_i + D_i \nabla^2 c_i$$

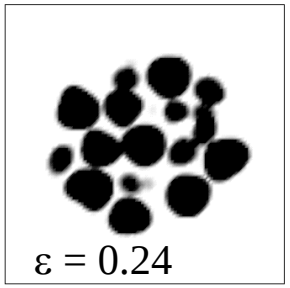
$$\eta \nabla^2 \mathbf{v} = \nabla p \quad \nabla \cdot \mathbf{v} = 0$$

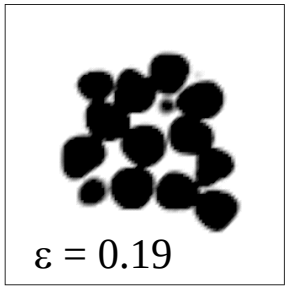
$$u_s = \frac{M_{w,i}}{\rho_{s,i}} \mathbf{n_s} \cdot (-D_i \nabla c_i)$$

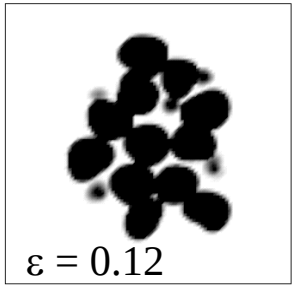


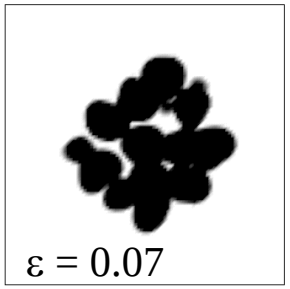
Effect of porosity on dissolution mechanism





