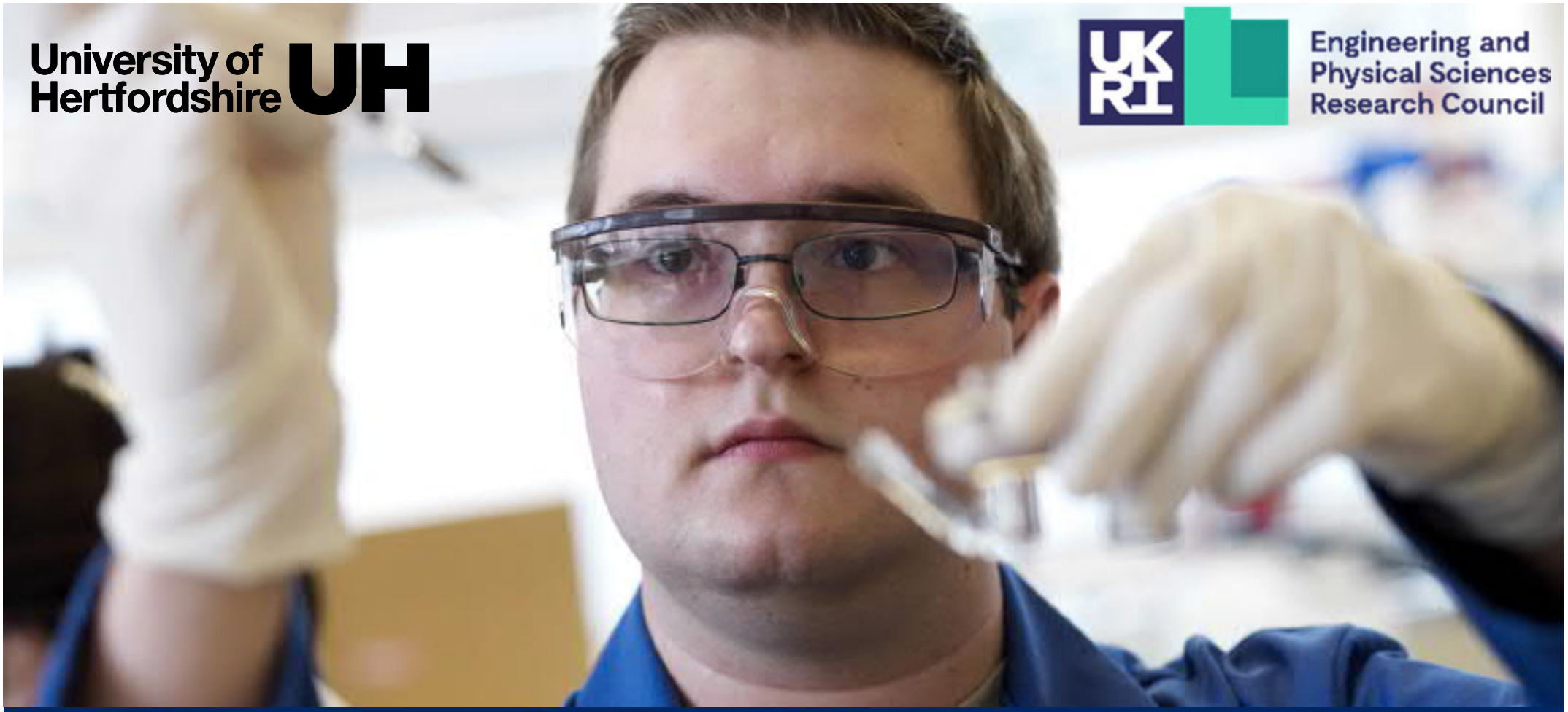

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Engineering and Physical Sciences Research Council

# INFORM 2020: Deconstructing the Role of Powder Agglomerates in Inhaled Powders

Darragh Murnane
Centre for Research in Topical Drug Delivery & Toxicology

TEF Gold

# INFORM 2020 – Molecules to Manufacture

EP/N025075/1 Academic investigators & commercial partners

Engineering and Physical Sciences Research Council

University of Hertfordshire UH

UNIVERSITY OF LEEDS

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF BATH

MANCHESTER 1824 The University of Manchester

UC UNIVERSITY OF CANTERBURY Te Whare Wānanga o Waitaha CHRISTCHURCH NEW ZEALAND

Tim Burnett, David Chau, Simon Connell, James Elliott, Robert Hammond, Victoria Hutter, Darragh Murnane, Robert Price, Kevin Roberts, Digby Symons, & Philip Withers

3M Drug Delivery Systems Division

AstraZeneca

gsk

Malvern Panalytical

Intertek

MELBOURN scientific

neutec

DFE pharma

ZEISS

team. medical design and development

# The future formulation of inhaled therapies?
# INFORM 2020 – Molecules to Manufacture

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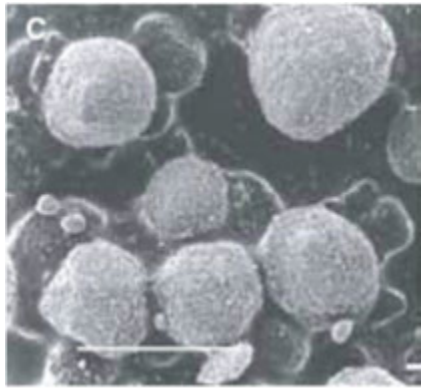

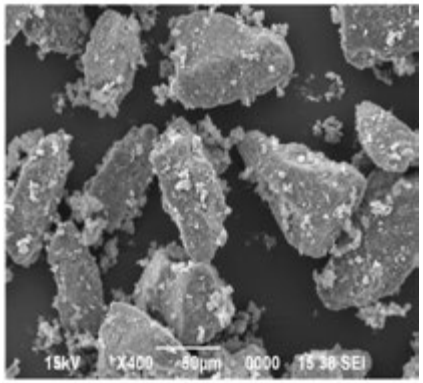

**Can we develop predictive models of formulation behaviour, manufacturing processes and aerosolization events to increase understanding of product performance, and stability in order to accelerate development?**

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# Factors determining inhaled product bioavailability

## Combination drug formulation & device products

Engineering and Physical Sciences Research Council

Pre-aerosolized formulation

+

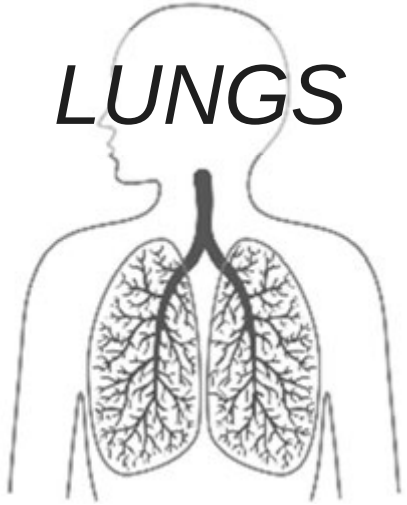
Device

+

Patient variable airflow

*aerosolization*

Post-aerosolized formulation

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# Factors determining inhaled product bioavailability

## Characterising aerosol product performance impacts on bioavailability

Pre-aerosolized formulation

+

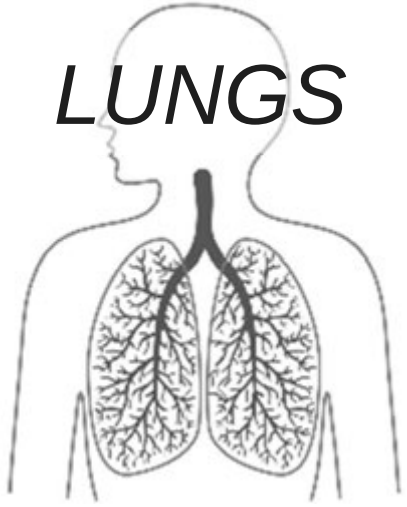
Device

+

Patient variable airflow

*aerosolization*

Post-aerosolized formulation




Demonstrating Q3 structural equivalence of dry powder inhaler blends: New analytical concepts and techniques

Price *et al*, RDD 2018

# Factors determining inhaled product bioavailability

## What links the manufactured product & aerosolization performance?

Engineering and Physical Sciences Research Council

Pre-aerosolized formulation

+

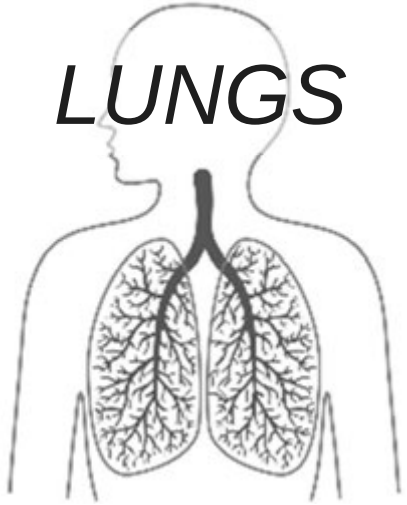
Device

+

Patient variable airflow

*aerosolization*

Post-aerosolized formulation

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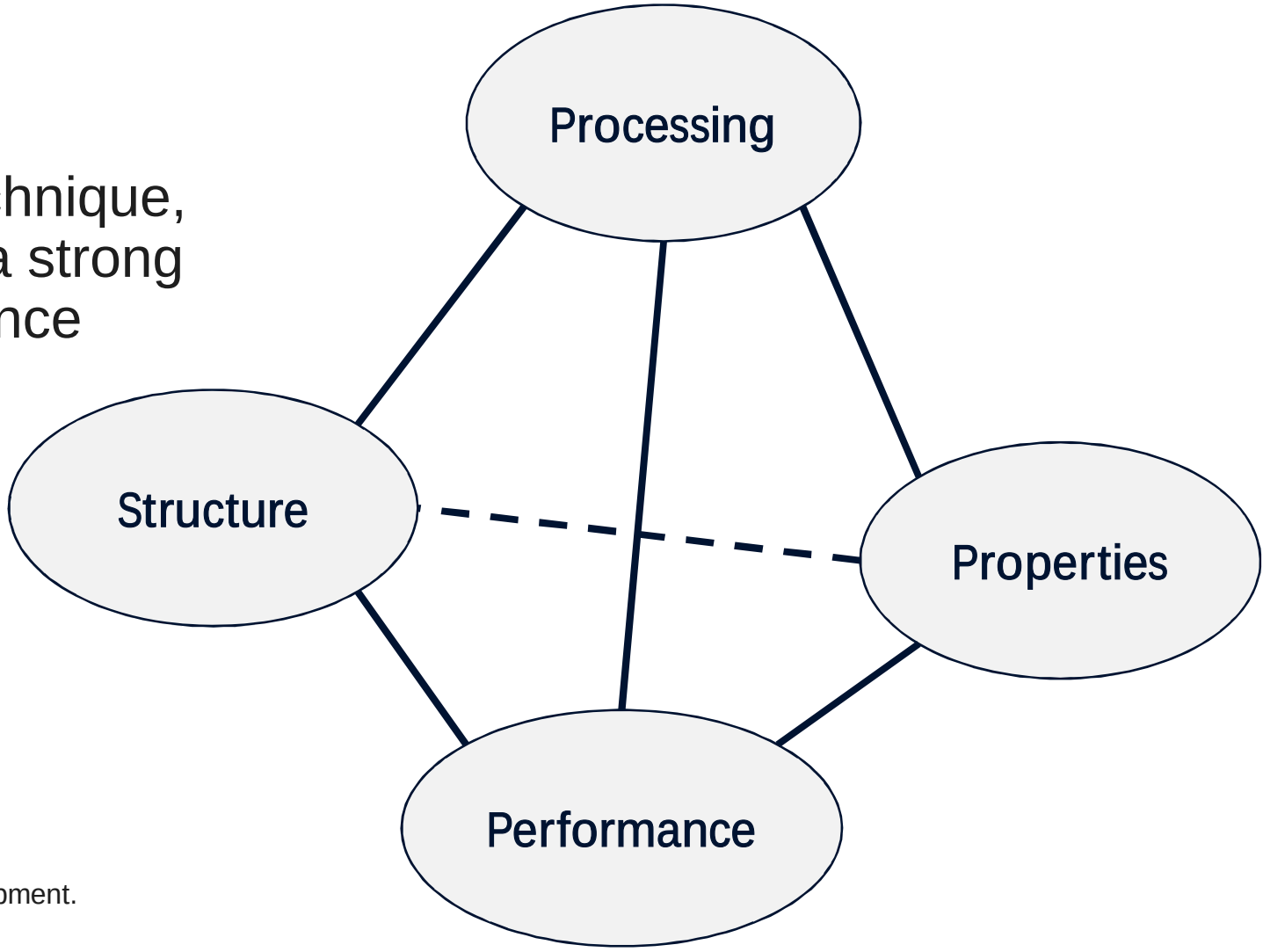
# A materials science predictive approach

## Role of formulation structure on aerosolization from inhalation devices

Even with good patient technique, formulation structure has a strong influence on performance

