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A Rational Single Particle Design Approach Using an Acoustic Levitation System and X-Ray Tomography

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8th World Congress on Particle Technology

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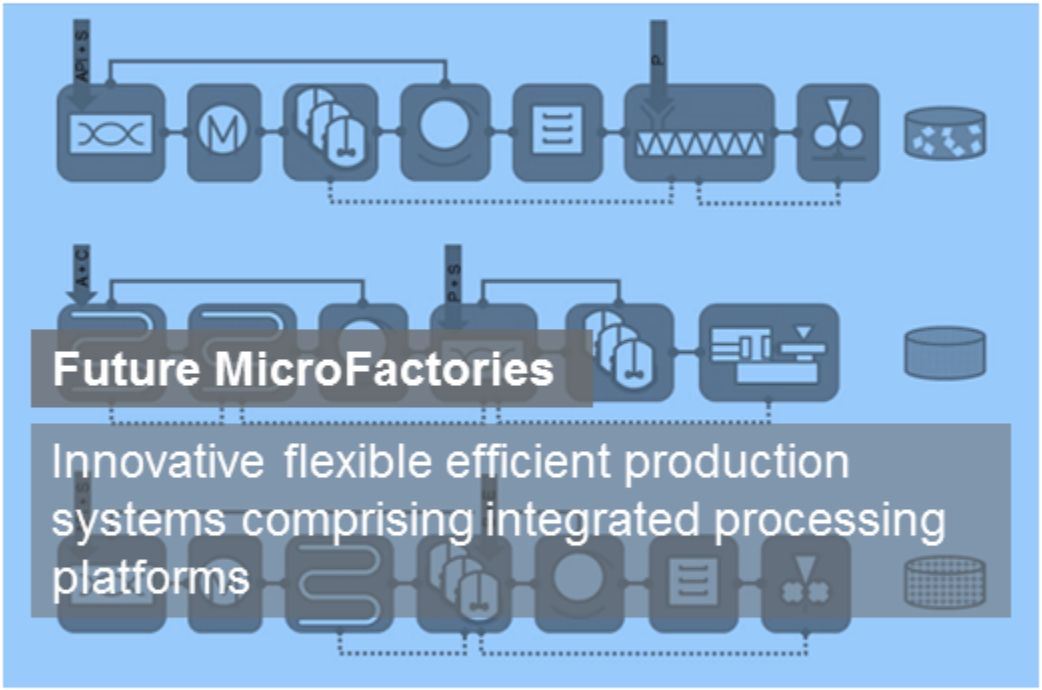
Overview

- Motivation - Focus and Application
- Single Particle Experiments
  - Acoustic Levitation Setup
  - XRT: Hardware and Data Collection
  - Image Processing & Analysis
- **Experimental Results**:
  - Single Droplet Evaporation Experiments - *Characterisation of Liquid Evaporation, Solidification and Drying*
  - XRT: Formulated Metformin Particles - *Investigation of the final Particle Morphology*
- Single Particle Experiments - Link to Performance
- Conclusion

Motivation - Focus and Application

CMAC: Aim for integrated, continuous pharmaceutical MicroFactories supported by a predictive design framework to enable fast product and process development.



Process integration and control require a reliable characterisation of the manufacturing process and of a vast variety of pharmaceutical (intermediate) products with complex multi-dimensional solid state attributes.

Motivation - Focus and Application

Motivation: Control and Optimisation of Particles from Continuous Droplet Drying Platforms (e.g. Spray Drying)

➞ Smallest Scale: Single Droplet Dying Experiments

Droplet Drying Techniques

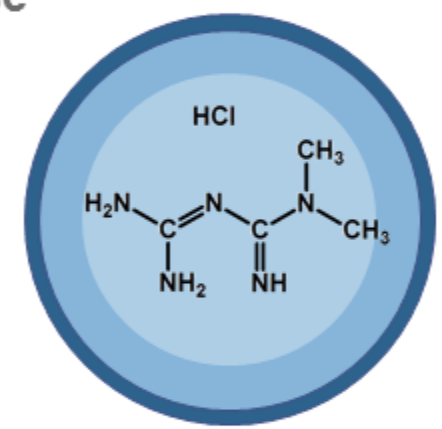
Case Study: Formulated Particles for Controlled Release

Drug: Metformin Hydrochloride

BCS III, high water solubility, low permeability, tablets with high drug loads of up to 50 wt.-%

Excipients:

HPMC K100LV PH: hydrophilic matrix former
D-Mannitol: high crystallinity, low moisture uptake



Objective: Improve Particle Properties with potential impact on critical Quality Attributes

Manufacturability for Direct Compaction

Dissolution and Drug Release

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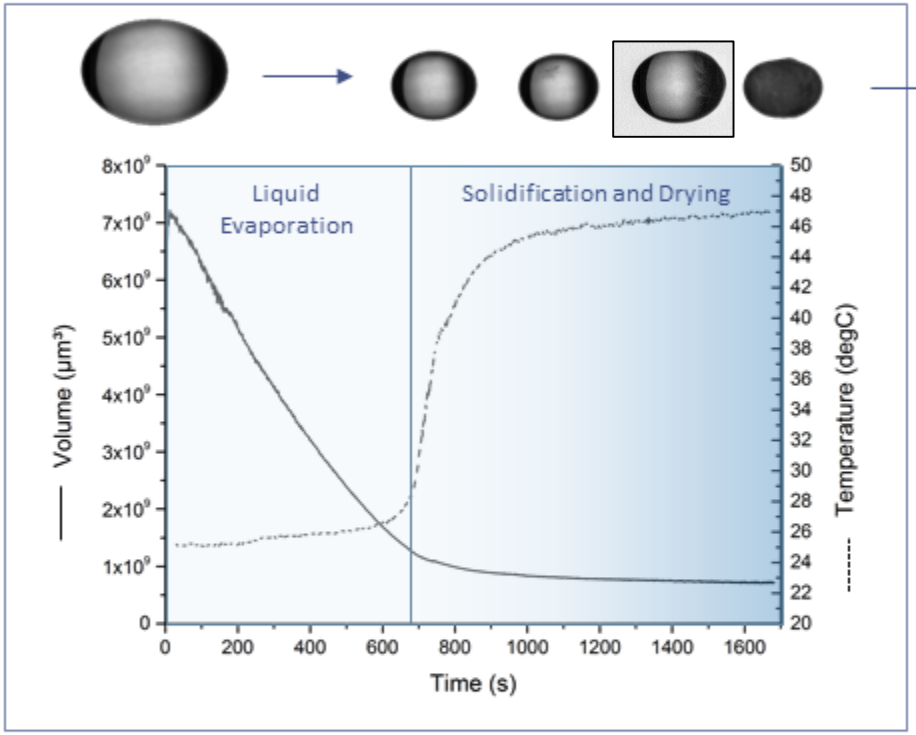
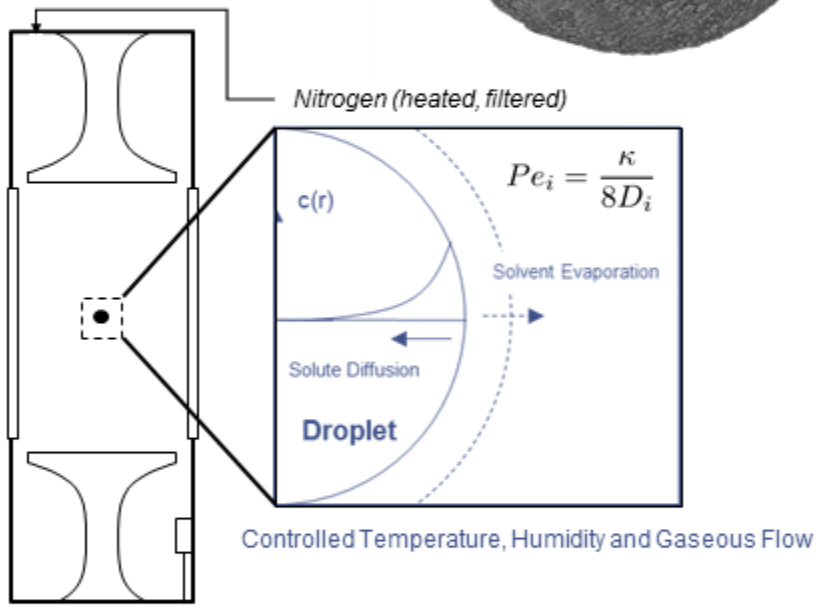
Single Particle Experiments
Acoustic Levitation Setup