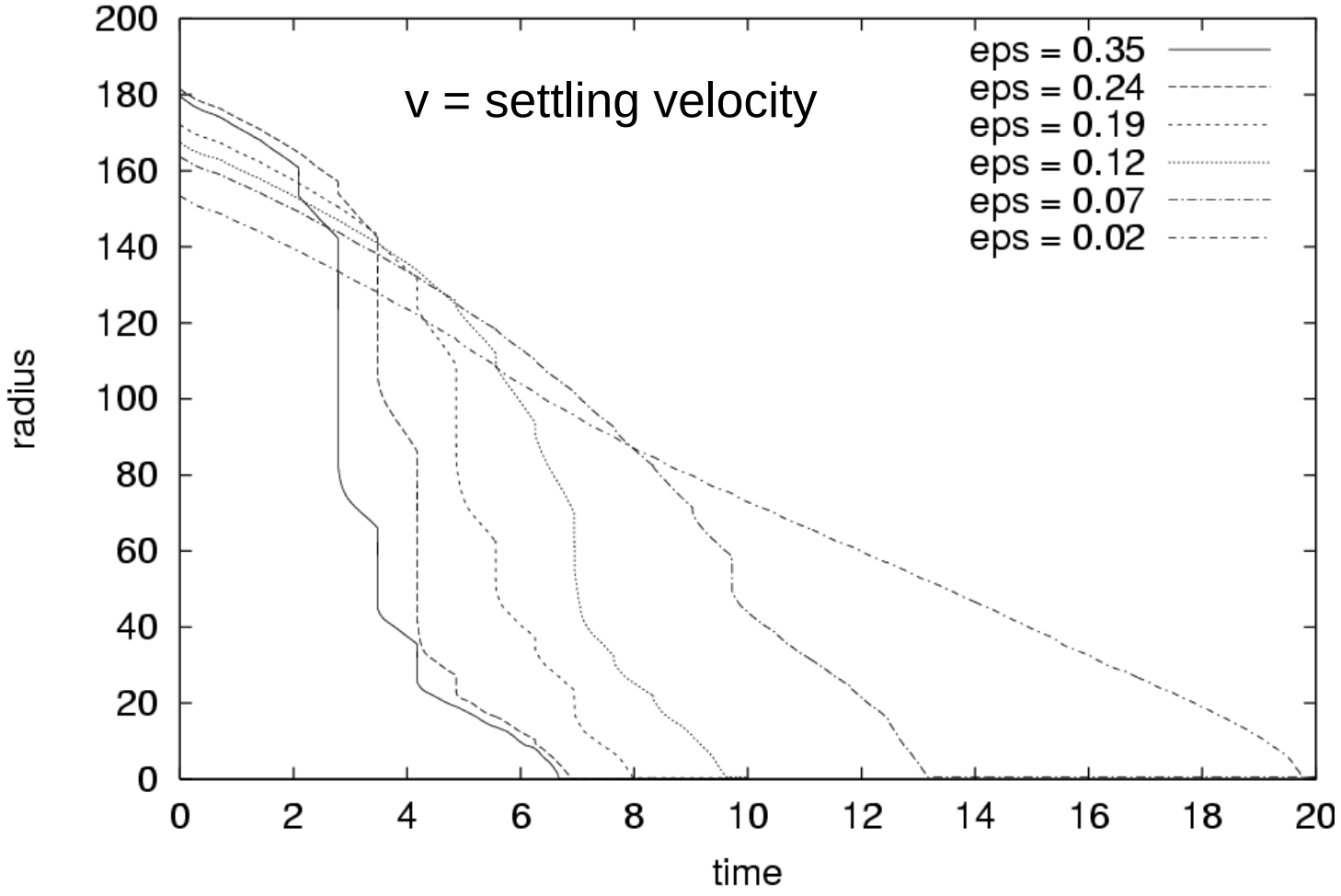


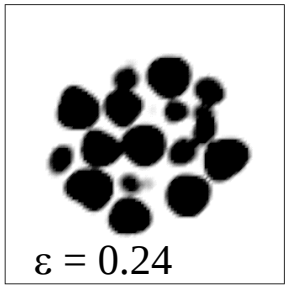


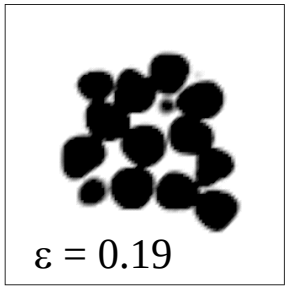


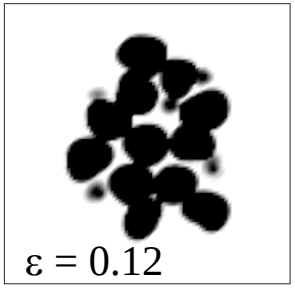
Low porosity, low Re: surface erosion

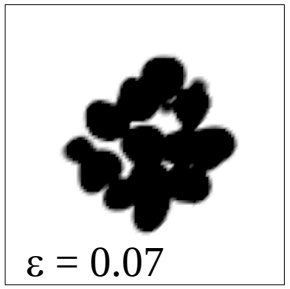
Effect of porosity on dissolution mechanism











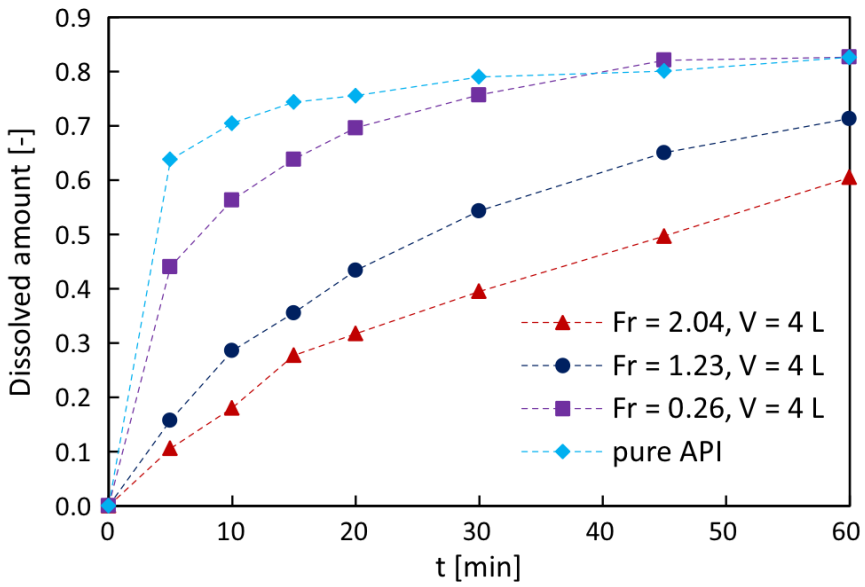
High porosity, high Re: disintegration

Case study: high-shear granulation scale-up

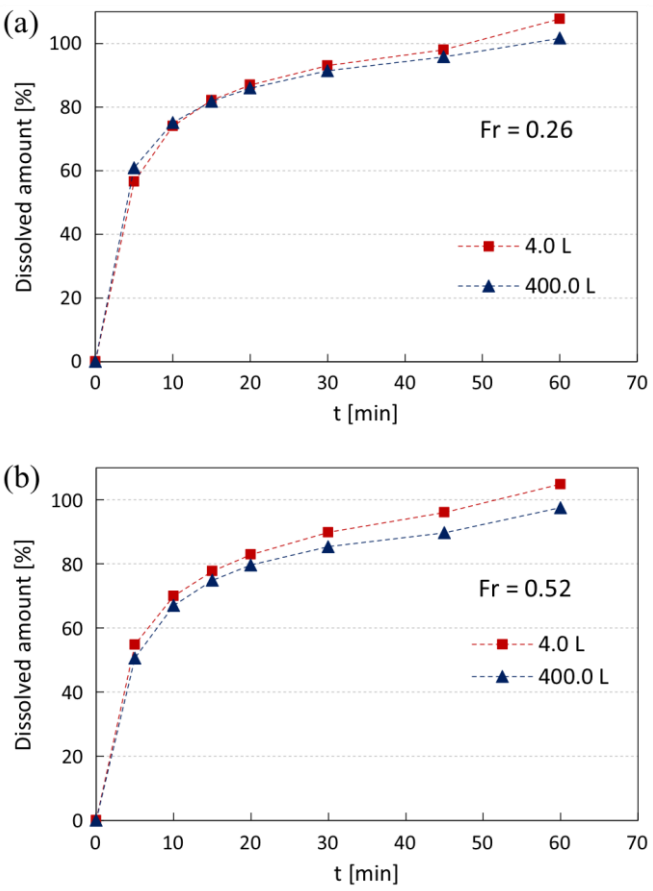
Table 2
Values of process parameters for granulation experiments at different scales.