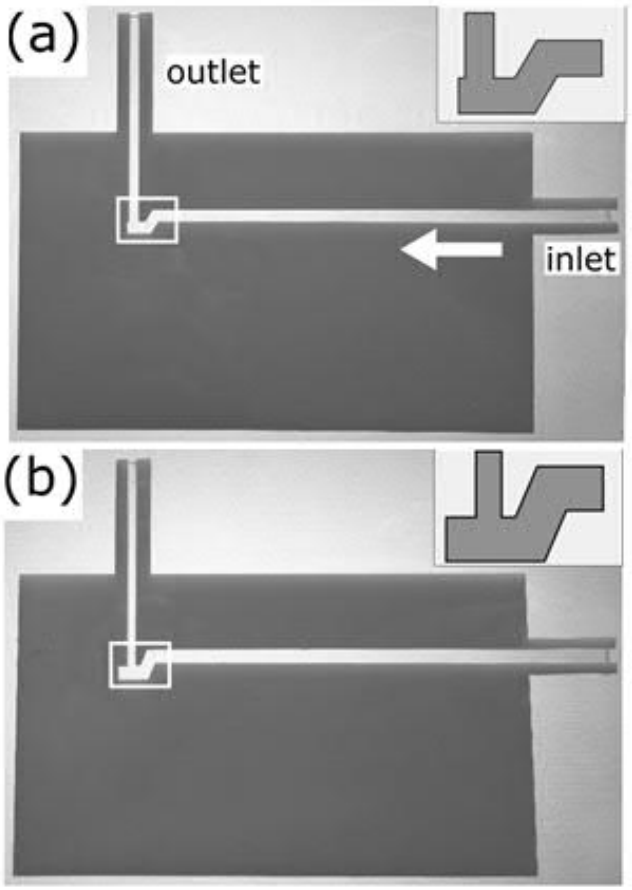


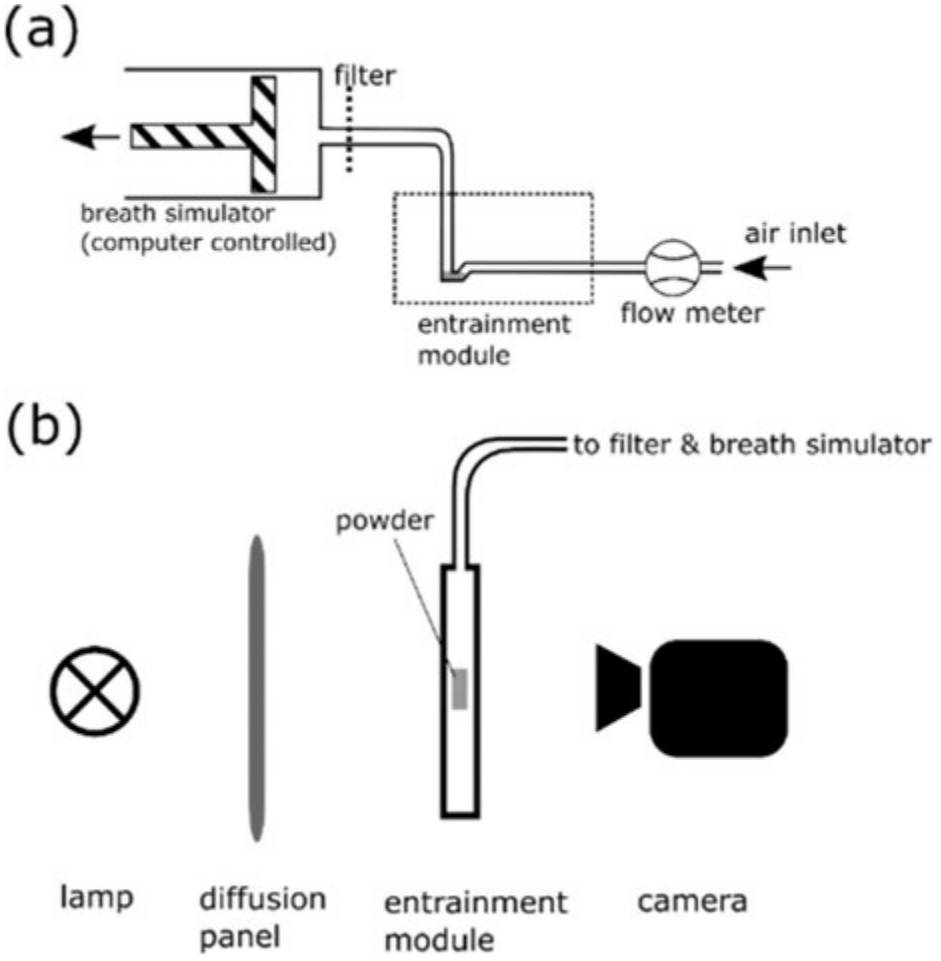

Sun, C.C. Materials Science Tetrahedron—
A Useful Tool for Pharmaceutical Research and Development.
*J. Pharm. Sci.* **2009**, *98*, 1671–1687.

# Examining the inhalation behaviour of powders

# Aerosolization studies and inhaler design for DPIs

## Experimental studies of high density powder fluidization

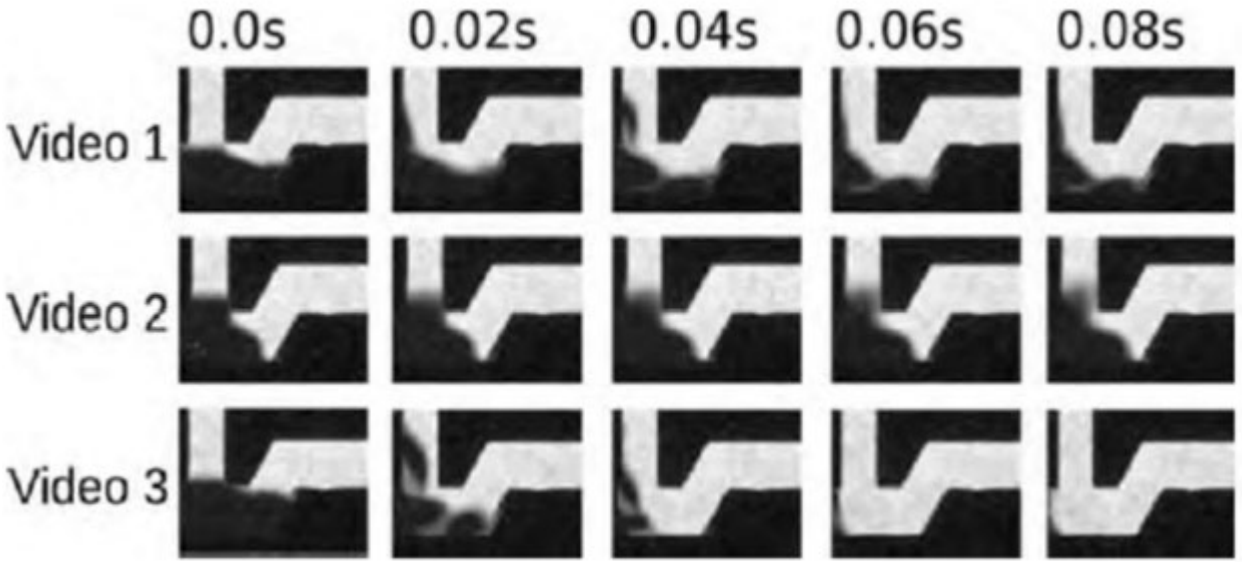


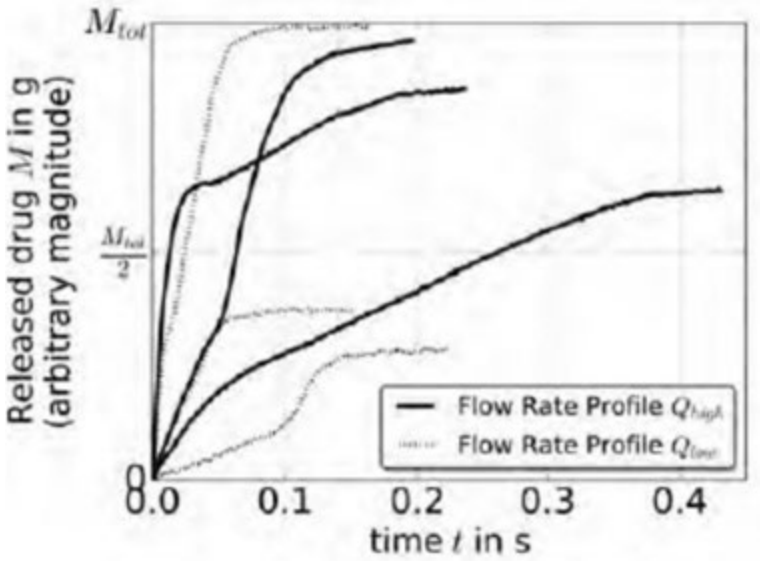




Kopsch et al. (2018) Int. J. Pharm. 553: 37-46

# Aerosolization studies and inhaler design for DPIs

## Experimental studies of high density powder fluidization




See highly chaotic and variable fluidization for lactose mixtures containing a significant portion of fine particles. What governs the powder cohesion?

Kopsch et al. (2018) Int. J. Pharm. 553: 37-46

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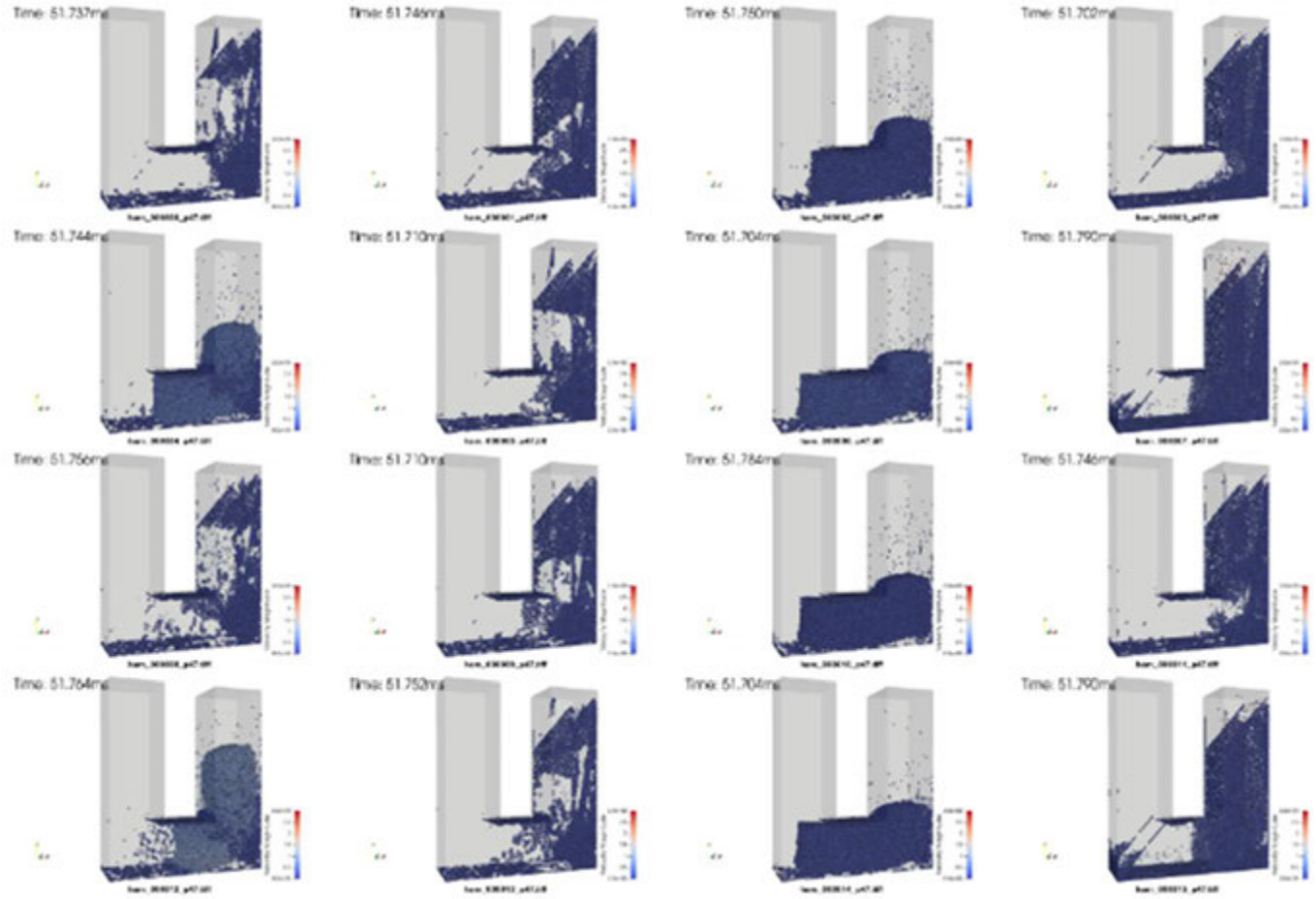
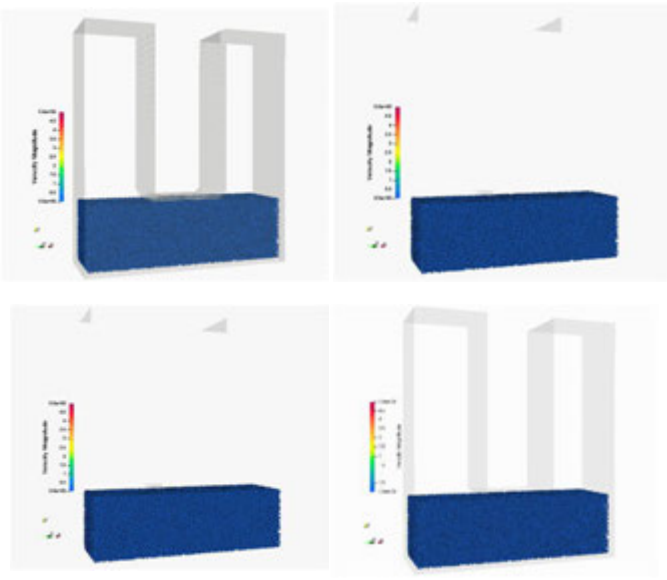
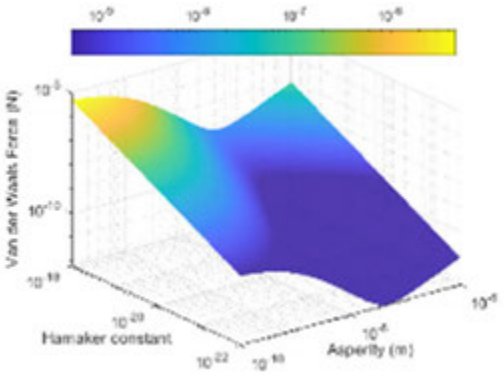
# CFD of DPI emission: Model input parameterization

## Is it possible to link material properties during product development?





Simulation results




Sensitivity analysis

Batch design-of-experiment simulation cases: with varying Hamaker constant and particle asperity. Is it possible to include accurate powder structures and cohesive force balances?

