

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

Darragh Murnane Centre for Research in Topical Drug Delivery & Toxicology



## INFORM 2020 – Molecules to Manufacture



Academic investigators & commercial partners

#### University of UH Hertfordshire



EP/N025075/1









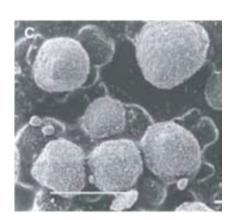
Tim Burnett, David Chau, Simon Connell, James Elliott, Robert Hammond, Victoria Hutter, Darragh Murnane, Robert Price, Kevin Roberts, Digby Symons, & Philip Withers



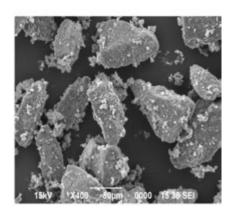
## The future formulation of inhaled therapies? INFORM 2020 – Molecules to Manufacture



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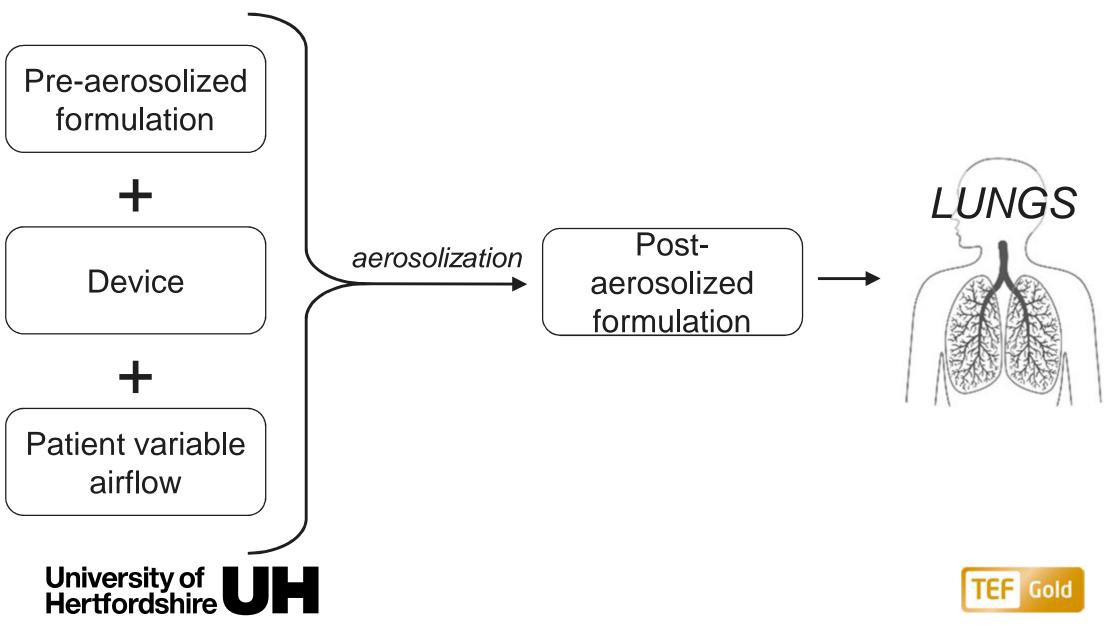


Can we develop predictive models of formulation behaviour, manufacturing processes and aerosolization events to increase understanding of product performance, and stability in order to accelerate development?