Vessel volume (dm^3)	Agitator diameter (m)	Batch size (kg)	Agitation rate (rpm)	Froude number (–)	L/S ratio (–)
4.0	0.21	0.735	209	0.26	0.39
4.0	0.21	0.735	297	0.52	0.39
4.0	0.21	0.735	467	1.23	0.39
4.0	0.21	0.735	602	2.04	0.39
400	1.00	73.5	95	0.26	0.39
400	1.00	73.5	135	0.52	0.39

$$Fr = \frac{N^2 d}{g}$$



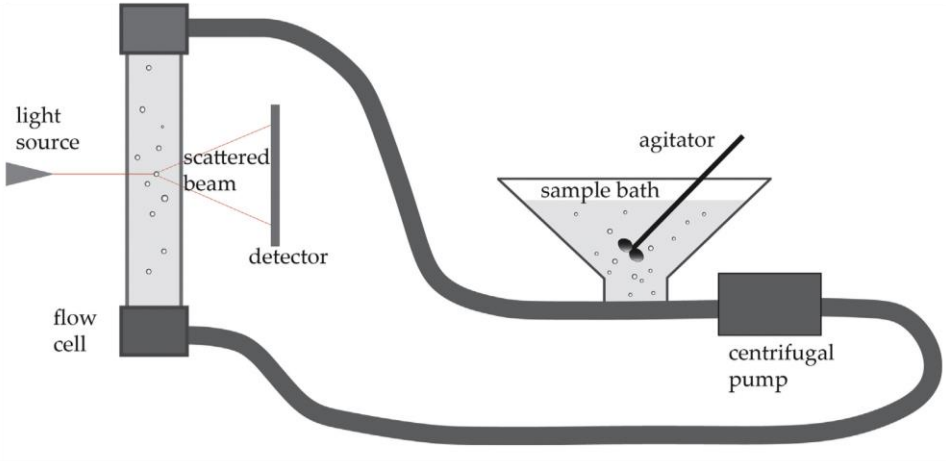
Scale-up from 4 L to 400 L

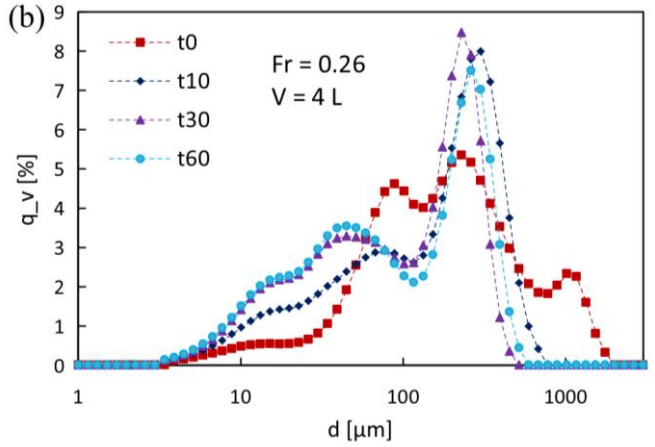


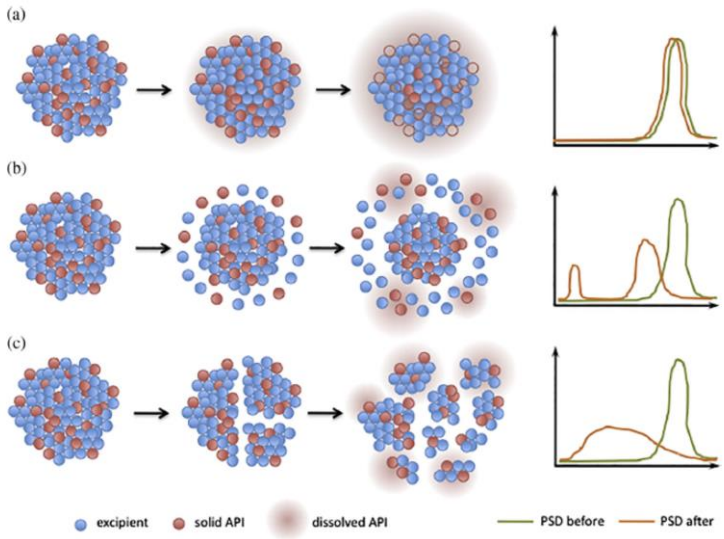
Eur. J. Pharm. Biopharm. **106**, 107-116 (2016)
Powder Technol. **285**, 88-95 (2015)

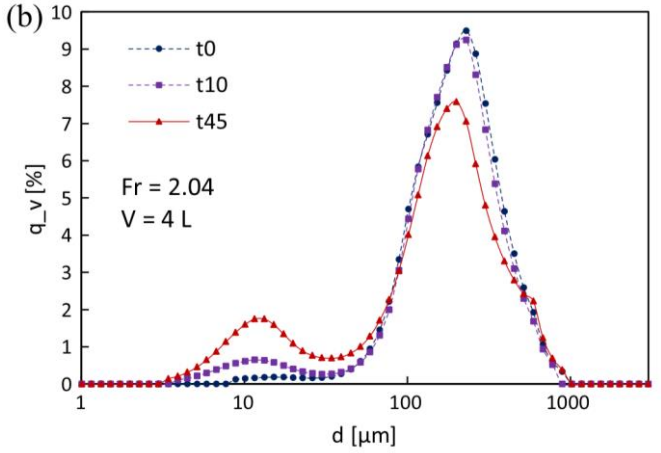
Case study: high-shear granulation scale-up