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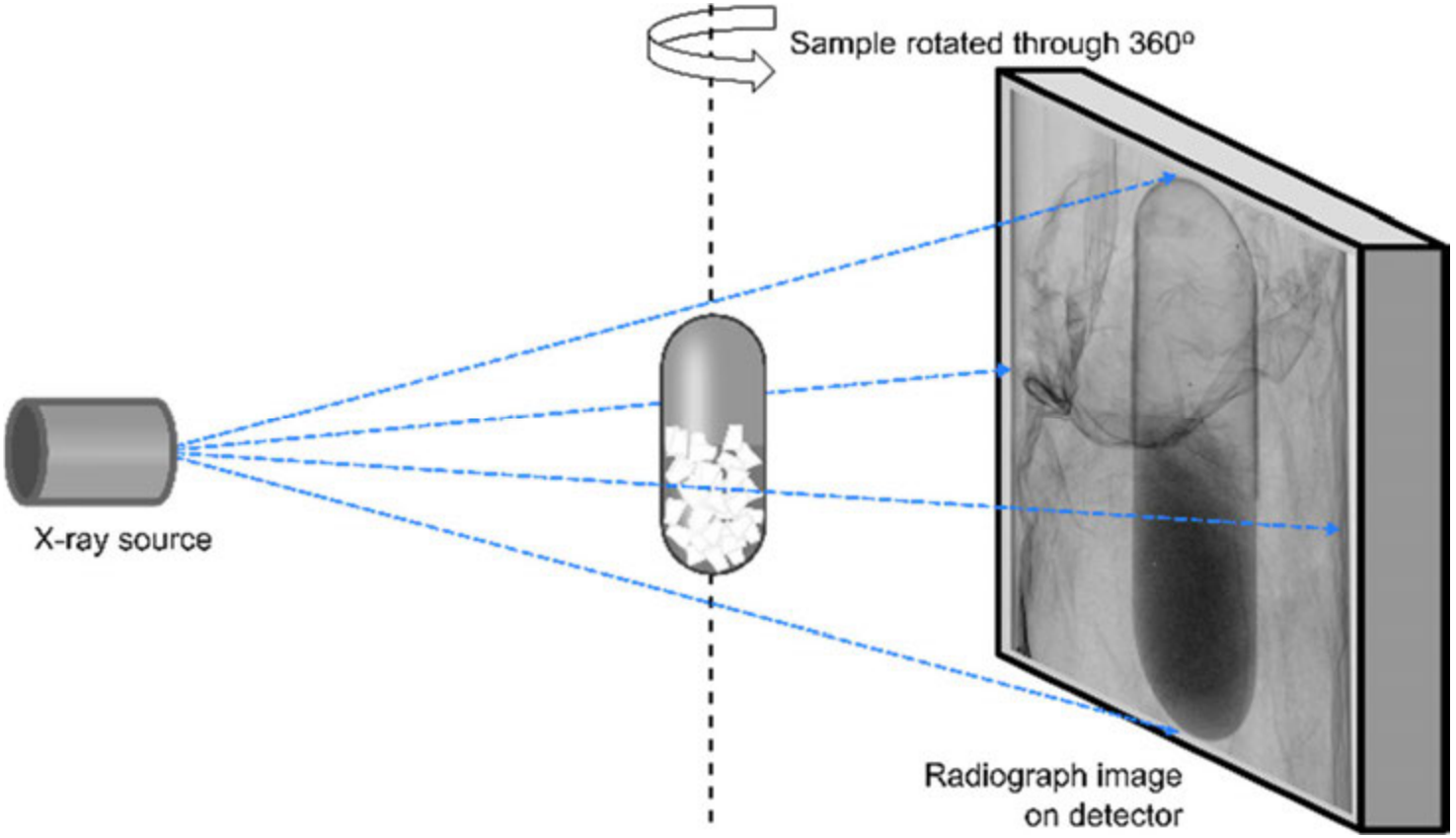
# Approaches to measuring formulation properties and structure on inhalation powder performance

# Deconstructing the powder microstructure

## X-ray tomographical insight into inhaled pharmaceuticals

Engineering and Physical Sciences Research Council




Gajjar, P. et al Eur. J. Pharm. Biopharm.
Open Access: DOI 10.1016/j.ejpb.2020.02.013

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# Deconstructing the powder microstructure
## X-ray tomographical insight into inhaled pharmaceuticals

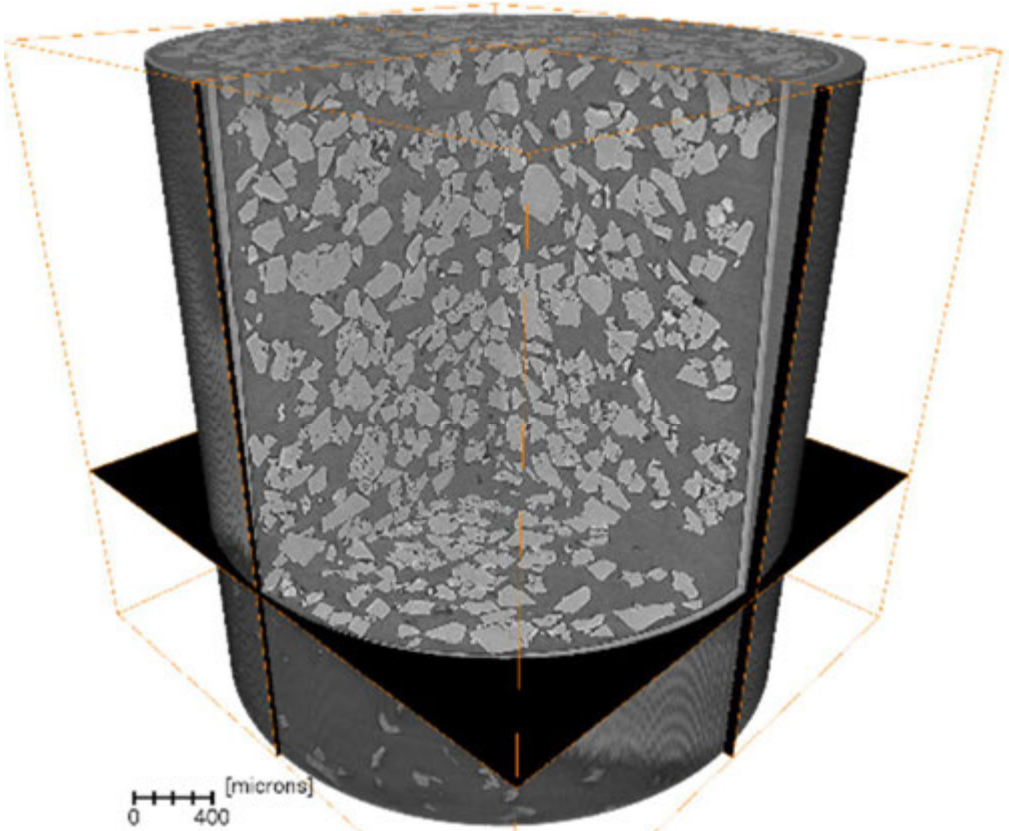
Engineering and Physical Sciences Research Council

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

3D characterisation of dry powder inhaler formulations: Developing X-ray micro computed tomography approaches

P. Gajjar, I.D. Styliari, T.T.H. Nguyen, J. Carr, X. Chen, J.A. Elliott, R.B. Hammond, T.L. Barnett, K. Roberts, P.J. Withers, D. Murnane




3D Characterisation of Dry Powder Inhaler Formulations: Developing X-ray Micro Computed Tomography Approaches

Gajjar, P. et al *Eur. J. Pharm. Biopharm.*

*Open Access: DOI* [10.1016/j.ejpb.2020.02.013](https://doi.org/10.1016/j.ejpb.2020.02.013)

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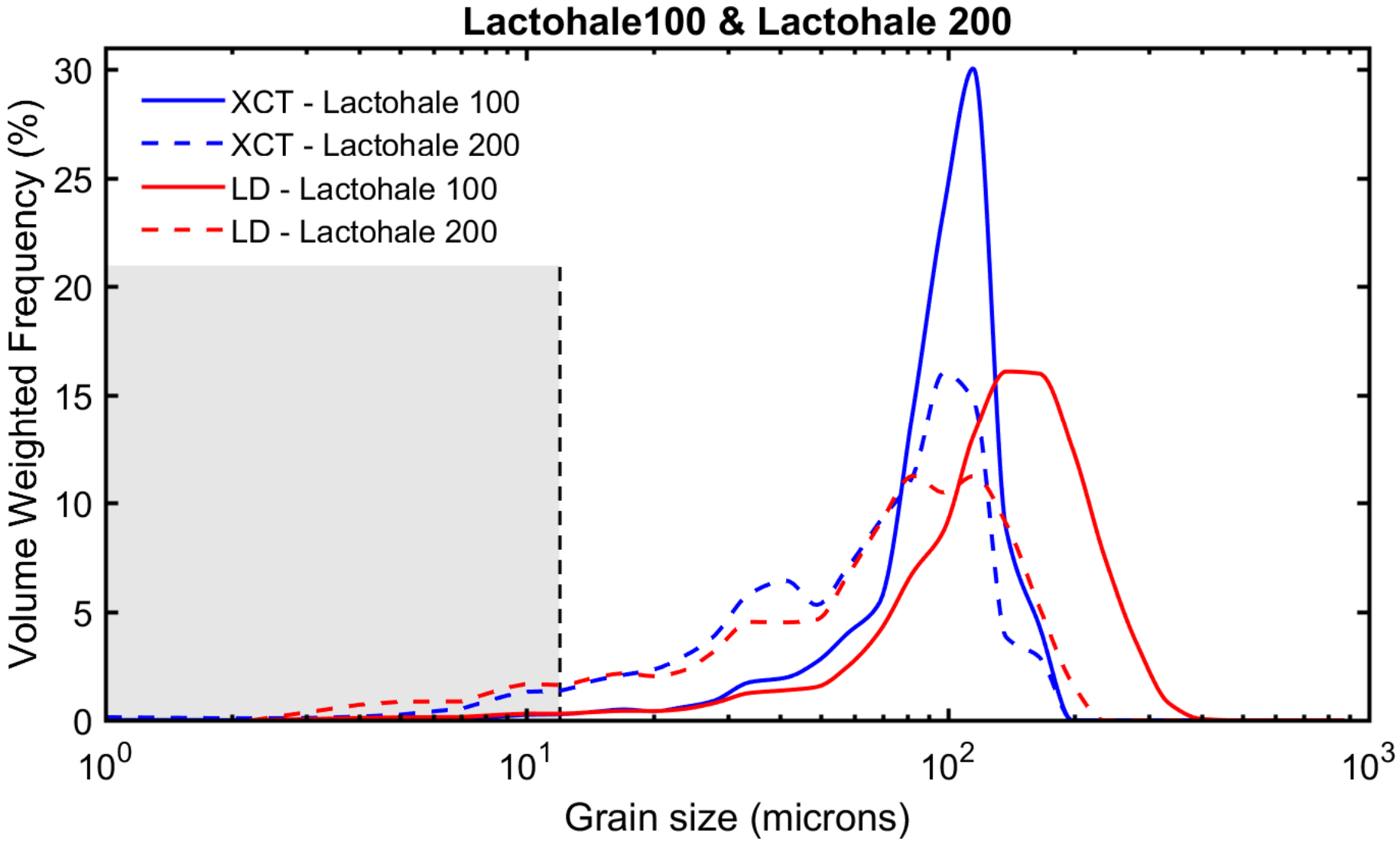
# X-ray tomographical insight into inhalation lactose

## Non-destructive determination of particle size distributions




Gajjar, P. et al *Eur. J. Pharm. Biopharm.*
*Open Access: DOI* [10.1016/j.ejpb.2020.02.013](https://doi.org/10.1016/j.ejpb.2020.02.013)

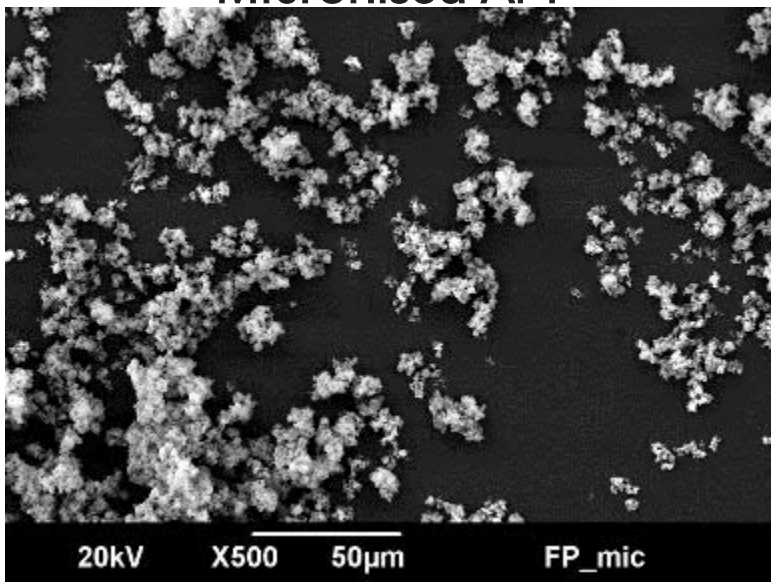
# Deconstructing powder agglomerates and formulation components

# Characterisation of typical DPI formulated products

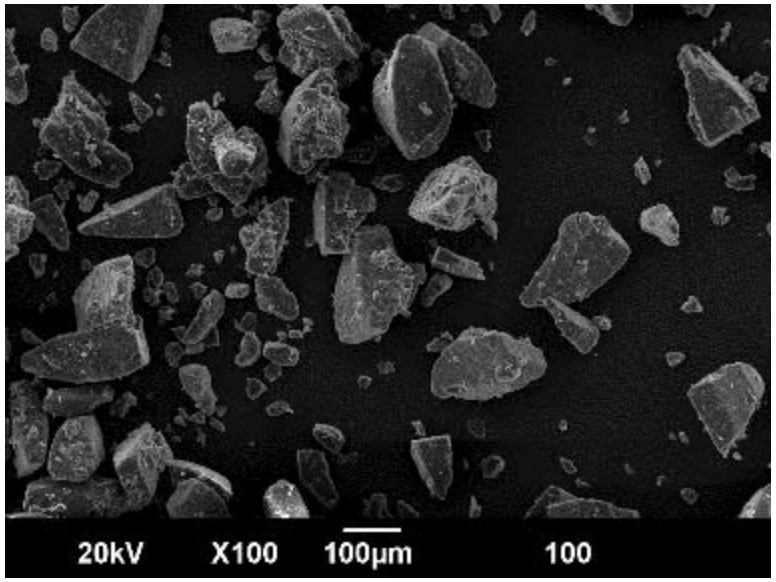
## Formulation components in 2 dimensions