Evaporation and Solid Phase Formation



Investigation of Particle Structure



D²-law $\left(\frac{d(t)}{2}\right)^2 = \left(\frac{d_0}{2}\right)^2 - \kappa t$

with $\kappa = 8D_{AB}\frac{\rho_{gas}}{\rho_{liquid}} \cdot ln\left(\frac{1-Y_\infty}{1-Y_S(T)}\right)$

Single droplet evaporation experiments in an acoustic levitator used as a particle design platform. Investigation of Solid Phase Formation.

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Single Particle Experiments
XRT: Hardware and Data Collection

Scanning

Acquiring raw Data (2D, 14bit images) from sample.

Reconstruction

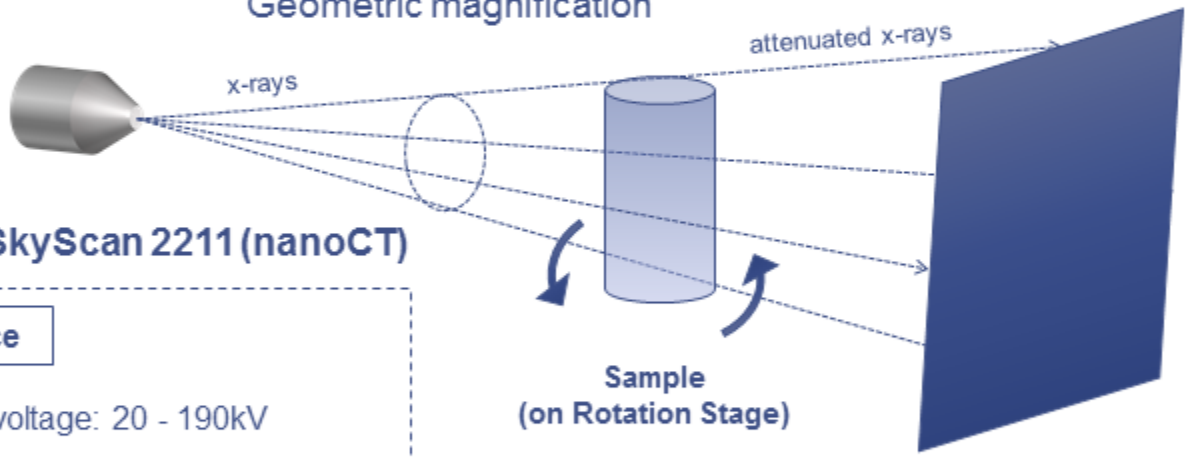
Transformation of 2D projections into a 3D-reconstruction of the sample

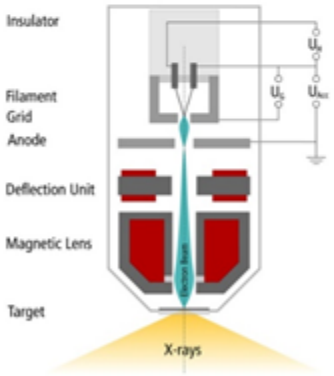
Analysis / 3D Rendering

Image analysis to extract desired sample information. 3D volume rendering to produce an interactive 3D model for visualisation.

SkyScan 2211 (nanoCT)

Geometric magnification





X-ray Source

Accelerating voltage: 20 - 190kV

Emission power: 4 W (Be window)

Transmission Target material: Tungsten

Beam spot size: nanomode 900nm, micromode 2um

Detector

- 11Mp CCD-Sensor
- CCD temperature stabilization
- central 4000x2670 pixel, 9um /pixel
- 14bit digitalization, 70dB dynamic range

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Single Particle Experiments
XRT: Image Processing & Analysis

Image Processing

Raw Image (8bit, grayscale)