Simultaneous measurement of drug concentration (UV/Vis) and PSD





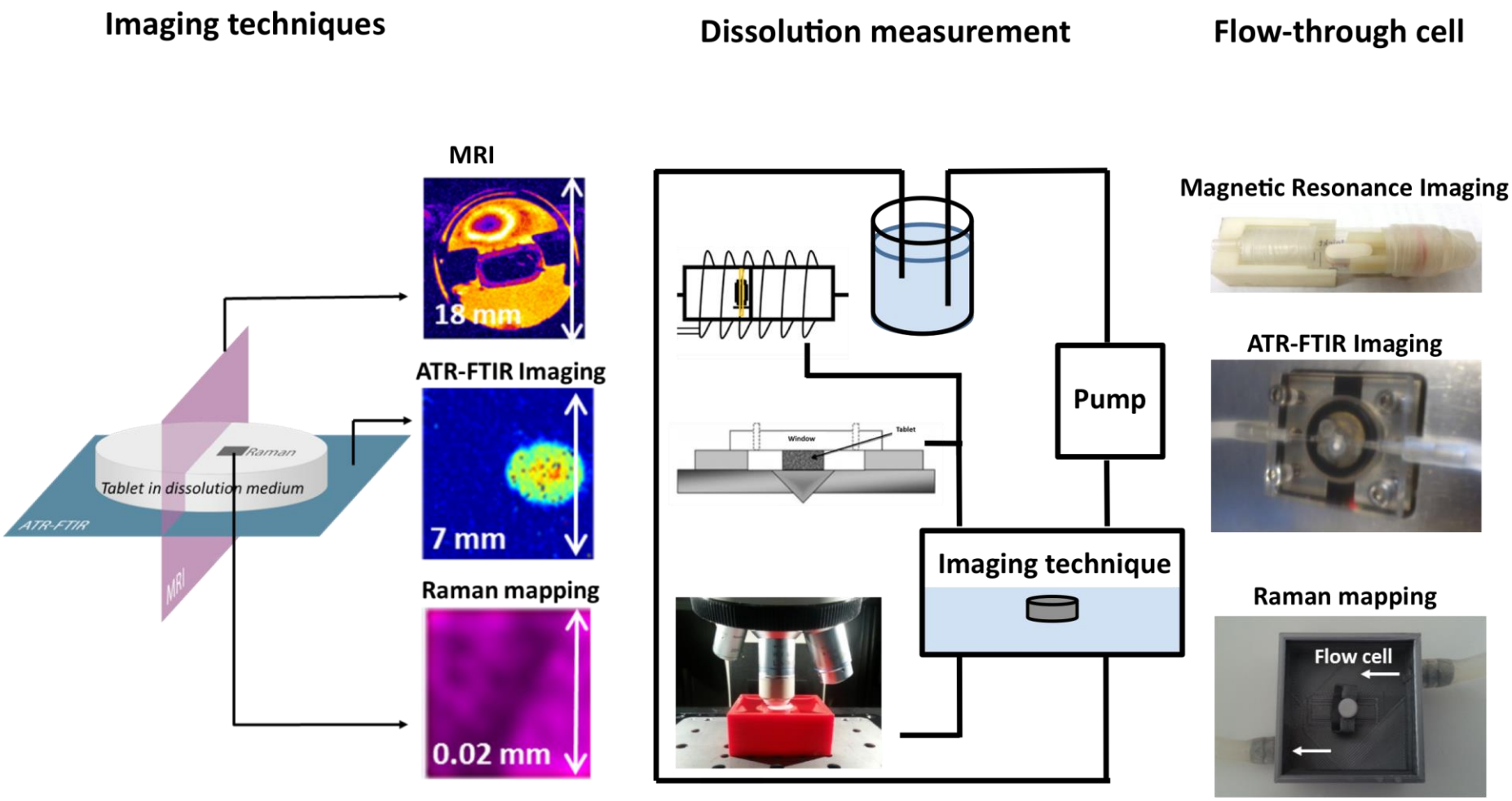




Eur. J. Pharm. Biopharm. **106**, 107-116 (2016)
Powder Technol. **285**, 88-95 (2015)

Validation of microstructure-based models

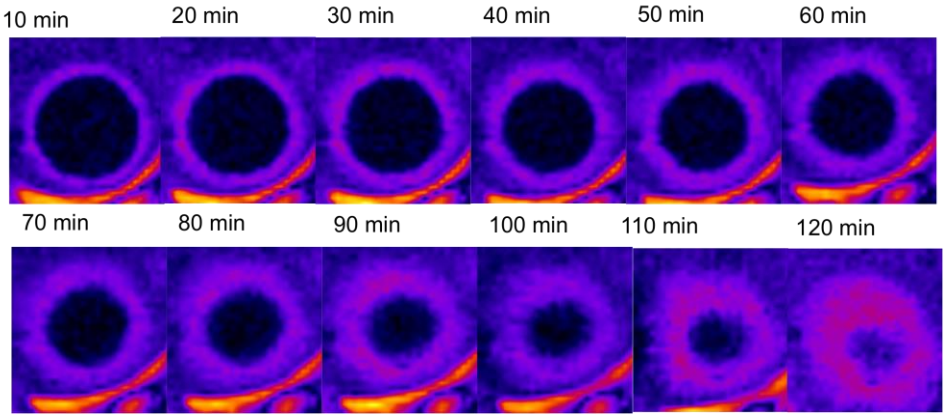
“non-standard” dissolution tests + imaging methods