Engineering and Physical Sciences Research Council

Micronised API

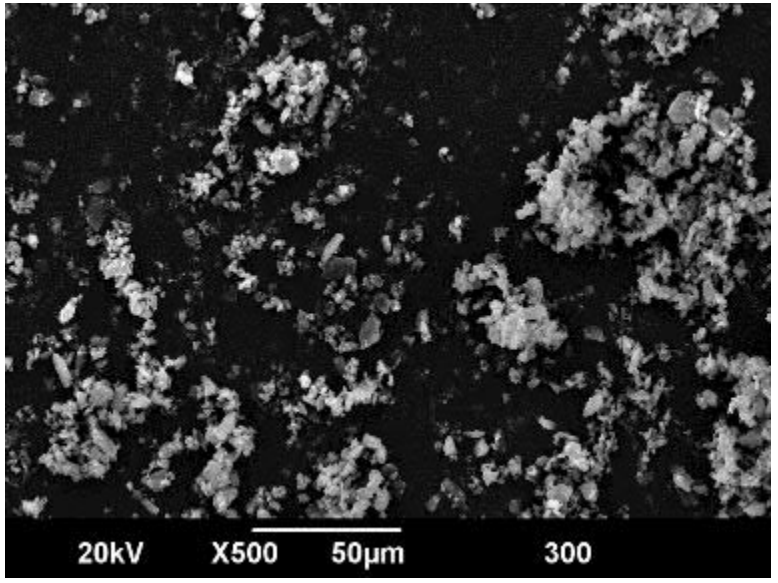



Lactose (Carrier)




+

Micronised lactose

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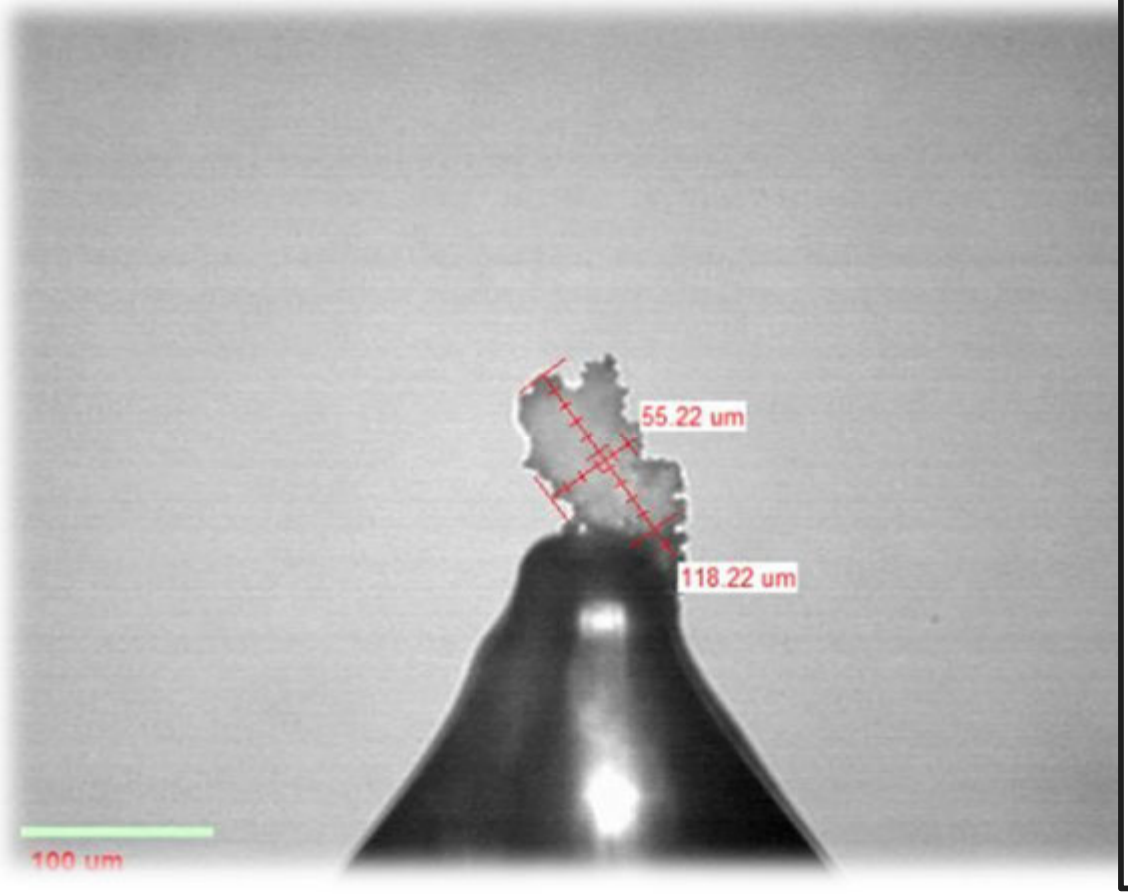
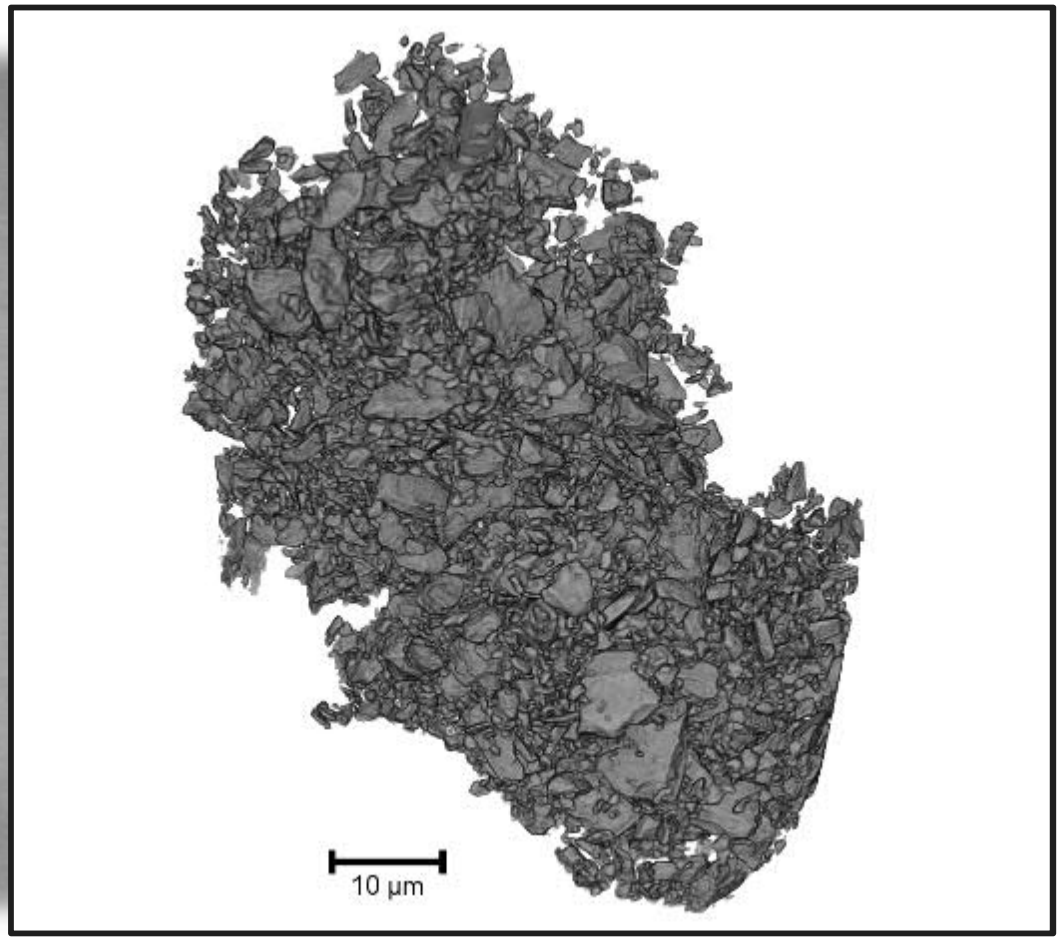
# Nano-scale XRM with Zeiss Ultra

# Deconstructing the agglomerates found in powders

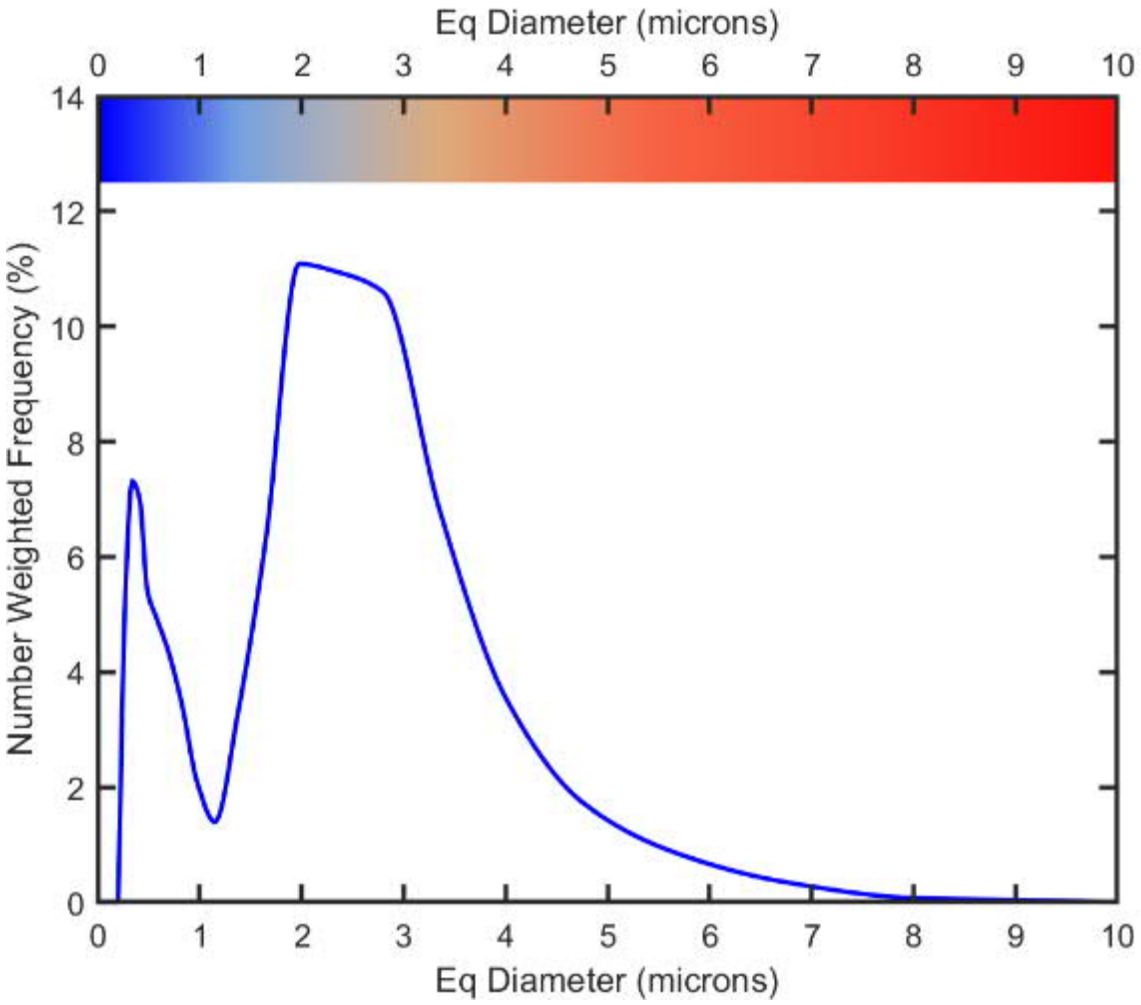


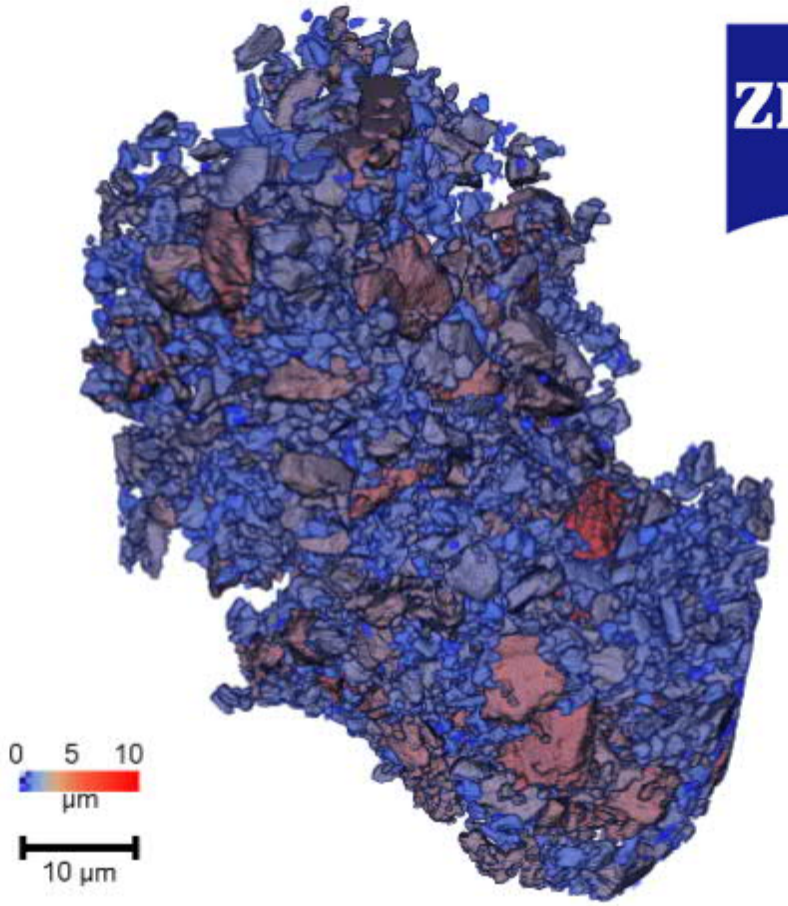




**Parmesh Gajjar, Hrishikesh Bale et al.,** Digital RDD 2020 – Unlocking the Microstructure of Inhalation Blends Using X-Ray Microscopy