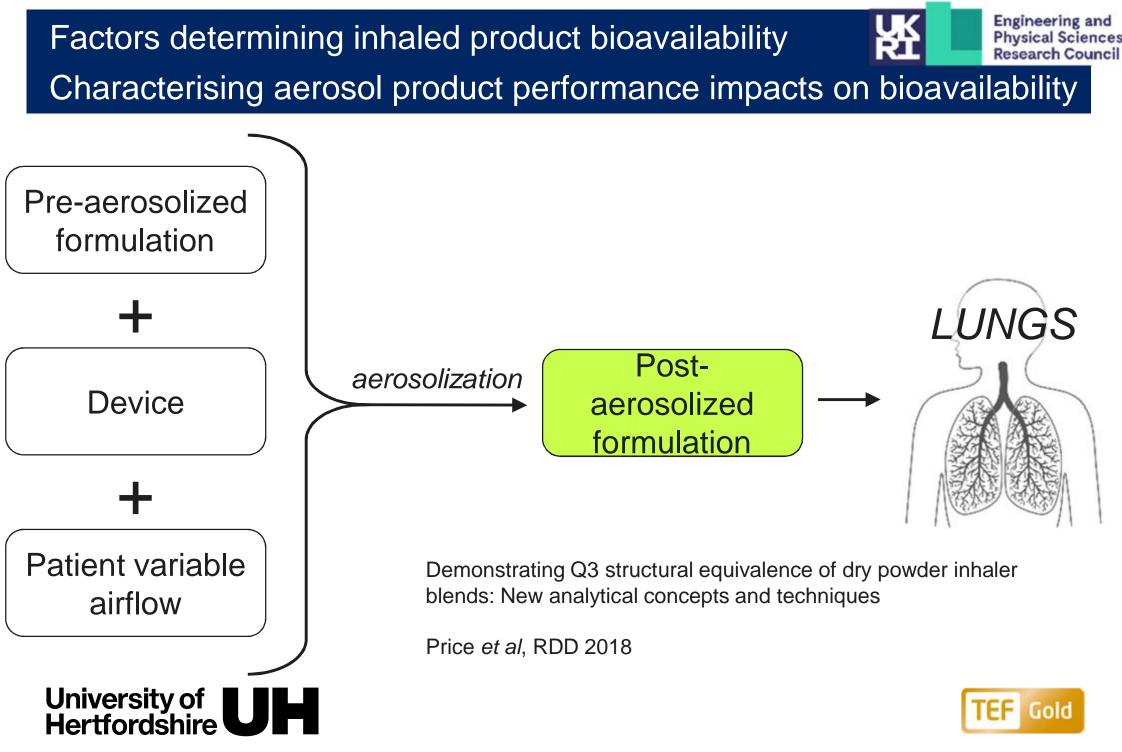
Factors determining inhaled product bioavailability Combination drug formulation & device products