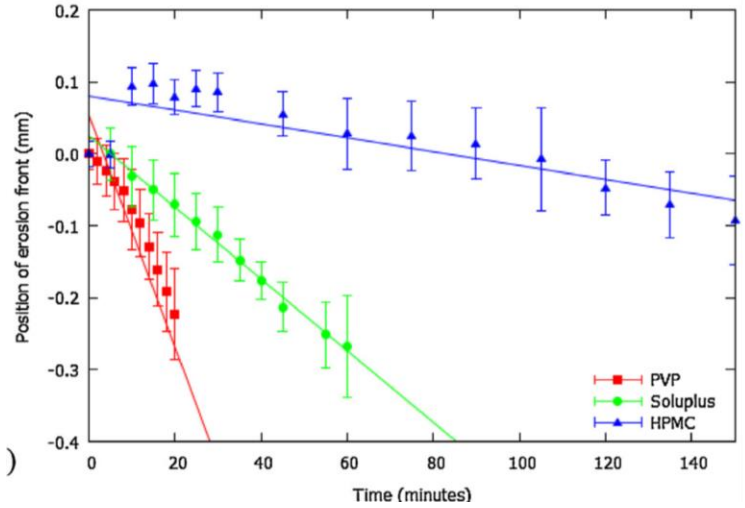


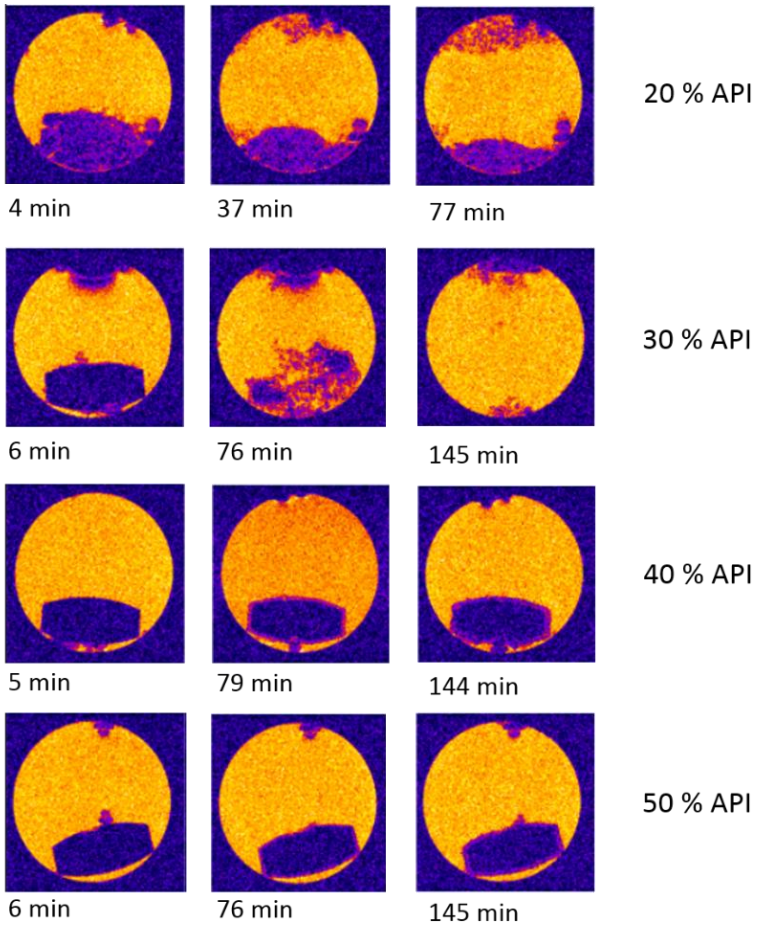
Magnetic Resonance Imaging

⇒ Penetration rate of dissolution medium into tablet

⇒ Swelling / erosion rates