# Nano-scale measurements of micronized lactose

## Non-destructive determination of agglomerate properties




Accurate determination of porosity:
LH300: 71.1% ± 0.7%

**Parmesh Gajjar, Hrishikesh Bale et al.,** Digital RDD 2020 – Unlocking the Microstructure of Inhalation Blends Using X-Ray Microscopy

# Deconstructing agglomerates in inhalation powders

## Realistic inhalation blends

Engineering and Physical Sciences Research Council

Excipient: Lactohale 100

Drug: Micronised Fluticasone Propionate

Mixing: Picomix® high shear mixer module, 1000 rpm, 2 min

Ratio: 10% w/w of API

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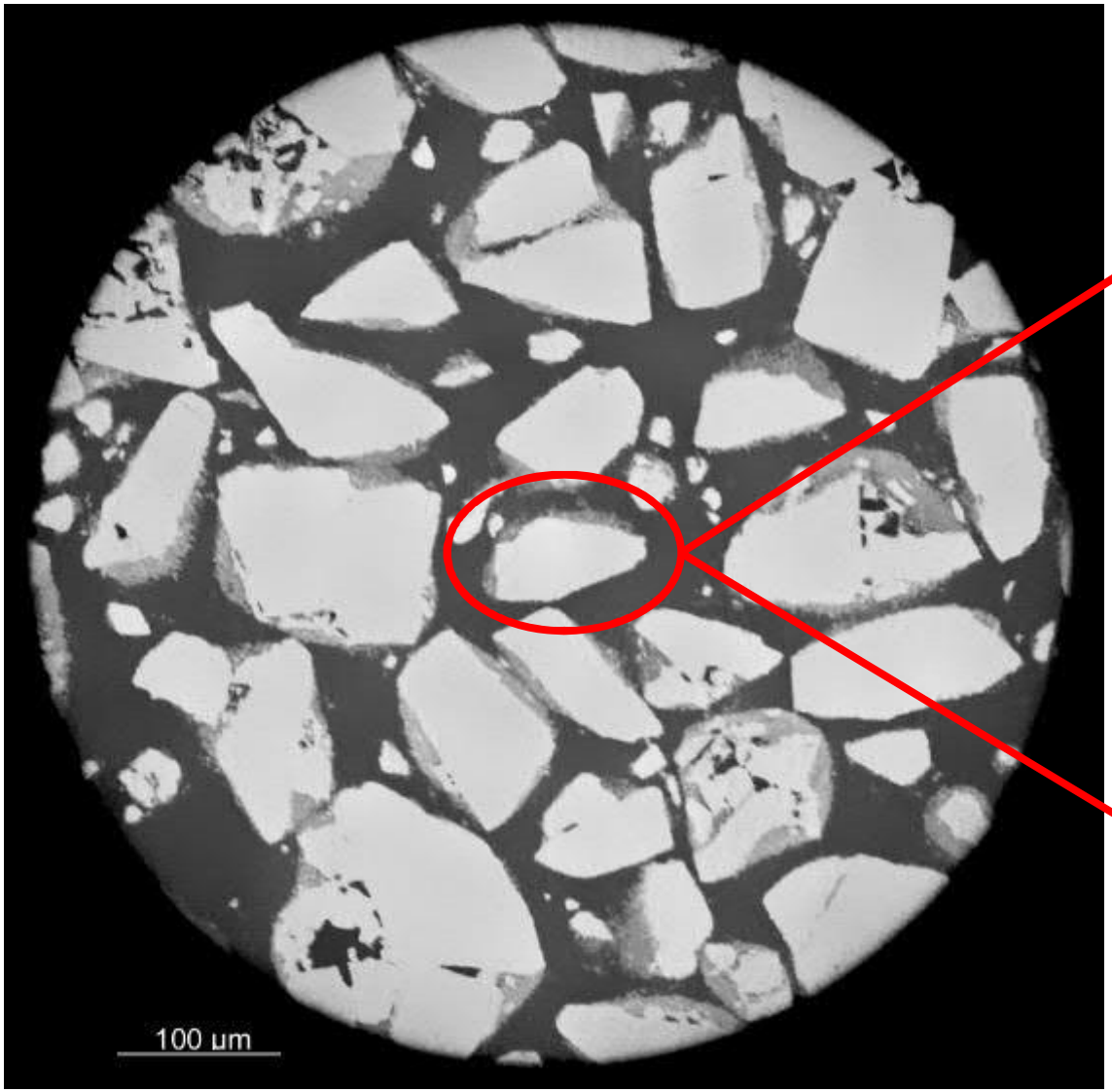
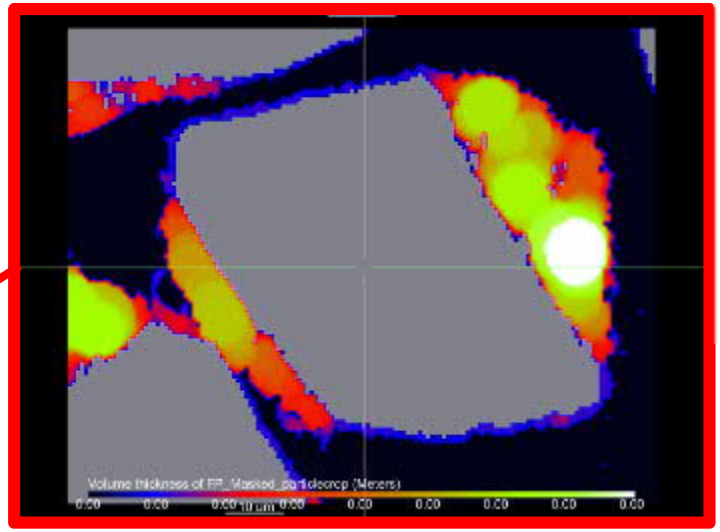
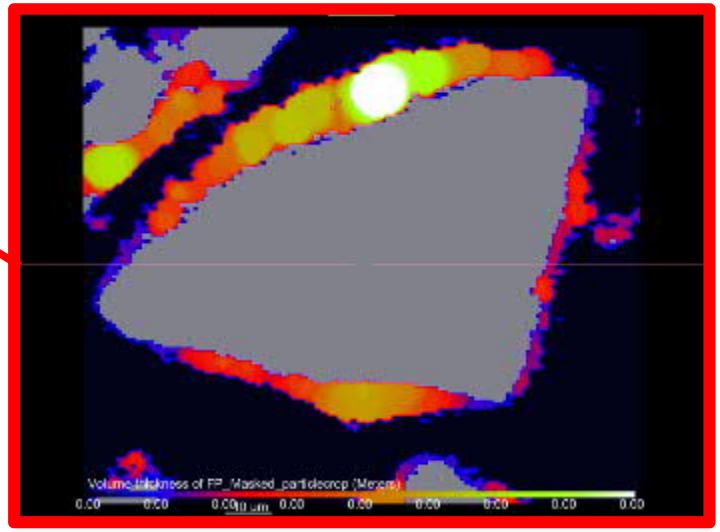
# Deconstructing agglomerates in inhalation powders

## Measuring the location of the micronized agglomerates/particles





Differential coating on different facets

(Slightly different slices of same particle in zoomed in section shown)

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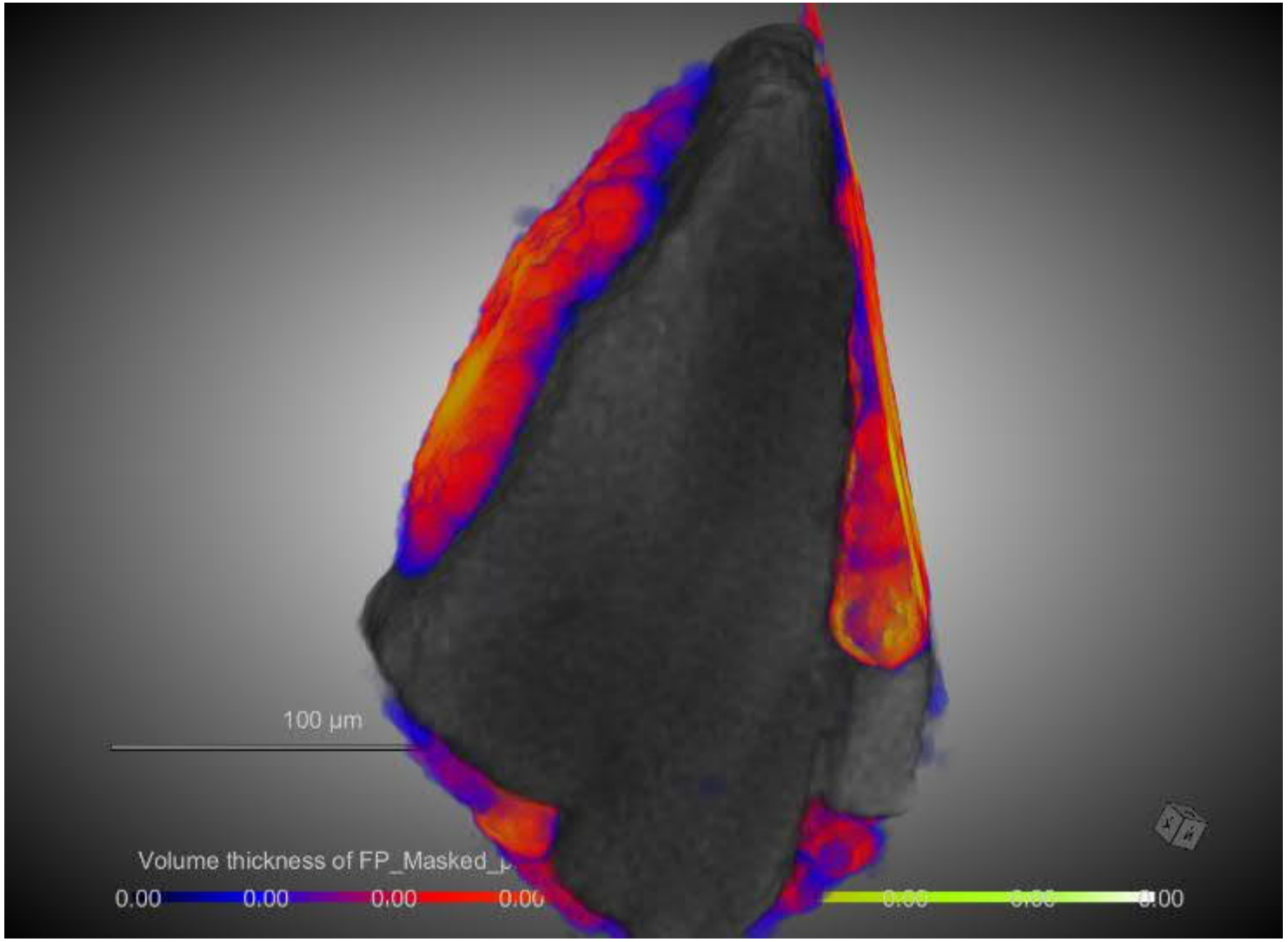
**Parmesh Gajjar, Hrishikesh Bale et al.,** Digital RDD 2020 – Unlocking the Microstructure of Inhalation Blends Using X-Ray Microscopy

# Deconstructing agglomerates in inhalation powders

## Measuring the location of the micronized agglomerates/particles




**Parmesh Gajjar, Hrishikesh Bale et al.,** Digital RDD 2020 – Unlocking the Microstructure of Inhalation Blends Using X-Ray Microscopy

# Deconstructing agglomerates in inhalation powders

## Measuring the location of the micronized agglomerates/particles

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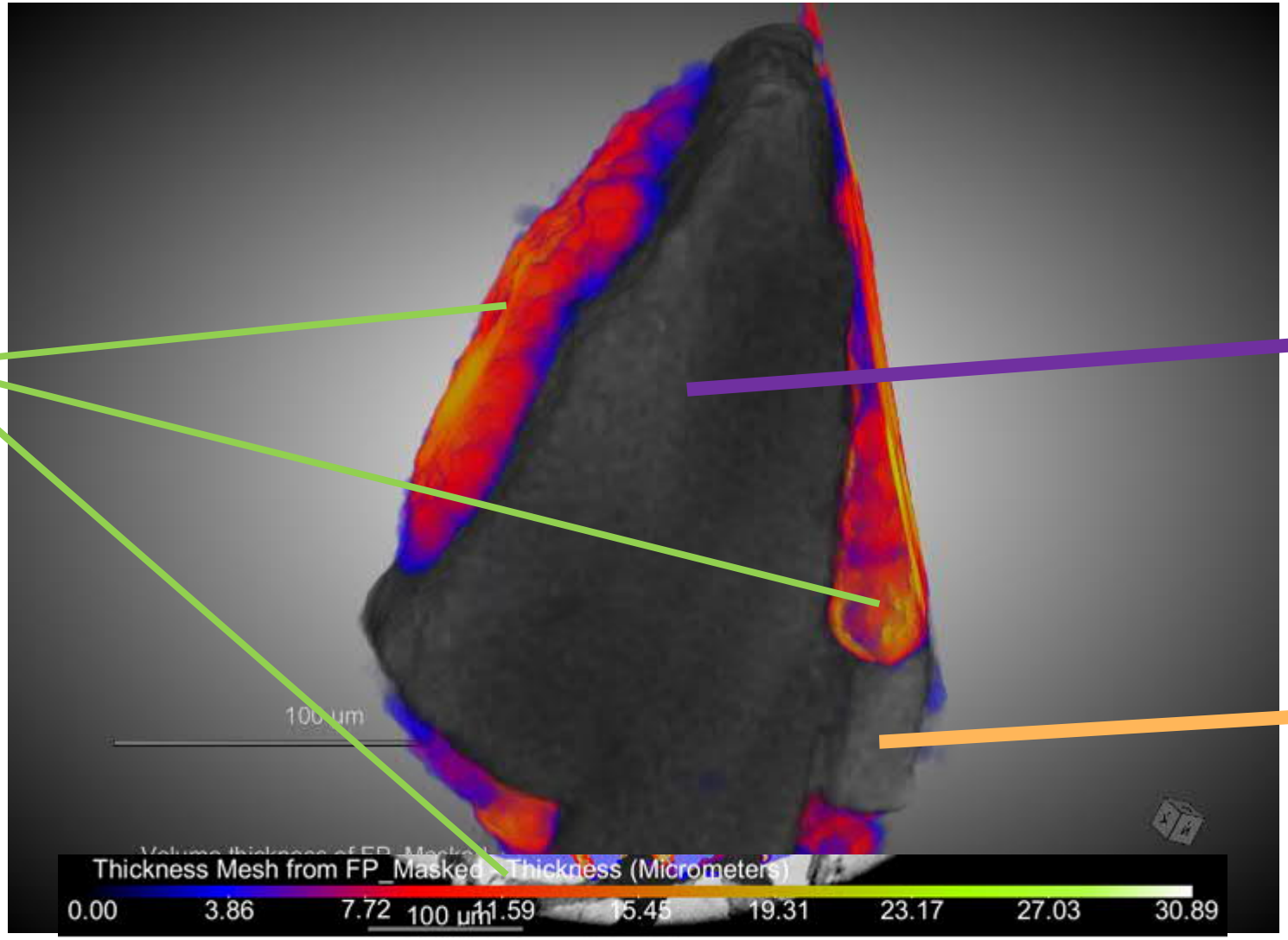
Significant amounts of mFP on these facets