1 *Image Filter*

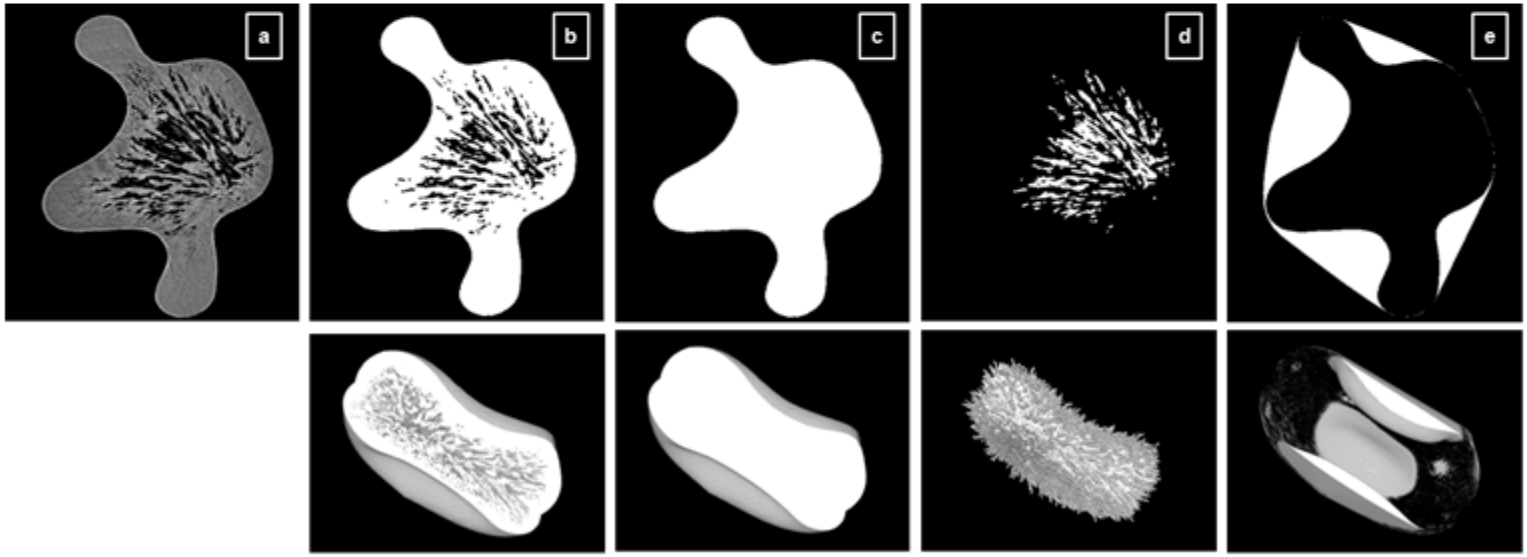
2 *Thresholding*

3 *Noise Reduction*

Binary Image (bw)

3D Image Analysis

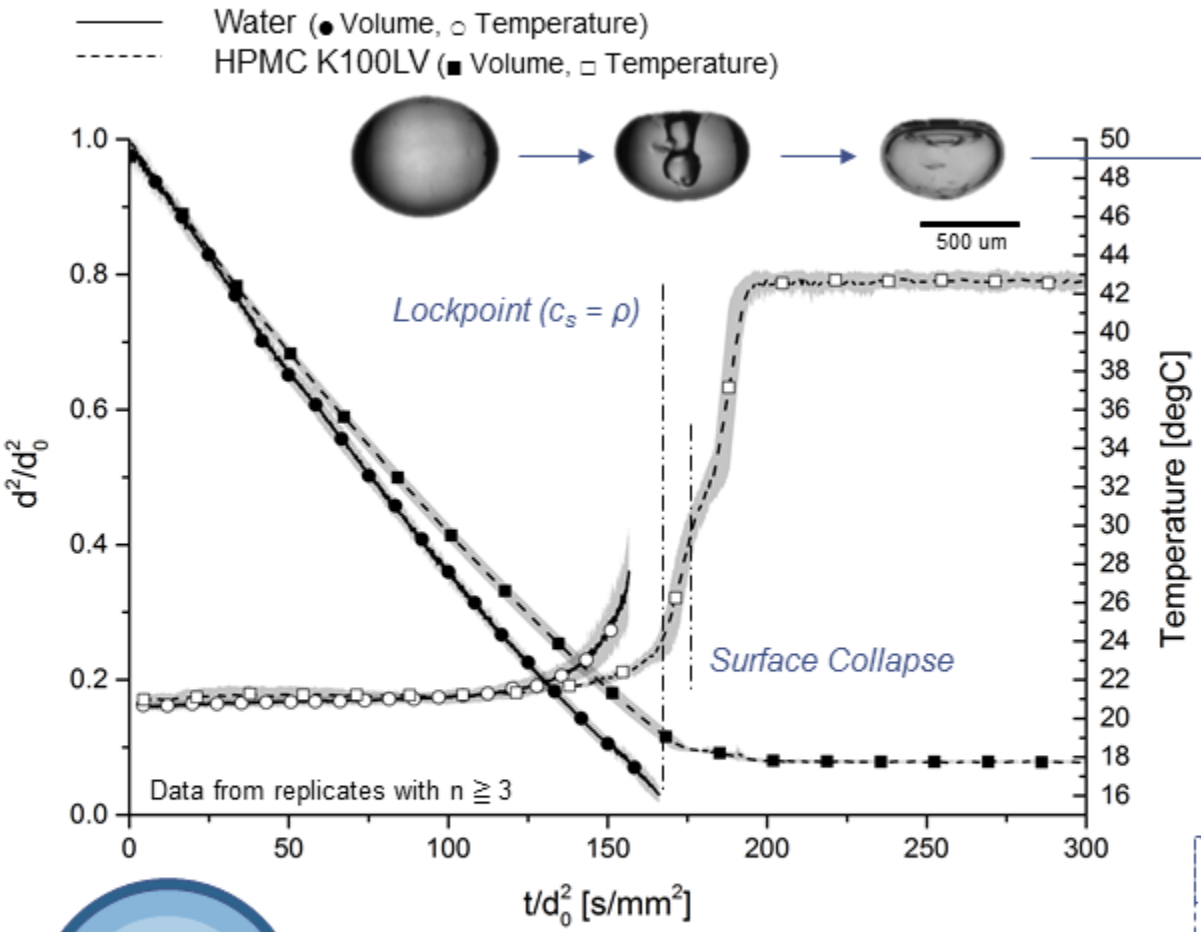
- *CT_3DAnlys_VolumeAnlys*
- *CT_3DAnlys_SurfaceAnlys*
- *CT_3DAnlys_PorosAnlys*
- *CT_3DAnlys_VolumeSegmentation*
- *CT_3DAnlys_GrayScaleEval*

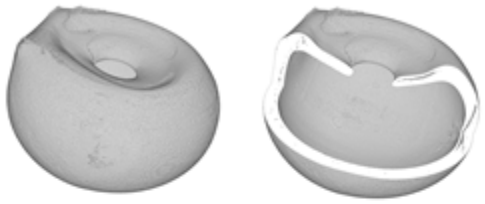


a) Raw cross-sections, (b) binary images, (c) particle ROI, (d) particle porosity, (e) particle concave volume

Adapted from Doerr et al (manuscript in preparation)

Single Droplet Evaporation Experiments
HPMC K100LV PH





Solid Phase Volume (V_{CT})

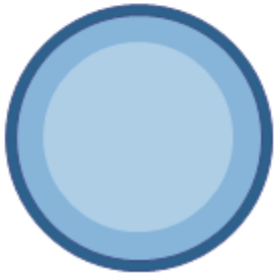
$$\rho = \frac{m}{V} = \frac{c_0 \cdot V_{\mathrm{Droplet},0}}{V_{CT}}$$

(ρ = 1.36 +/- 0.02 g cm^{-3})