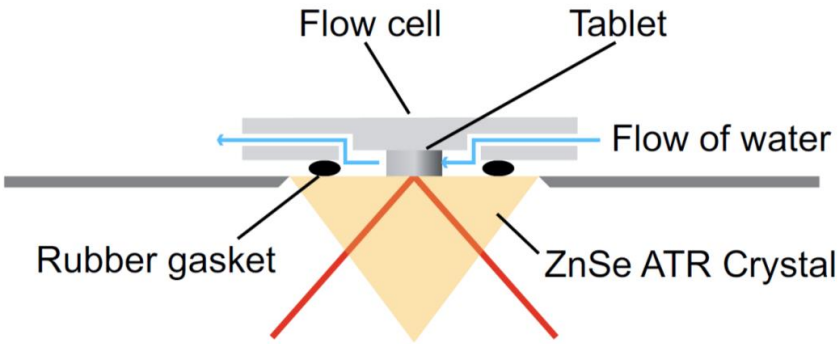


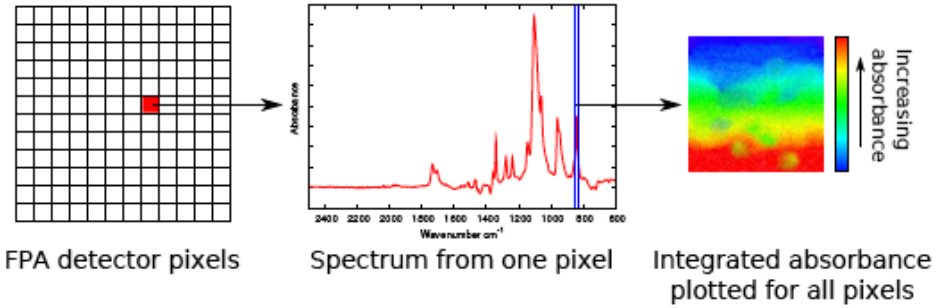


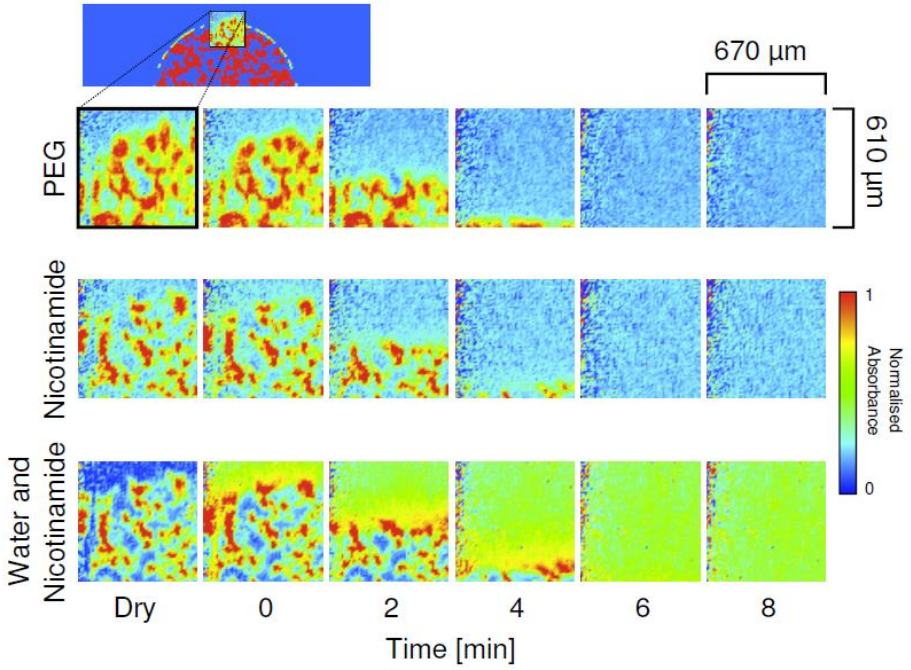


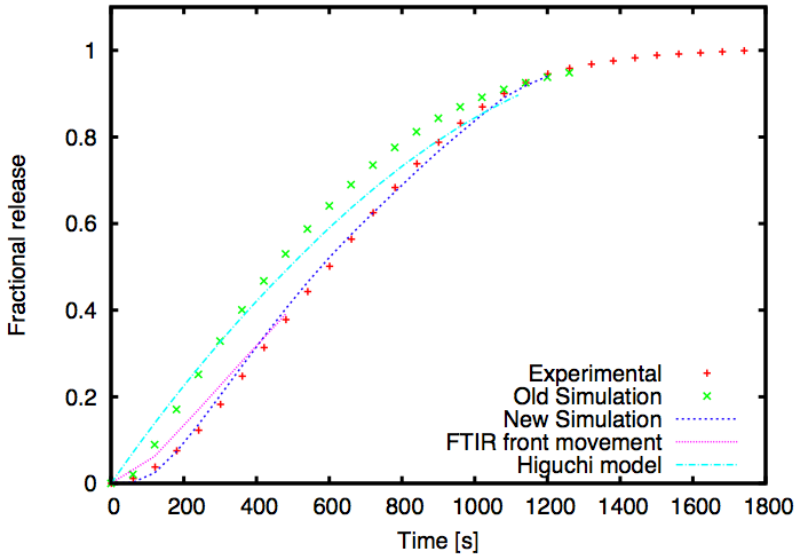
Gajdosova et al. / Int. J. Pharm. ***500****, 136-143 (2016)*