Less mFP on this facet

Smaller lactose particle

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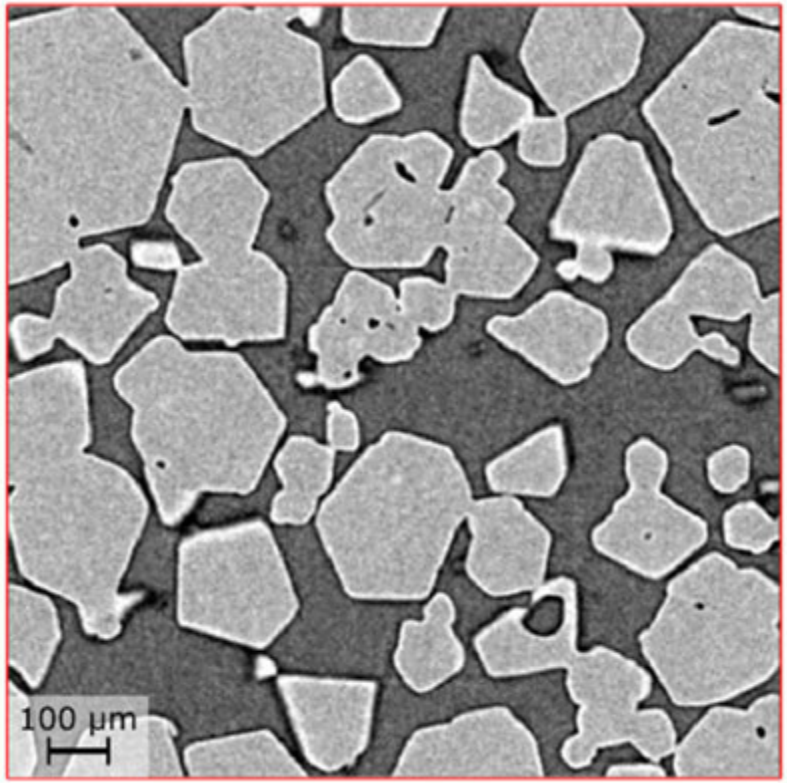
Is it possible to identify to which particle surfaces the drug particles adhere in a formulation?

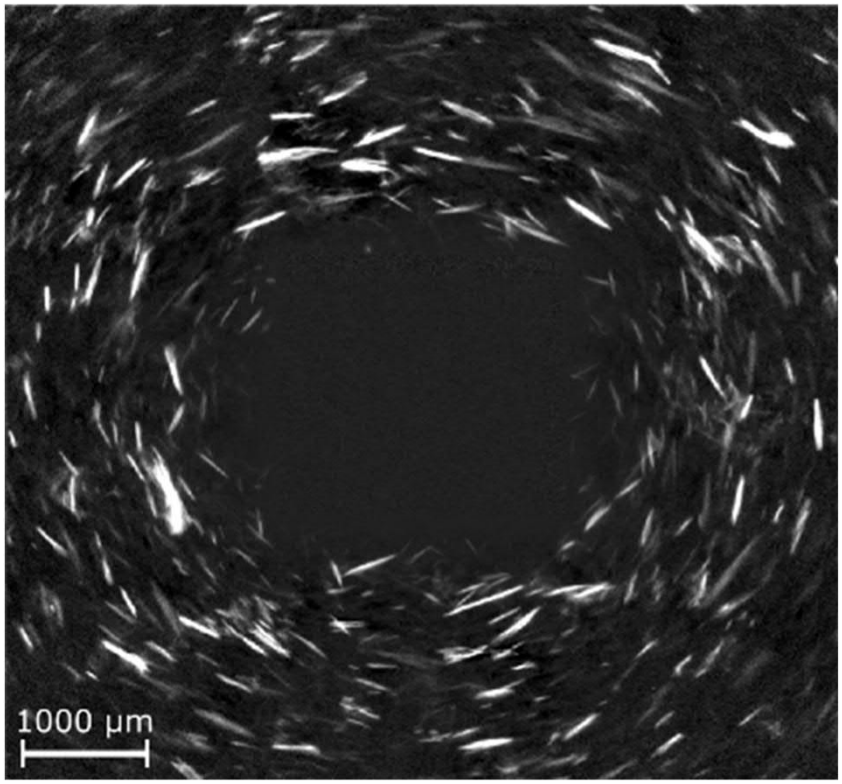
# Direct measurement of powder crystallography

## Laboratory diffraction contrast tomography Xray Microscopy

Engineering and Physical Sciences Research Council




Absorption Mask




Diffraction Spots

**Hrishikesh Bale, Jun Sun,** et al. Digital RDD 2020 Poster - Laboratory Diffraction Contrast Tomography

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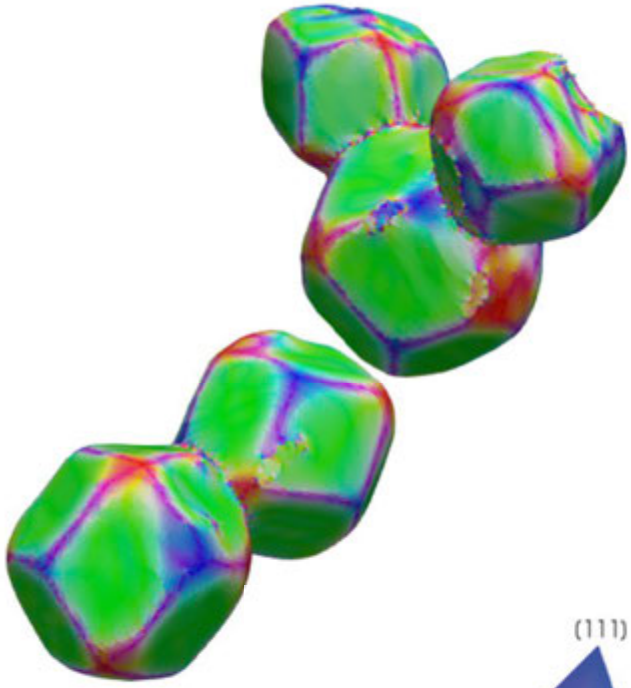
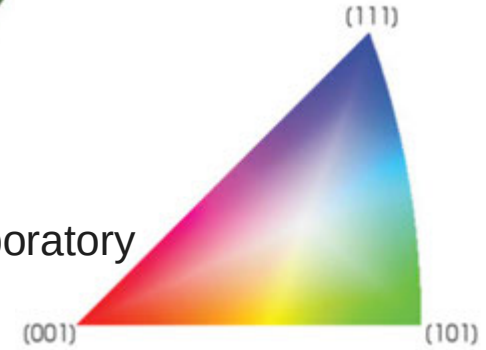
# Laboratory diffraction contrast tomography

## Hexamine as a model power

Engineering and Physical Sciences Research Council






**Hrishikesh Bale, Jun Sun,** et al. Digital RDD 2020 Poster - Laboratory Diffraction Contrast Tomography

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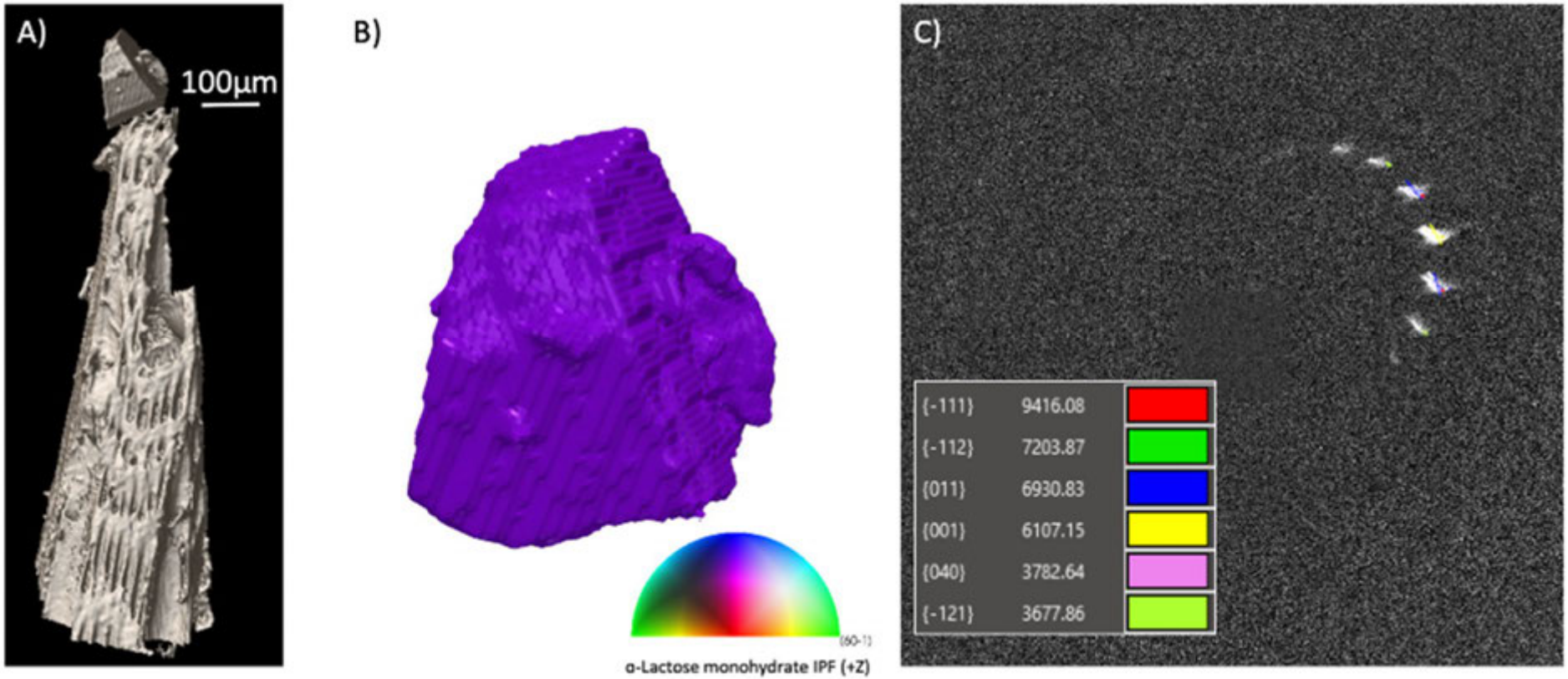
# Laboratory diffraction contrast tomography
# α-Lactose Monohydrate

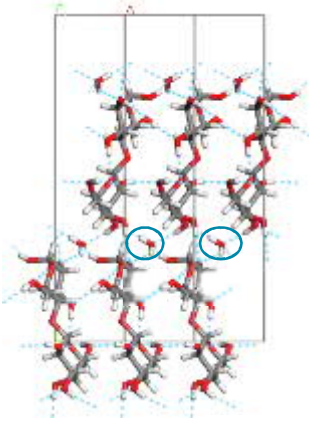



**Hrishikesh Bale, Jun Sun,** et al. Digital RDD 2020 Poster - Laboratory Diffraction Contrast Tomography

Is it possible to identify cohesive or adhesive force balances within those formulations?

