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

Frederik Doerr

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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
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 Drying Experiments

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

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

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

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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.

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**SkyScan 2211 (nanoCT)**

**X-ray Source**
- Accelerating voltage: 20 - 190kV
- Emission power: 4 W (Be window)
- Transmission Target material: Tungsten

**Beam spot size**
- nanomode 900nm, micromode 2um

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**Geometric magnification**

**Sample (on Rotation Stage)**

**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

1. Raw Image (8bit, grayscale)
2. Image Filter
3. Thresholding
4. 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**

- **Water (● Volume, ○ Temperature)**
- **HPMC K100LV (■ Volume, □ Temperature)**

**Solid Phase Volume ($V_{CT}$)**

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

($\rho = 1.36 \pm 0.02 \text{ g cm}^{-3}$)

From Vehring et al for $Pe < 20$:

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

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

**Diffusion Coefficients in Water**

- $D_{K100LV} = 4.621 \cdot 10^{-11} m^2 \cdot s^{-1}$
- $D_{\text{MET}} = 1.17 \cdot 10^{-9} m^2 \cdot s^{-1}$
- $D_{\text{MAN}} = 7.56 \cdot 10^{-10} m^2 \cdot s^{-1}$
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.
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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Adapted from Doerr et al (manuscript in preparation)
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

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Metformin HCl
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+ HPMC K100LV
Solid Mass [wt.-%]

Particle Volume Distribution
Solid Phase Volume

Porosity Volume

Concave Volume

Particle Shape
Aspect Ratio
Sphericity

Adapted from Doerr et al (manuscript in preparation)
Microscopy (XRT) analysis of formulated Metformin particles shows concave volume differences across various samples.

- **MS_0**: 0.99 wt.-%
- **MS_1**: 1.96 wt.-%
- **MS_2**: 5.66 wt.-%
- **MS_4**: 10.71 wt.-%

**Particle Volume Distribution**
- Solid Phase Volume
- Porosity Volume
- **Concave Volume**

**Particle Shape**
- Aspect Ratio
- Sphericity

Metformin HCl + D-Mannitol (1:1, w:w) + HPMC K100LV

Solid Mass [wt.-%]

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Adapted from Doerr et al (manuscript in preparation)
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):
\[ \Psi = \frac{\pi^{\frac{1}{3}} \left(6V_p\right)^{\frac{2}{3}}}{A_p} \]

Particle Volume Distribution
- Solid Phase Volume
- Porosity Volume
- Concave Volume

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

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

Particle Shape
- Aspect Ratio
- Sphericity

<table>
<thead>
<tr>
<th>n</th>
<th>Aspect Ratio</th>
<th>Sphericity</th>
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<tbody>
<tr>
<td>MS_0</td>
<td>7</td>
<td>1.20 ± 0.05</td>
</tr>
<tr>
<td>MS_1</td>
<td>8</td>
<td>1.96 ± 0.52</td>
</tr>
<tr>
<td>MS_2</td>
<td>3</td>
<td>1.93 ± 0.28</td>
</tr>
<tr>
<td>MS_3</td>
<td>5</td>
<td>2.49 ± 0.35</td>
</tr>
<tr>
<td>MS_4</td>
<td>5</td>
<td>2.52 ± 0.20</td>
</tr>
</tbody>
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Single Particle Experiments - Link to Performance

1) Particle Compaction

SAL → CT

One-Step Formulation and Solidification

Mechanical Strength Testing

Acknowledgement: Prof Marcial Gonzalez, Ankit Agarwal
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2) Particle Dissolution

SAL → CT

One-Step Formulation and Solidification

Dissolution Testing

Drug Release vs Time

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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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