FTIR spectroscopic imaging



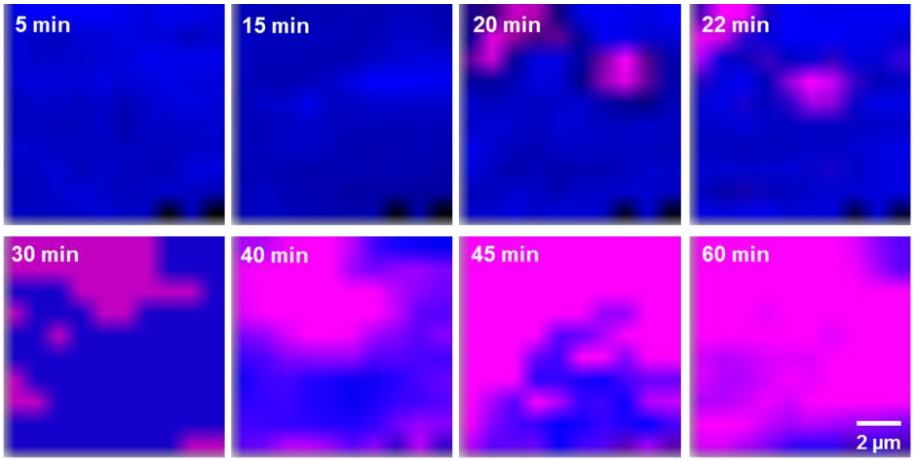


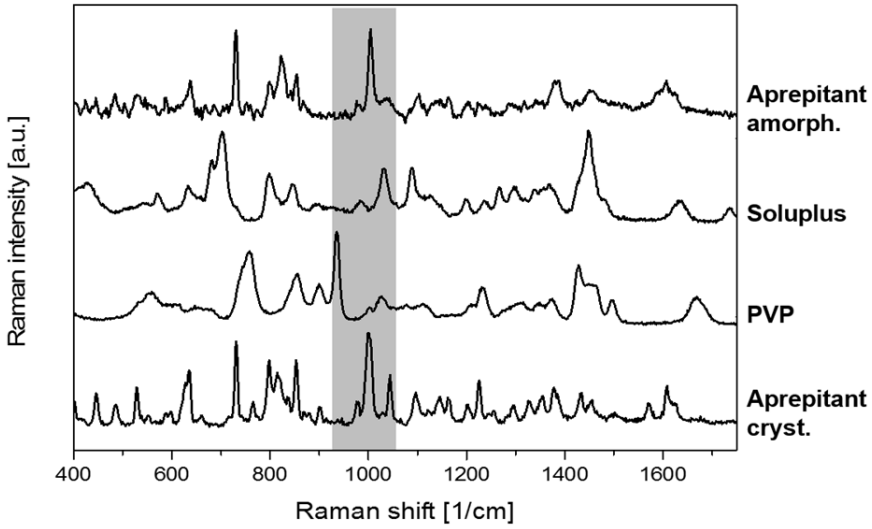


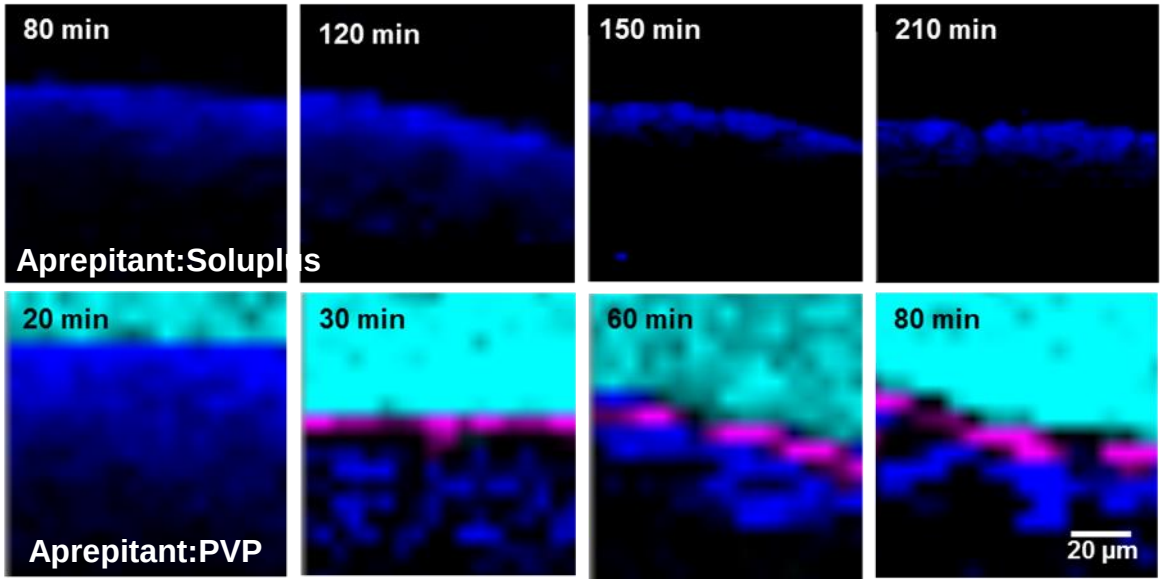


Comput. Chem. Eng. **35**, 1328–1339 (2011)
Powder. Technol. **214**, 415–422 (2011)
Chem. Eng. Sci. **69**, 394–403 (2012)
Powder Technol. **248**, 68-76 (2013)
Powder Technol. **236**, 179-187 (2013)