# Crystallographic structure particle property predictions

## α-Lactose Monohydrate

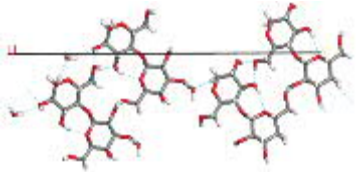


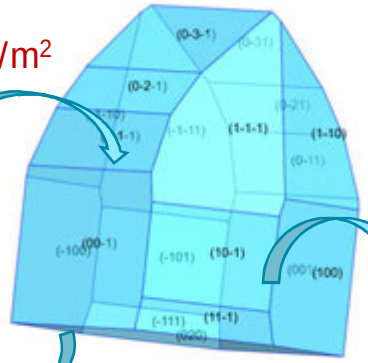
C12H22O11.H2O
LACTOS11

a = 4.78; b = 21.54; c = 7.76
β=105.91$^0$; V= 768.8

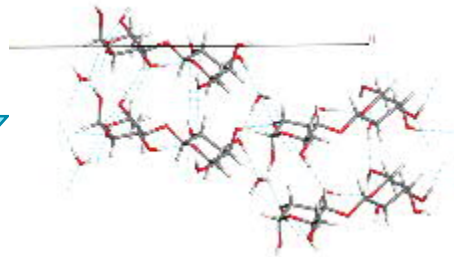
| Face {hkl} | $E_{att}$ (kcal/mol) | Dispersive SE (mJ/m$^2$) | Total SE (mJ/m$^2$) |
|---|---|---|---|
| {020} | -13.64 | 71.64 | 82.90 |
| {001} | -16.79 | 70.96 | 82.59 |
| {01-1} | -20.4 | 83.81 | 96.73 |
| {02-1} | -23.87 | 80.82 | 92.64 |
| {031} | -27.07 | 77.87 | 89.54 |
| {100} | -20.67 | 55.39 | 63.83 |
| {1-10} | -22.14 | 58.21 | 66.97 |
| {10-1} | -20.37 | 51.61 | 58.26 |
| {1-20} | -23.96 | 59.32 | 68.23 |

{0-31}
Surface Energy (SE): 84.21 mJ/m$^2$

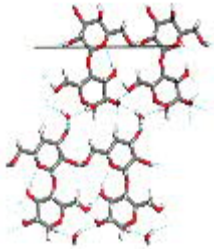




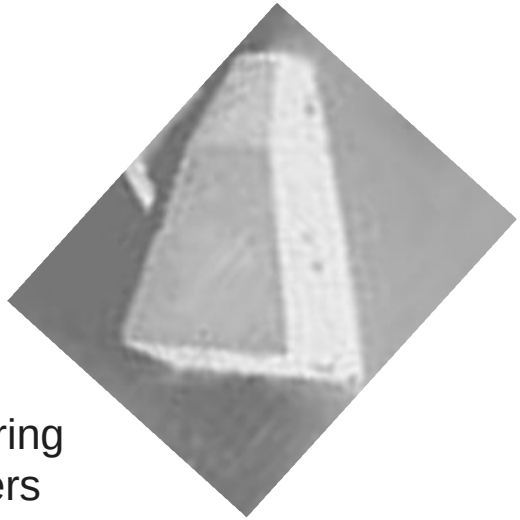
{100}: 59.1mJ/m$^2$



{020}: 77.96 mJ/m$^2$



**Calculated SE for LMH: 73.69 mJ/m$^2$ (Dispersive: 64 mJ/m$^2$)**



**Styliari, Nguyen** et al. Digital RDD 2020 Poster - On Measuring the Specific Surface Area of inhalation-grade lactose powders

University of Hertfordshire UH

Ramachandran, et al., Mol. Pharm., 2014. 12: 8-33;

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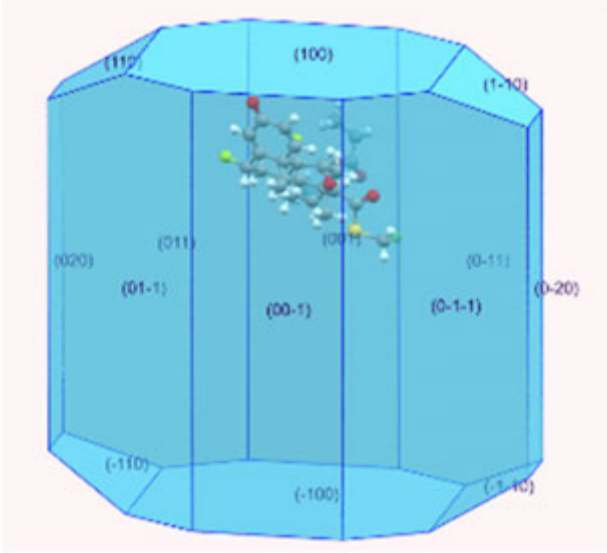
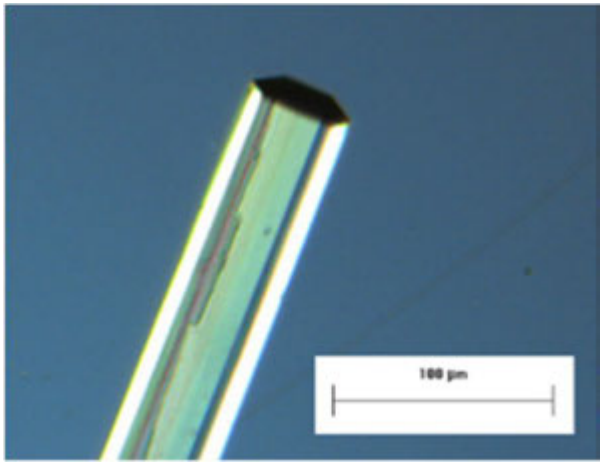
# Crystallographic structure particle property predictions

## Fluticasone propionate



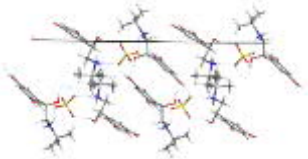

| Face {hkl} | Surface Area (%) | Total SE ($mJ/m^2$) |
|---|---|---|
| {011} | 22.3 | 9.63 |
| {0-11} | 22.3 | 9.63 |
| {100} | 23.0 | 10.83 |
| {001} | 17.1 | 11.38 |

**Vivian Walter Barron, Robert B Hammond et al.,** Digital RDD 2020 Poster on the Podium – Modelling Intermolecular Interactions between Solid and Liquid Components of pMDI Suspension Formulations

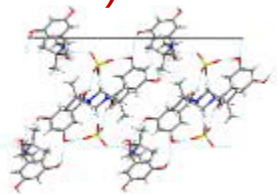
# Crystallographic structure particle property predictions

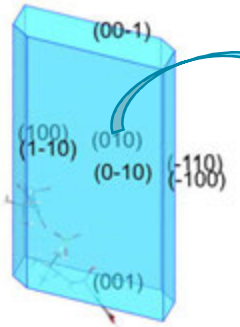
## Terbutaline Sulphate: Nguyen, et al., CrystEngComm. 2020 In Press

{1-10} surface:
45.6 (mJ/m$^2$)

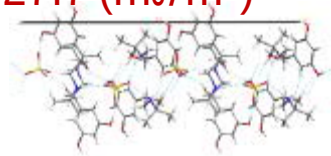


{001} surface:
109 (mJ/m$^2$)

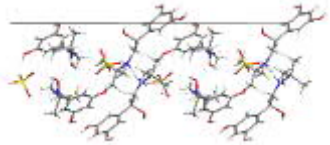


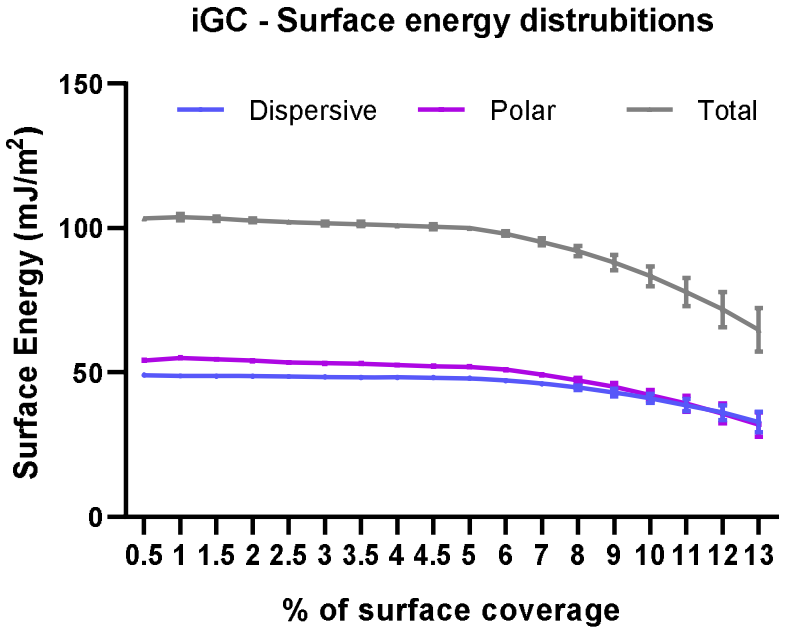



{010} surface:
27.7 (mJ/m$^2$)



{-100} surface:
50.6 (mJ/m$^2$)






| Surface energy | Dispersive SE (mJ/m$^2$) | Total SE (mJ/m$^2$) |
|---|---|---|
| Surface energy (weighting % surface area) | 28.27 | 48.2 |
| IGC Surface energy surface coverage [0.05-0.8] | 49.1 – 44.7 | 103.3 – 92.1 |

**Nguyen, Hammond** et al. Digital RDD 2020 Poster - Molecular Synthon Modelling of Inhalation Pharmaceuticals: A Digital Approach to Understanding and Engineering Particle Surface Interactions