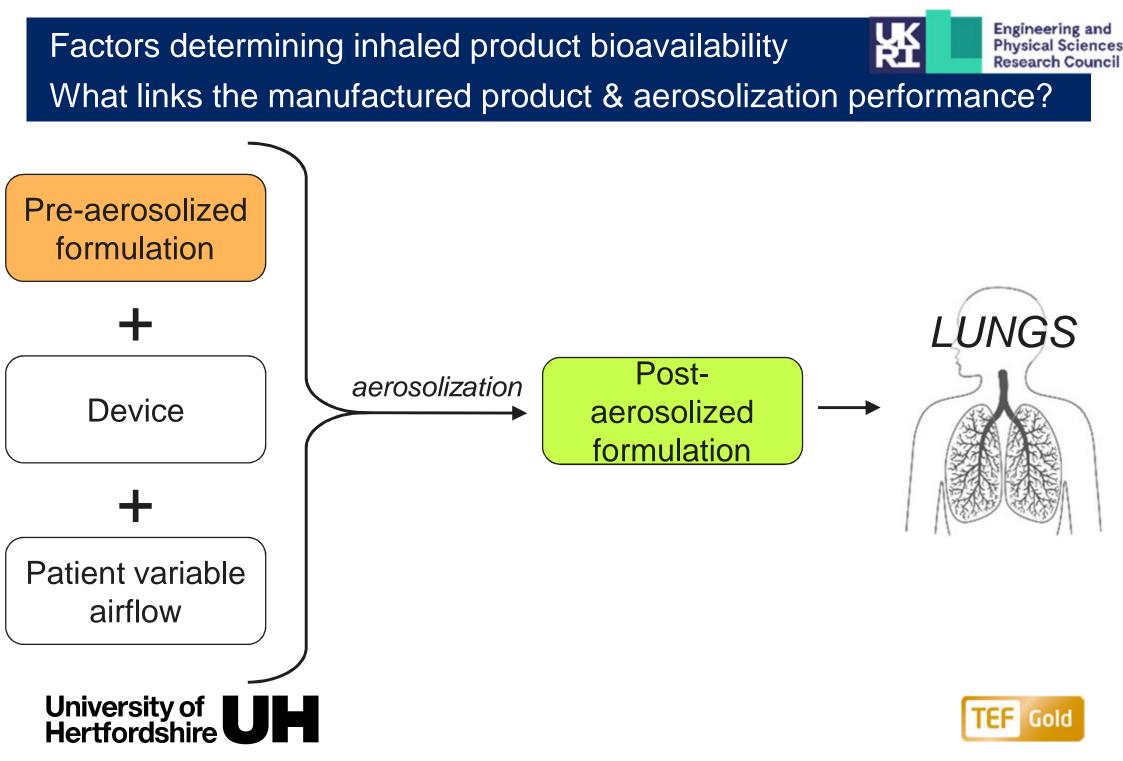


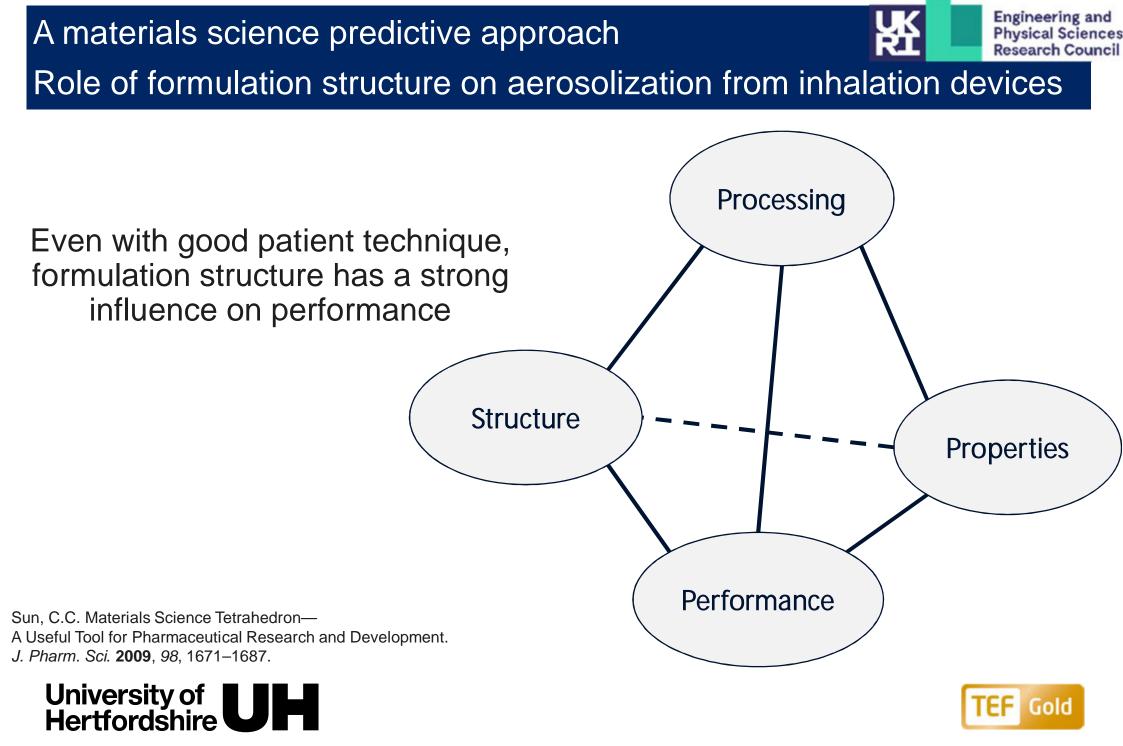
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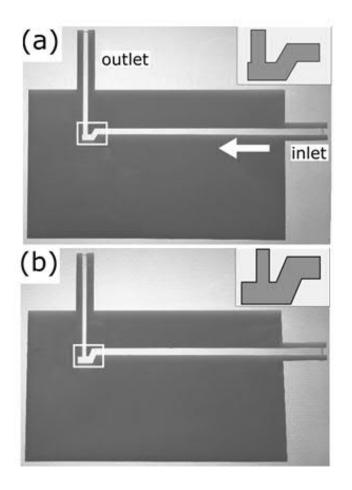


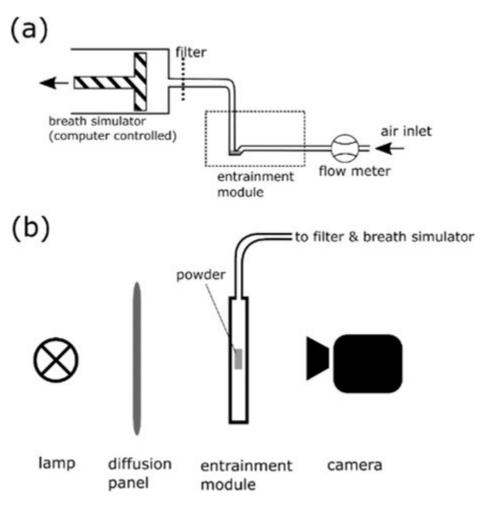
### Examining the inhalation behaviour of powders