Raman mapping







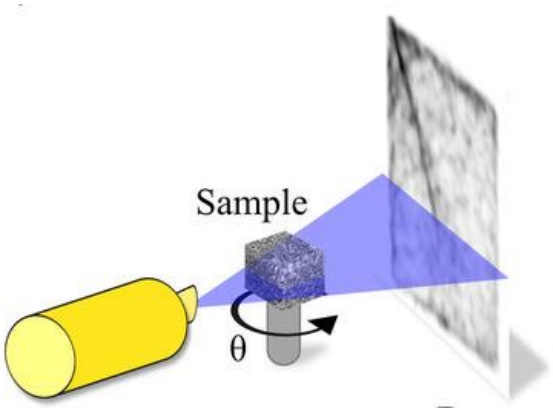
Amorphous solid dispersion

PVP

Crystalline Aprepitant

Int. J. Pharm. ***469***, *159-167 (2014)*
Int. J. Pharm. ***483***, *256-267 (2015)*
Eur. J. Pharm. Biopharm. ***101***, *119-125 (2016)*
Eur. J. Pharm. Sci. ***95***, *138-144 (2016)*
Pharm. Res. ***34***, *990-1001 (2017)*

X-ray micro-tomography (micro-CT)



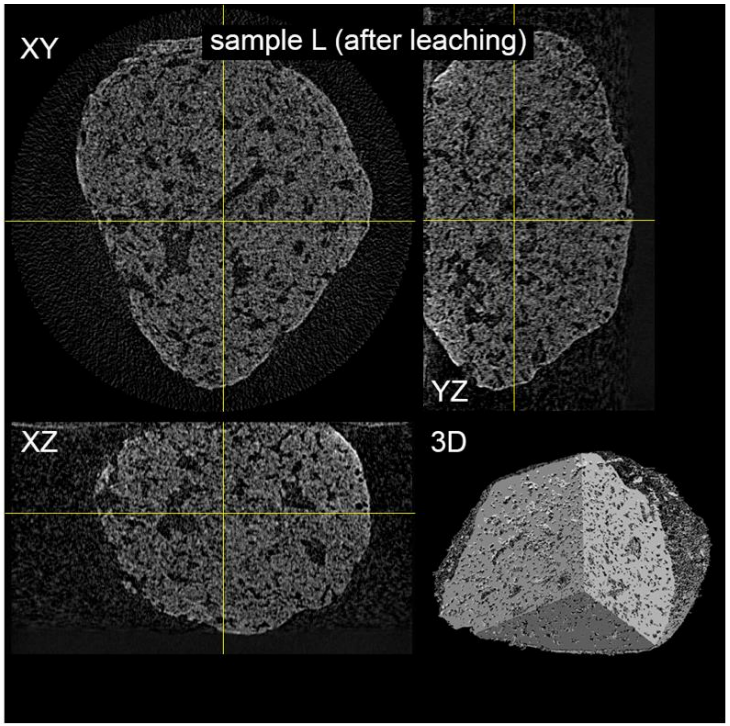
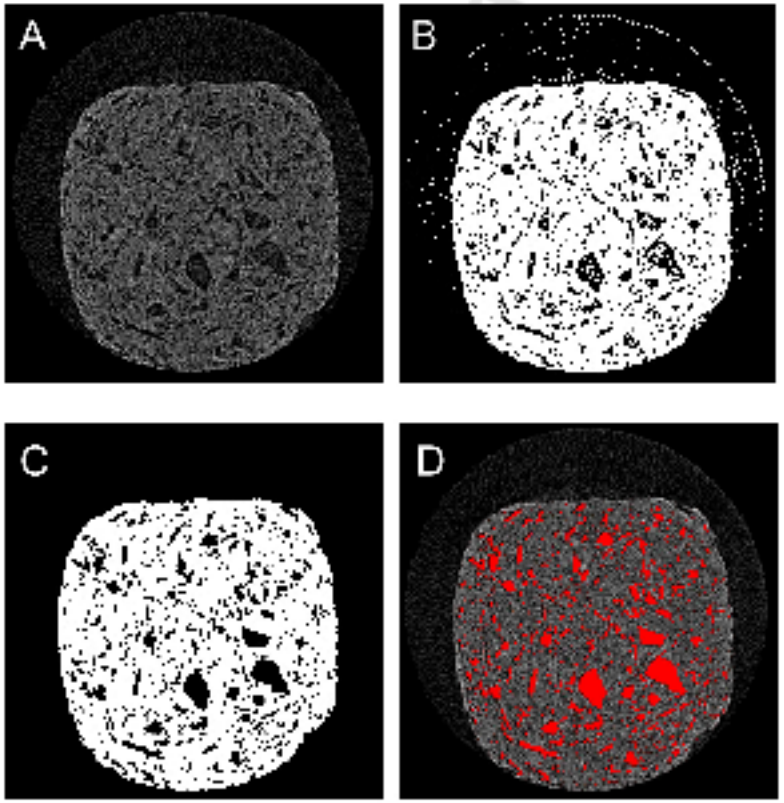


Image segmentation based on density

Spatial resolution < 1 µm



Int. J. Pharm. ***458****, 272-281 (2013)*
Adv. Powder Technol. ***26****, 315-322 (2015)*
Powder Technol. ***278****, 266-277 (2015)*

Conclusions

1. Mechanistic dissolution / disintegration models are available
2. Mechanistic understanding and experimental validation requires non-standard dissolution tests