From Vehring et.al for Pe < 20:

$$E = \frac{c_s}{c_m} = 1 + \frac{\mathrm{Pe}}{5} + \frac{\mathrm{Pe}^2}{100} + \frac{\mathrm{Pe}^3}{4000}$$

with $$Pe = \frac{\kappa}{8D_s}$$



Surface Layers: Metformin, Mannitol, **K100LV**

Core Layers: **Metformin, Mannitol**, K100LV

Diffusion Coefficients in Water

$$D_{\mathrm{K100LV}} = 4.621 \cdot 10^{-11} m^2 \cdot s^{-1}$$

$$D_{\mathrm{MET}} = 1.17 \cdot 10^{-9} m^2 \cdot s^{-1}$$

$$D_{\mathrm{MAN}} = 7.56 \cdot 10^{-10} m^2 \cdot s^{-1}$$

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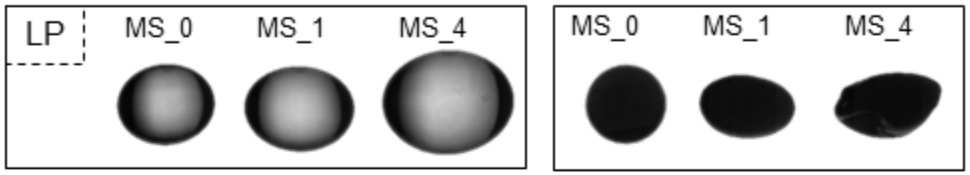
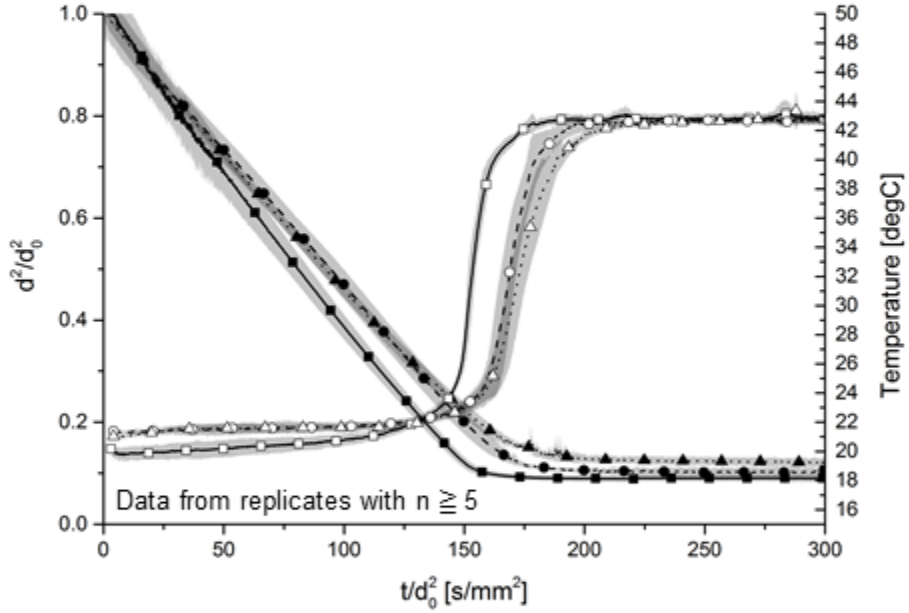
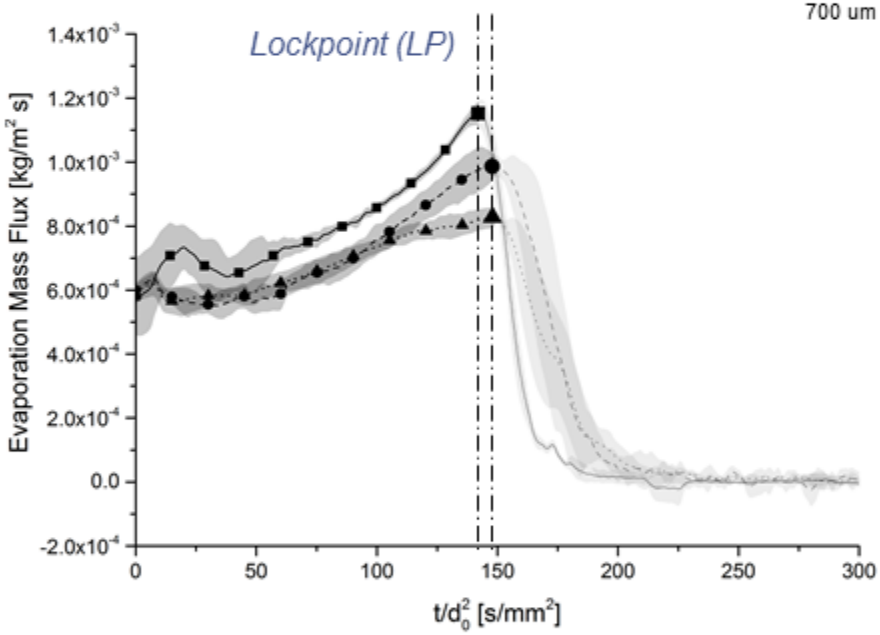
Single Droplet Evaporation Experiments
Formulated Metformin Hydrochloride

Formulations of Metformin HCl (18.75 mg/mL) with D-Mannitol (18.75 mg/mL) and increasing additions of HPMC K100LV:

- (MS_0) + 0.000 mg/mL (■ Volume, □ Temperature)
- (MS_1) + 0.375 mg/mL (● Volume, ○ Temperature)
- (MS_4) + 4.500 mg/mL (▲ Volume, △ Temperature)







- The addition of HPMC K100LV PH causes a significant reduction of the droplet evaporation and drying kinetics even at solid mass concentrations of less than 1wt.-% (b).
- The reduction in the evaporative mass transfer causes a delay of the solid skin formation despite higher solute concentrations.