University of Hertfordshire UH

**Nguyen, et al., CrystEngComm. 2020.** DOI: 10.1039/d0ce00026d

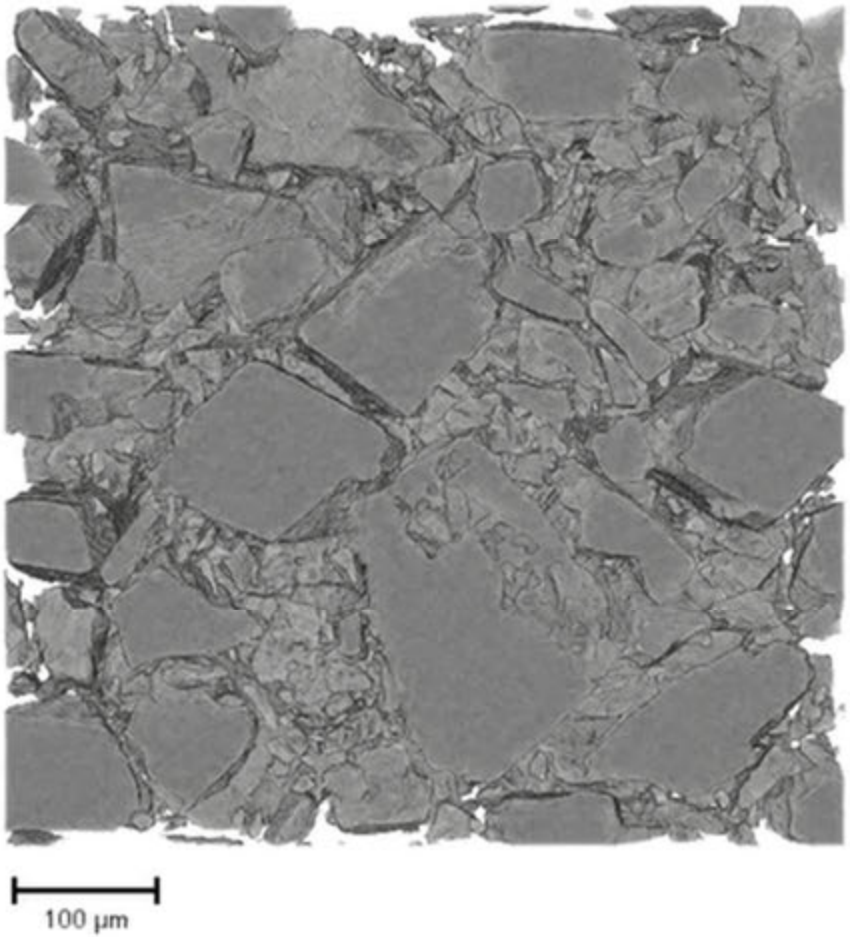
TEF Gold

# Reconstructing inhalation blends of powder agglomerates

# Reconstructing agglomerative inhalation powders

## The power of multi-scale correlative x-ray microscopy

Engineering and Physical Sciences Research Council

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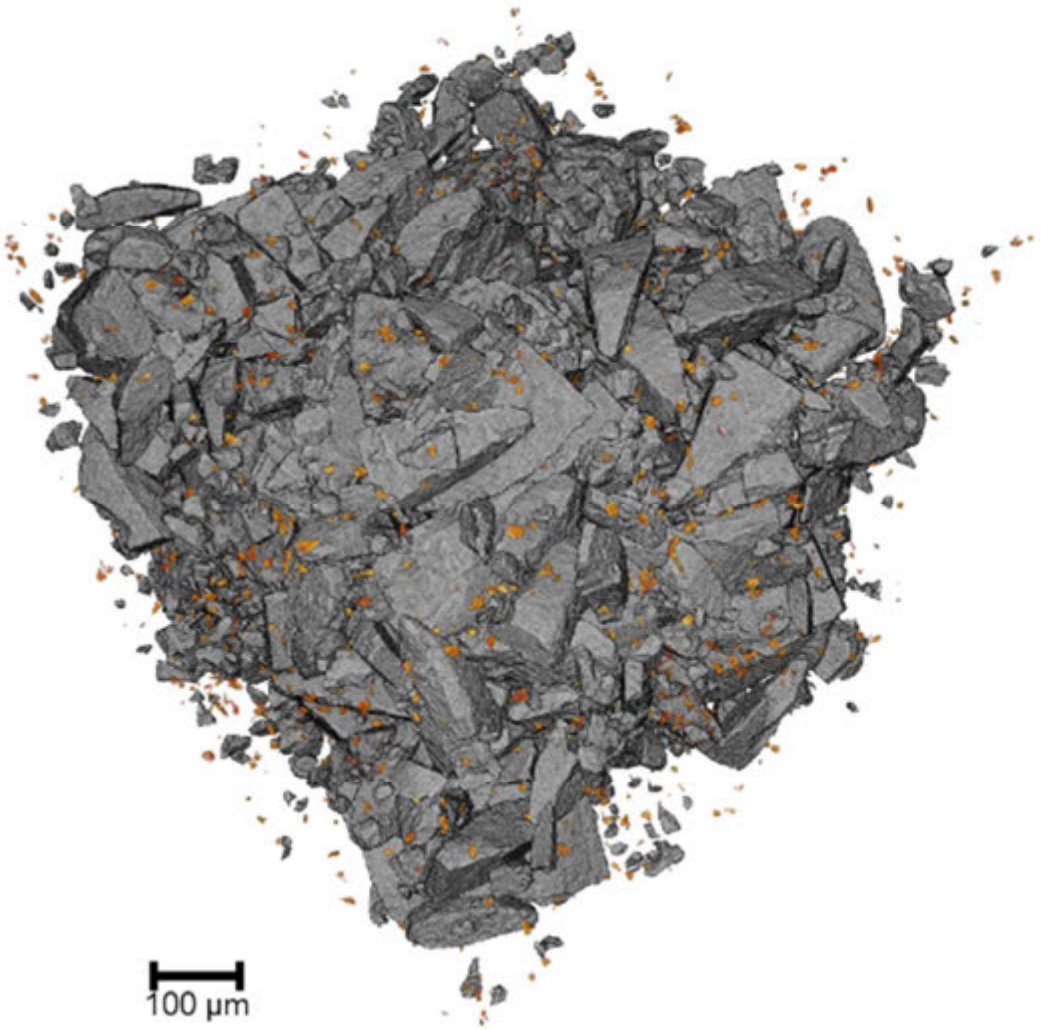
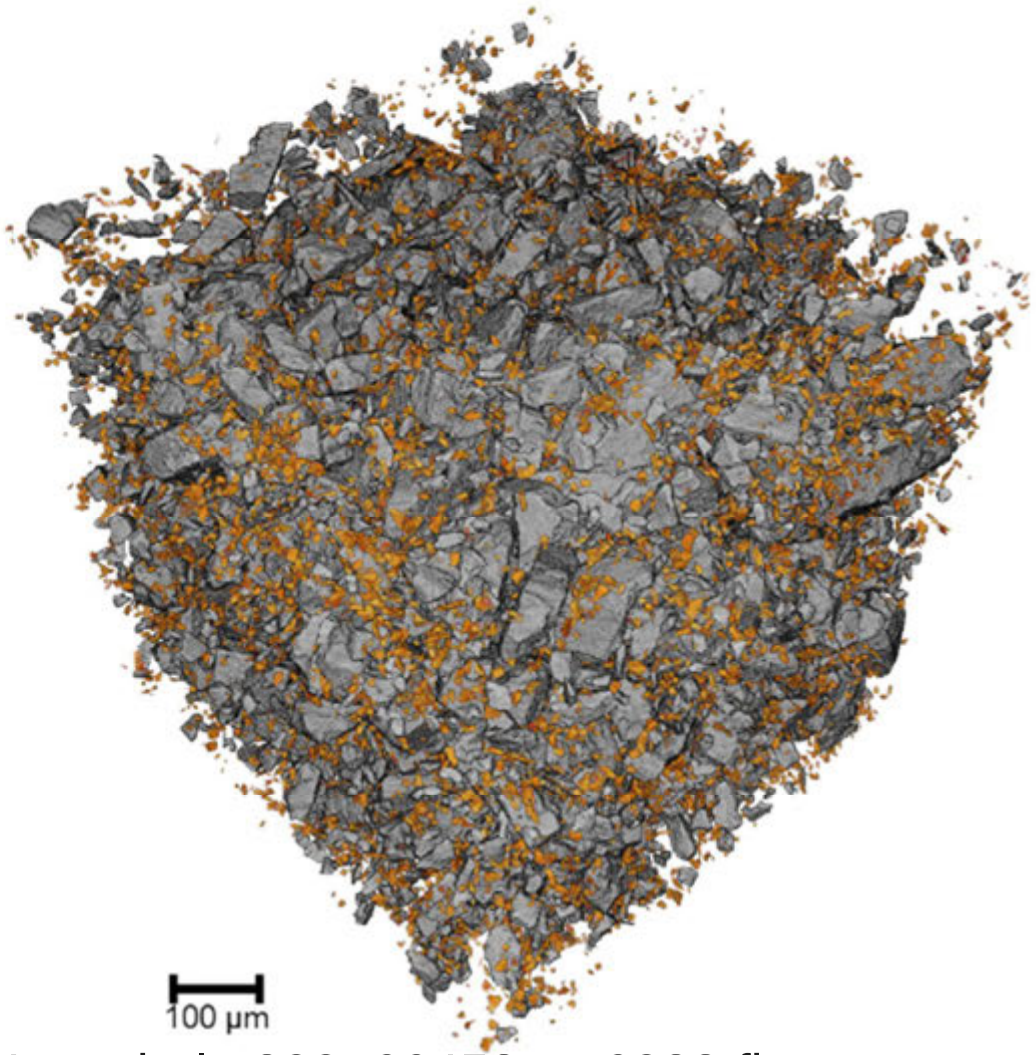
# Reconstructing agglomerative inhalation powders

## Identification of powder microstructure and processing

Engineering and Physical Sciences Research Council




Lactohale 100: 9426 ± 559 fines per $mm^3$

Lactohale 200: 66458 ± 6033 fines per $mm^3$

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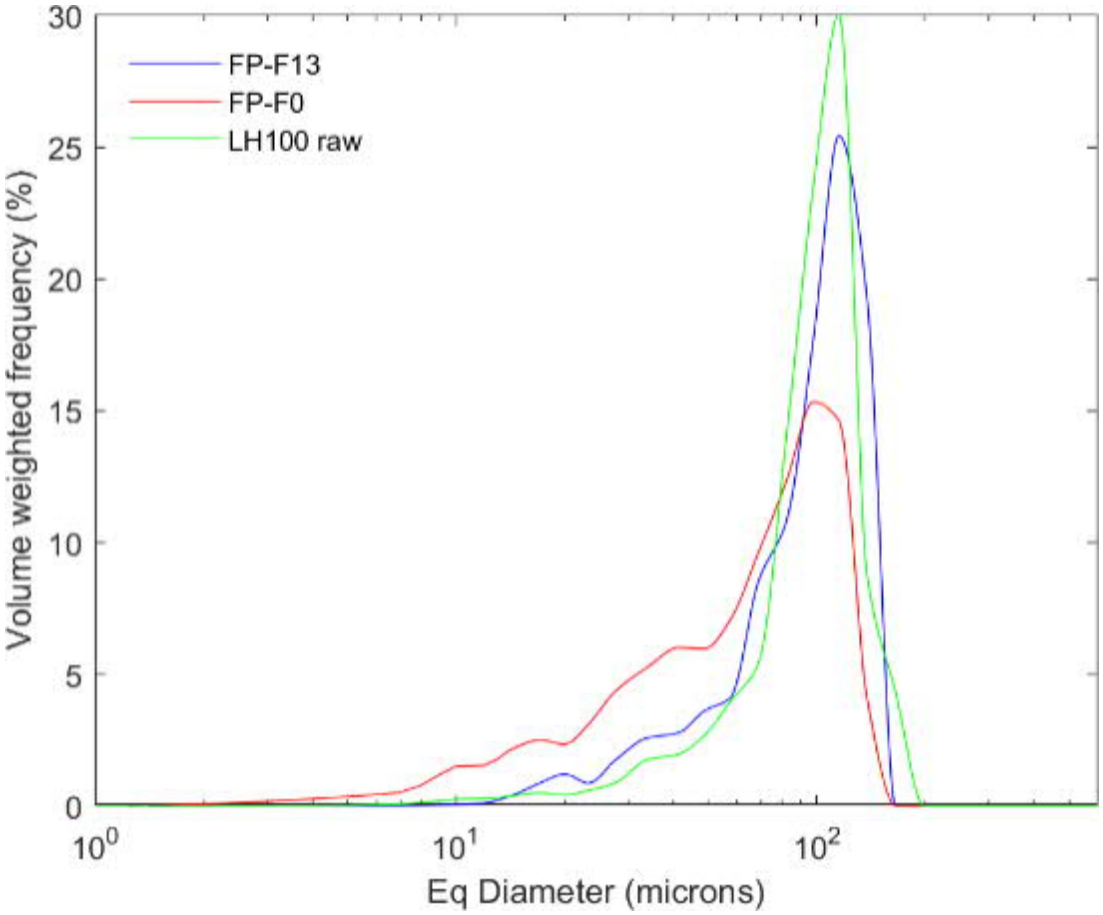
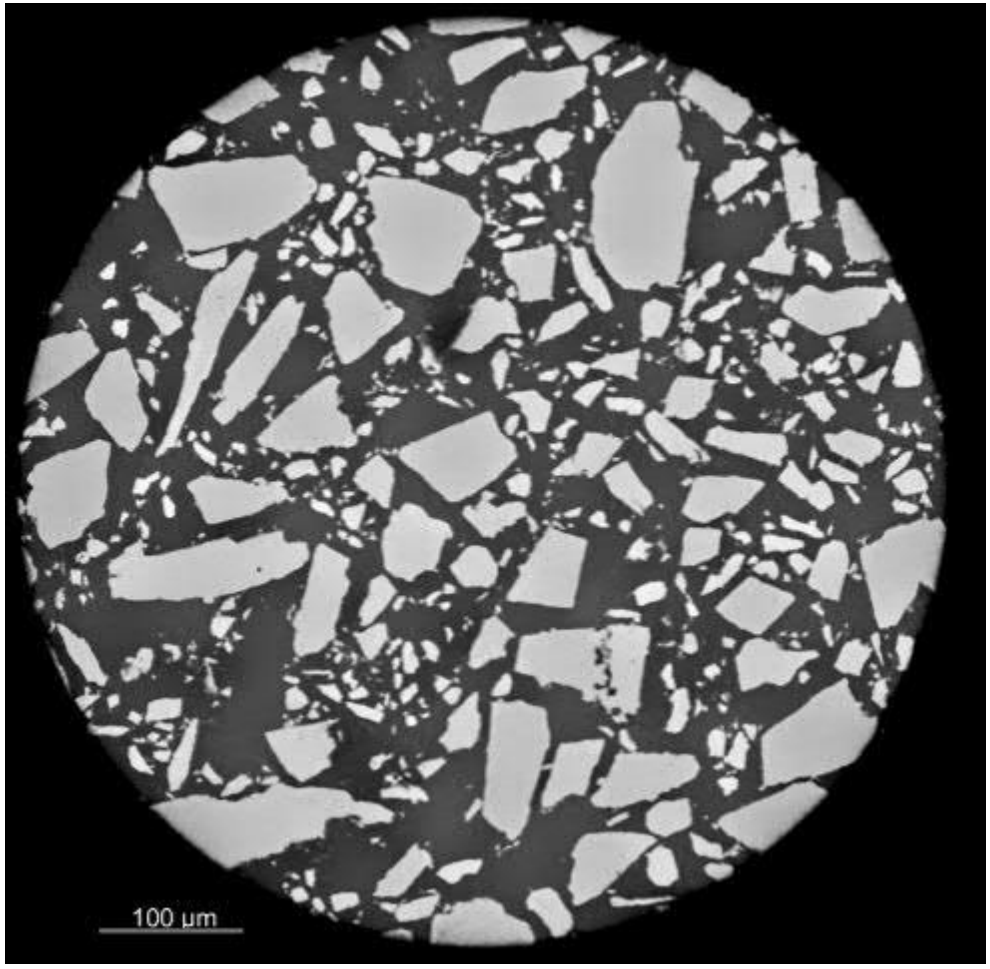
# Reconstructing agglomerative inhalation powders

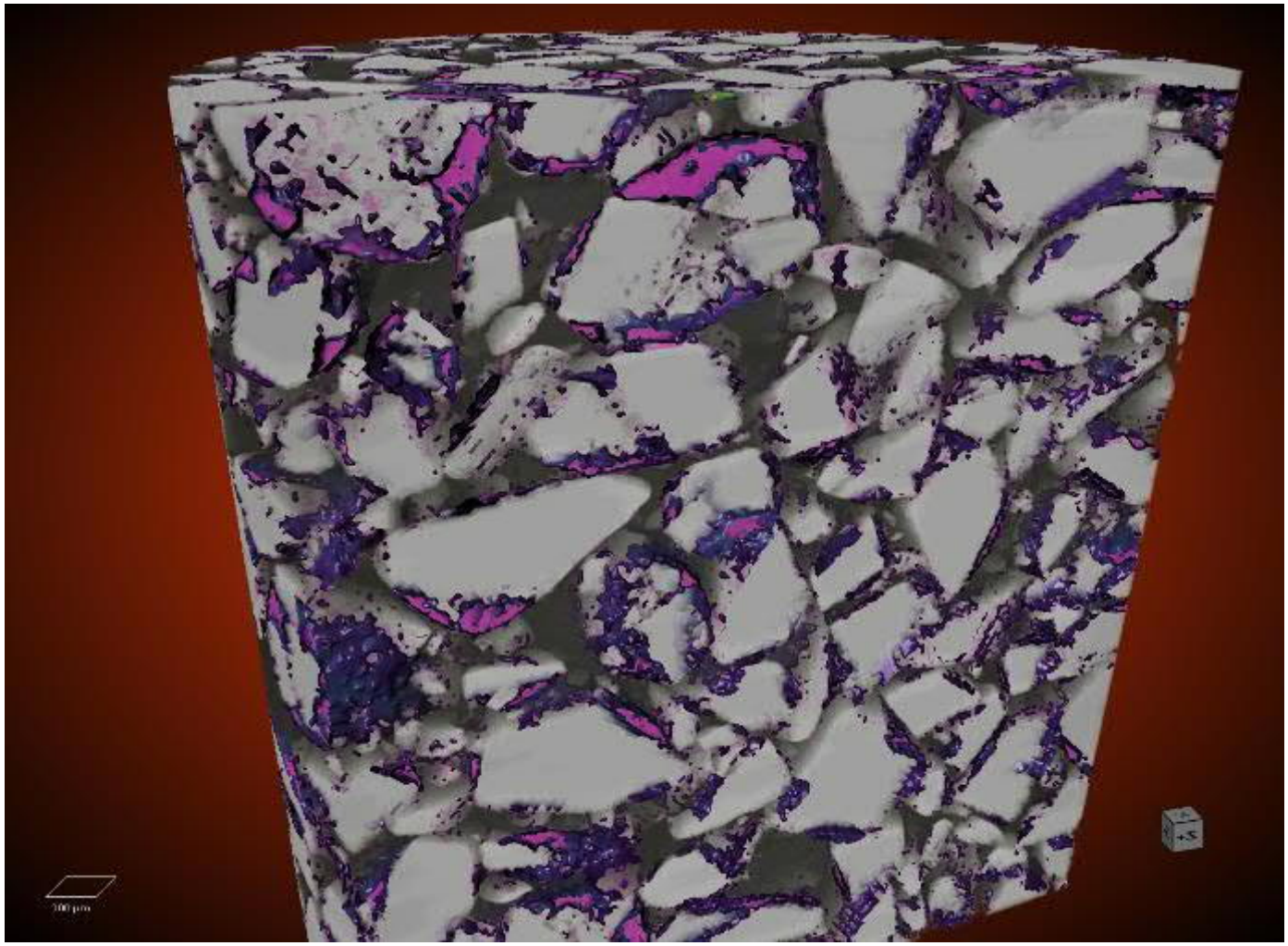
## Characterising the impact of high shear blending with micronized API



# Reconstructing agglomerated powder blends

## Is this what we mean by the Q3 microstructure?



Lactohale 100 + Fluticasone Propionate (10% w/w ratio)

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