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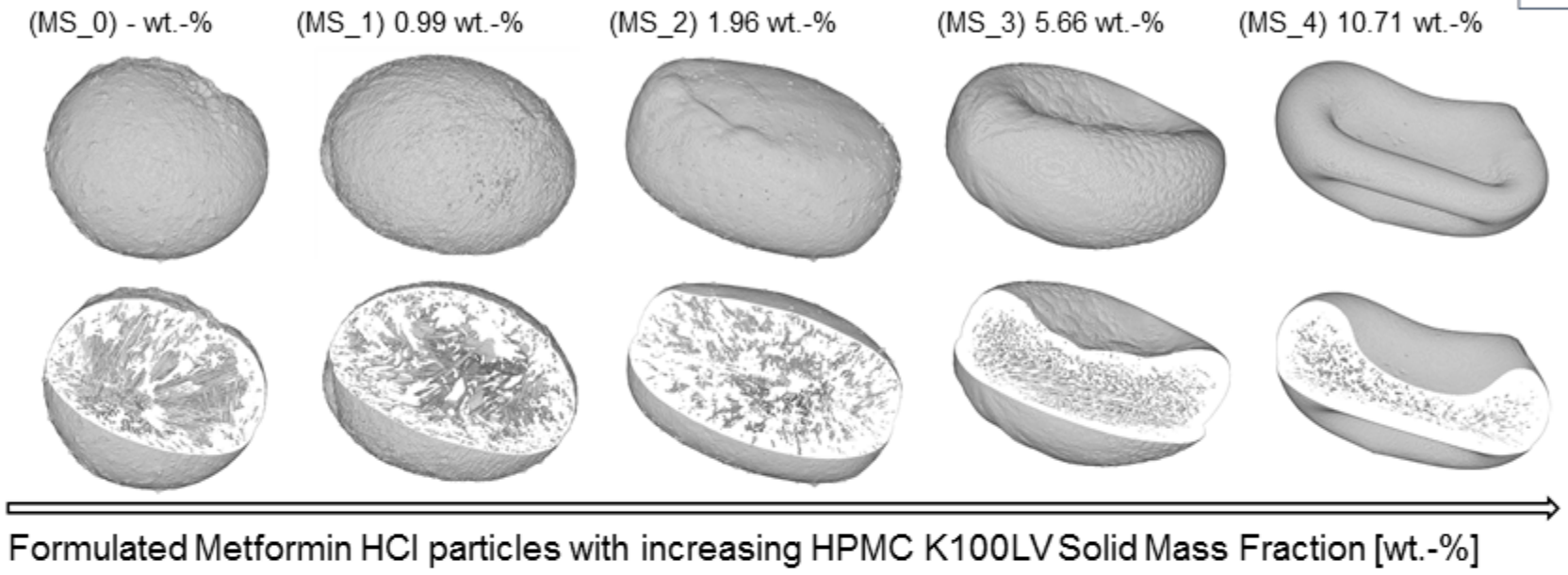
XRT: Formulated Metformin Particles

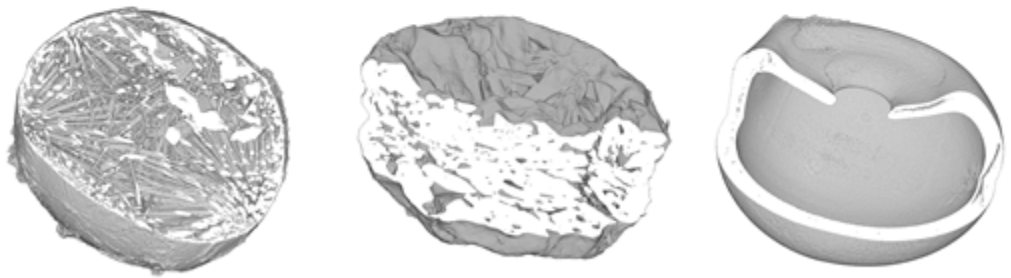
Particle Morphology Landscape



Formulated Metformin HCl particles with increasing HPMC K100LV Solid Mass Fraction [wt.-%]

Particle Solid Phase
Particle Concave Surface Volume
Particle Porosity

D-Mannitol | Metformin HCl | HPMC K100LV



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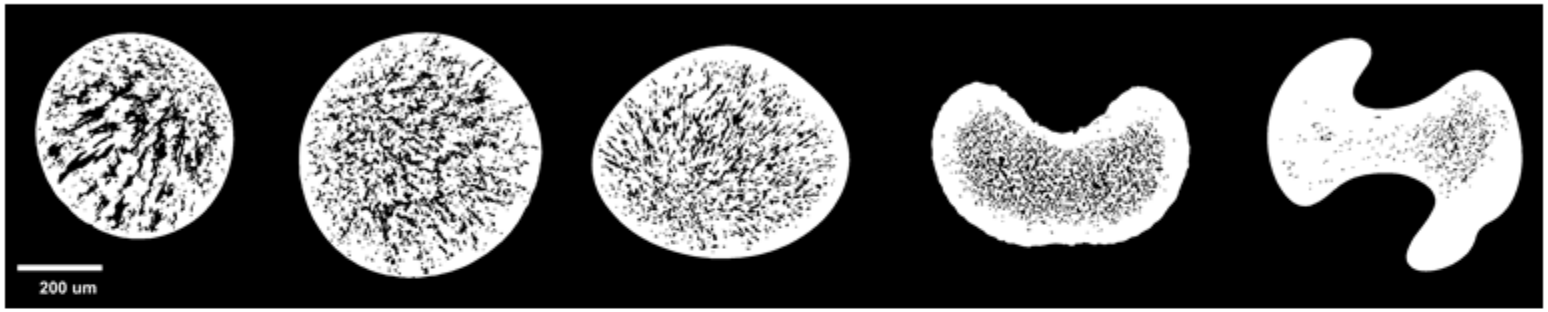
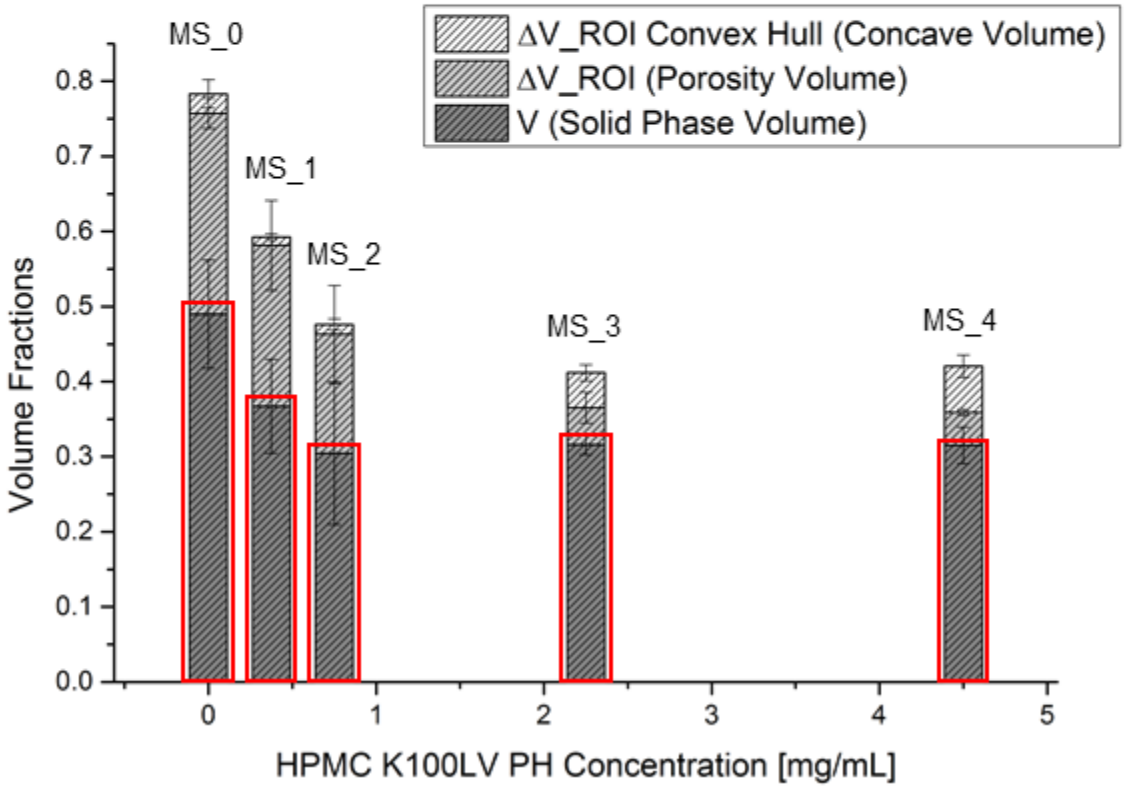
XRT: Formulated Metformin Particles

Solid Phase Volume

(MS_0) - wt.-% (MS_1) 0.99 wt.-% (MS_2) 1.96 wt.-% (MS_3) 5.66 wt.-% (MS_4) 10.71 wt.-%



Metformin HCl
D-Mannitol (1:1,w:w)
+ HPMC K100LV
Solid Mass [wt.-%]



Particle Volume Distribution

- Solid Phase Volume
- Porosity Volume
- Concave Volume

Particle Shape

- Aspect Ratio
- Sphericity

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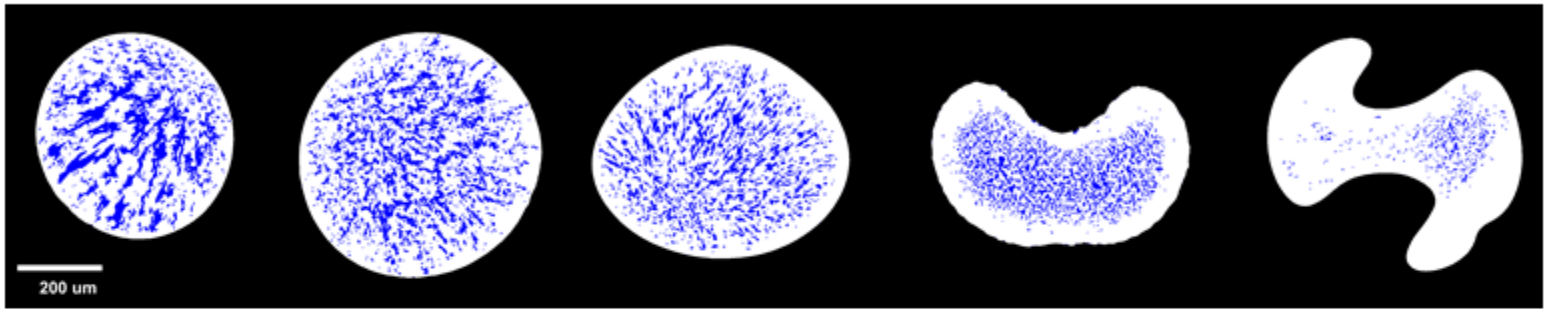
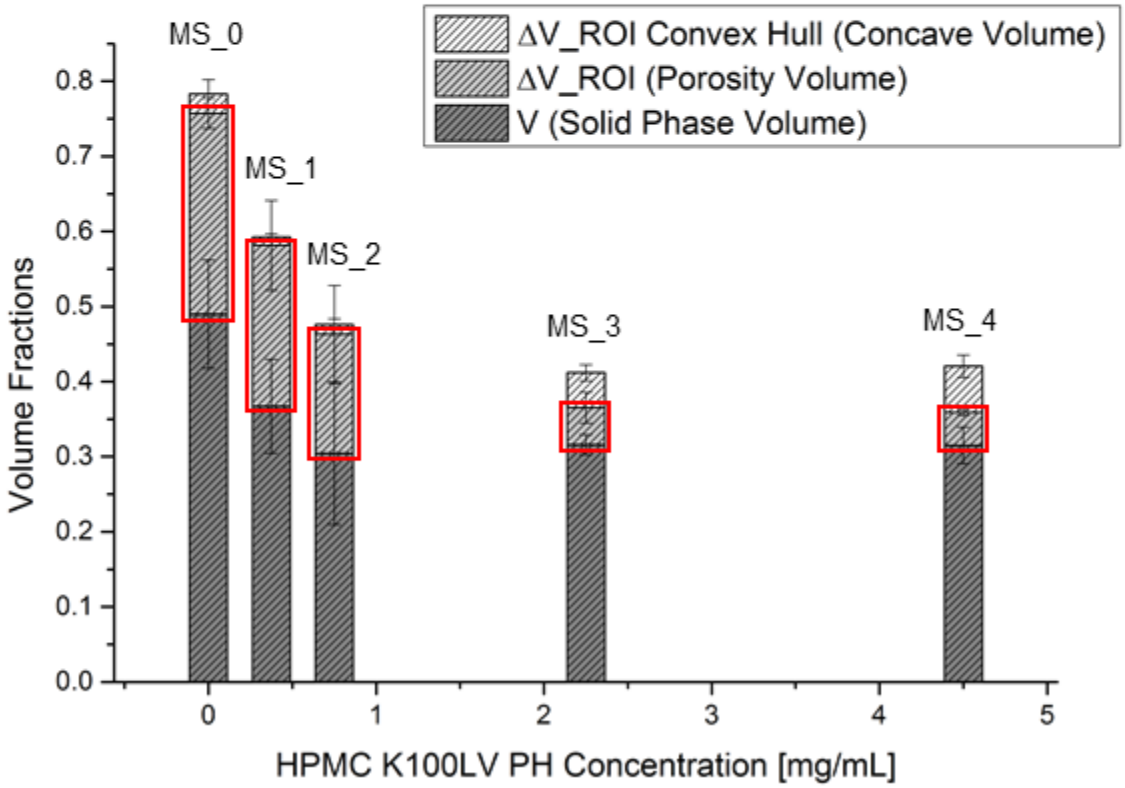
XRT: Formulated Metformin Particles
Porosity Volume

(MS_0) - wt.-% (MS_1) 0.99 wt.-% (MS_2) 1.96 wt.-% (MS_3) 5.66 wt.-% (MS_4) 10.71 wt.-%



Metformin HCl
D-Mannitol (1:1,w:w)
+ HPMC K100LV
Solid Mass [wt.-%]



Particle Volume Distribution

Solid Phase Volume

Porosity Volume

Concave Volume

Particle Shape

Aspect Ratio

Sphericity

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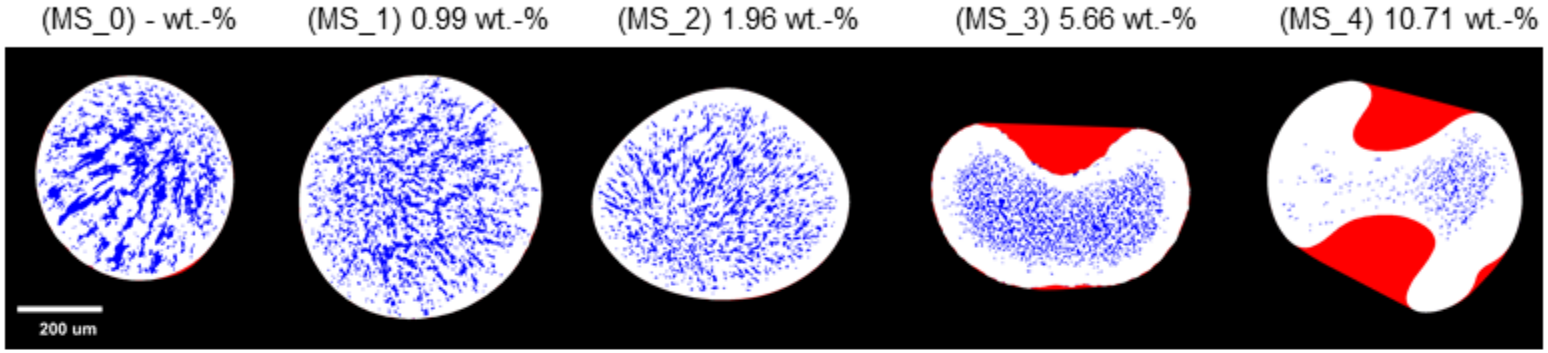
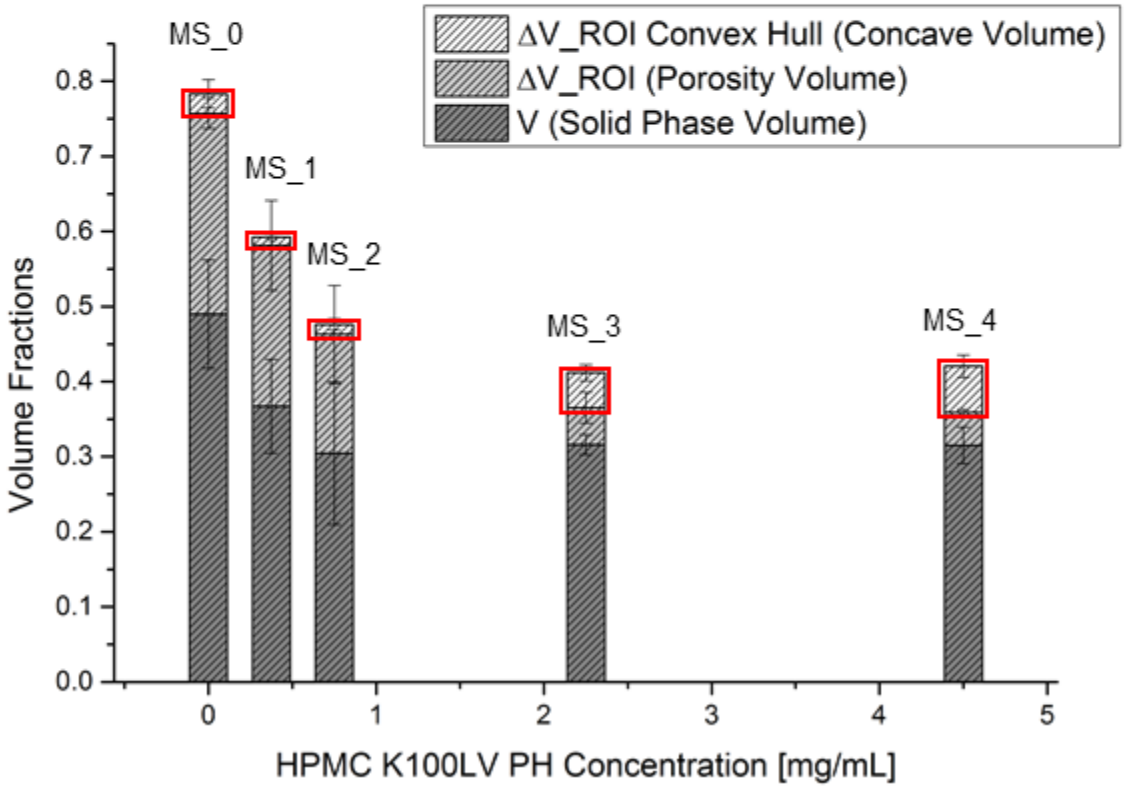
XRT: Formulated Metformin Particles
Concave Volume (Surface Buckling)



Metformin HCl
D-Mannitol (1:1,w:w)
+ HPMC K100LV
Solid Mass [wt.-%]



Particle Volume Distribution

Solid Phase Volume

Porosity Volume

Concave Volume

Particle Shape

Aspect Ratio

Sphericity

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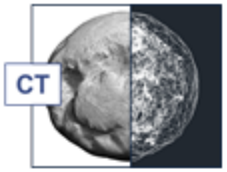
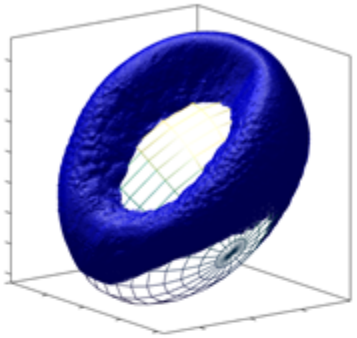
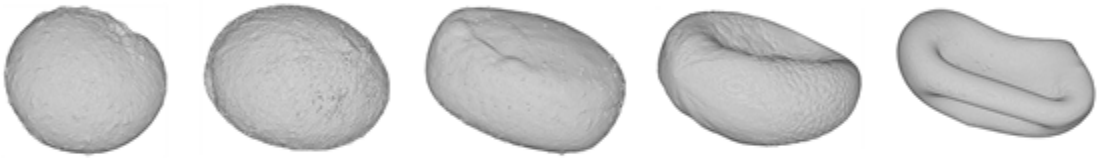
XRT: Formulated Metformin Particles
Shape Descriptors



Aspect Ratio (Ellipsoidal Shape Fit): $\frac{c}{a} = \frac{\text{Max Principal Axis}}{\text{Min Principal Axis}}$

Sphericity (Wadell): $\Psi = \frac{\pi^{\frac{1}{3}}(6V_p)^{\frac{2}{3}}}{A_p}$





(MS_0) - wt.-% | (MS_1) 0.99 wt.-% | (MS_2) 1.96 wt.-% | (MS_3) 5.66 wt.-% | (MS_4) 10.71 wt.-%

Metformin HCl : D-Mannitol (1:1,w:w) + HPMC K100LV Solid Mass Fraction [wt.-%]

	n	Aspect Ratio	Sphericity
MS_0	7	1.20 ± 0.05	0.95 ± 0.04
MS_1	8	1.96 ± 0.52	0.90 ± 0.05
MS_2	3	1.93 ± 0.28	0.89 ± 0.05
MS_3	5	2.49 ± 0.35	0.80 ± 0.05
MS_4	5	2.52 ± 0.20	0.73 ± 0.03

Particle Volume Distribution

Solid Phase Volume

Porosity Volume

Concave Volume

Particle Shape

Aspect Ratio

Sphericity

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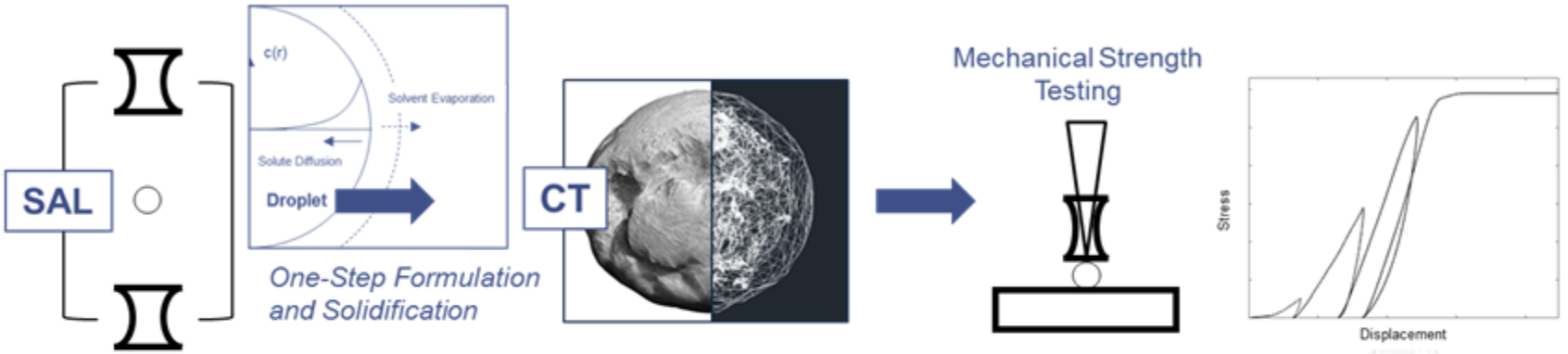
Single Particle Experiments - Link to Performance

1) Particle Compaction



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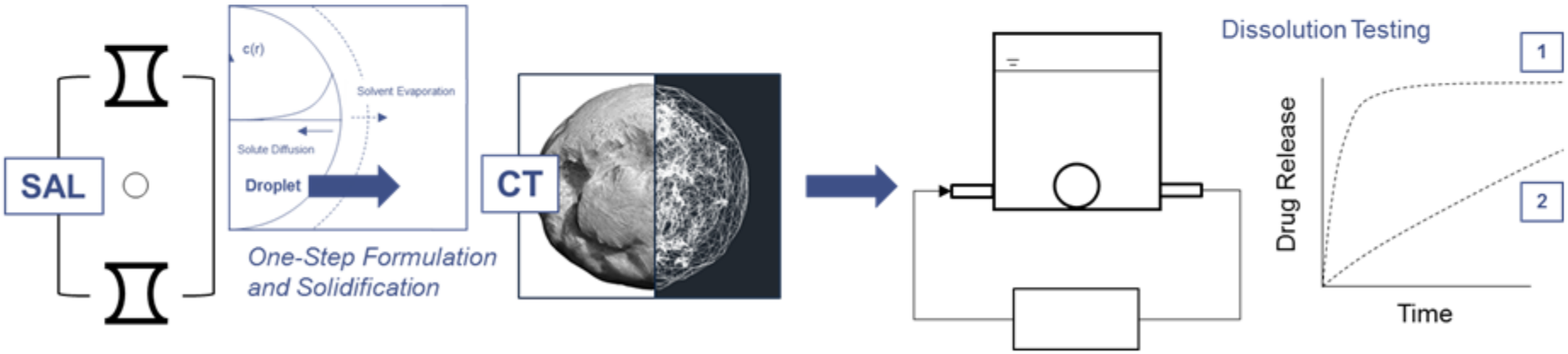
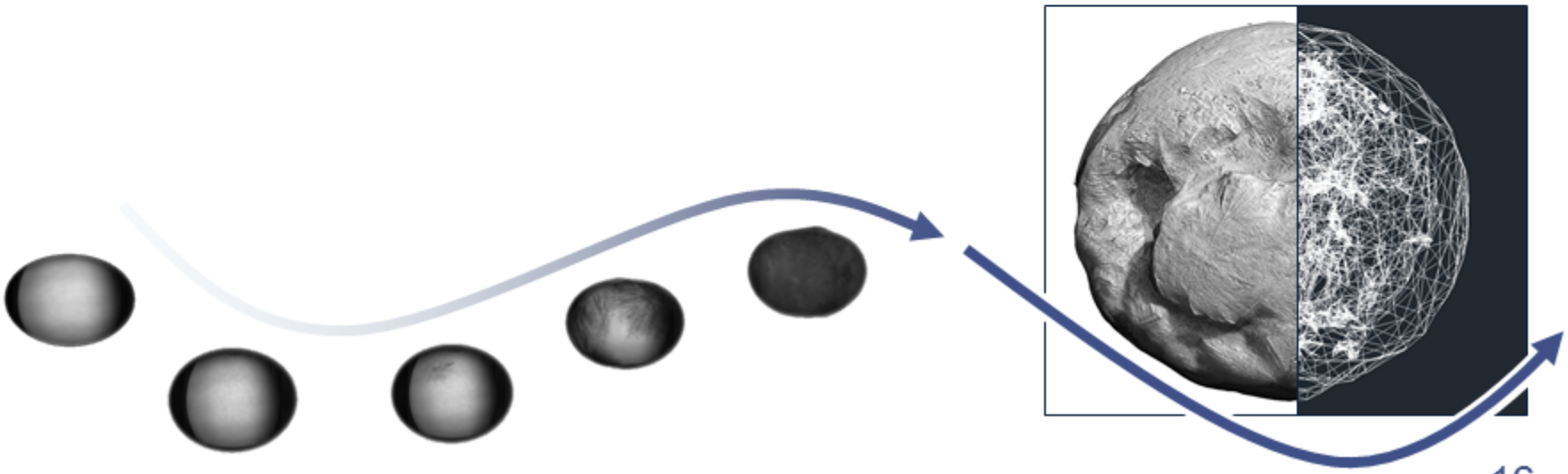
2) Particle Dissolution



Conclusion

- We demonstrated the use of Acoustic Levitation and X-ray Tomography to evaluate the particle design space for formulated Metformin Hydrochloride Particles with increasing additions of HPMC K100LV PH.
- The combined SAL & XRT platform allows an investigation of the evaporation and drying kinetics with an in-depth non-destructive characterisation of the final particle morphology working on a single droplet/particle scale with minimized material consumption.
- Future work will aim to link information on the particle formation process and its final structural properties to critical quality attributes with a potential impact on performance under direct compaction and during dissolution.



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