## Aerosolization studies and inhaler design for DPIs Experimental studies of high density powder fluidization





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

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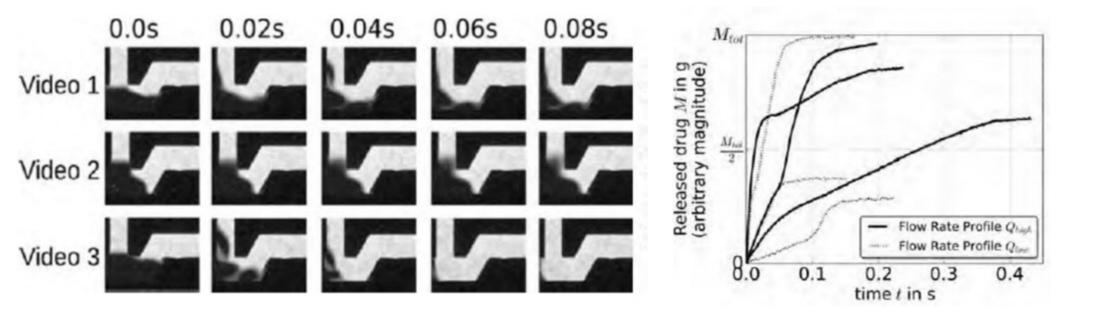


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Aerosolization studies and inhaler design for DPIs Experimental studies of high density powder fluidization



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



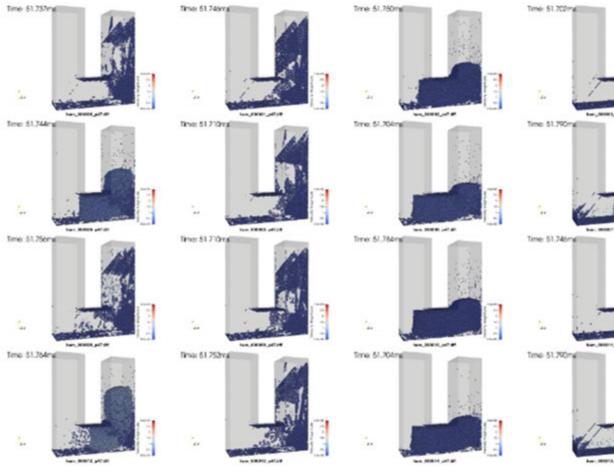


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## CFD of DPI emission: Model input parameterization

Is it possible to link material properties during product development?

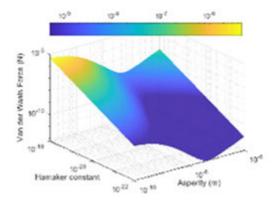


Batch design-of-experiment simulation cases: with varying Hamaker constant and particle asperity. Is it possible to include accurate powder structures and cohesive force balances?





Simulation results



Sensitivity analysis



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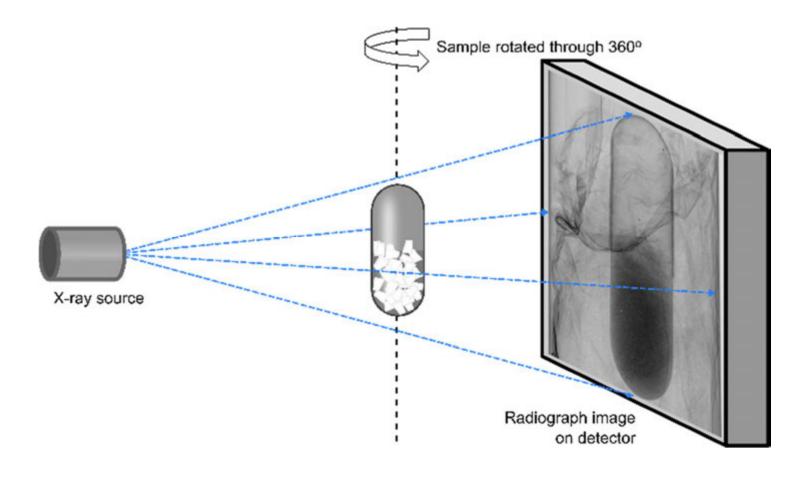


## Approaches to measuring formulation properties and structure on inhalation powder performance





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





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

### University of Hertfordshire





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

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	erisation of dry powder inhaler formulations: Developing X-ray evident tomography approaches
	3. Stylian <sup>17</sup> , T.T.H. Ngayen <sup>1</sup> , J. Carn <sup>4</sup> , X. Chen <sup>4</sup> , J.A. Elliott <sup>4</sup> , R.K. Hammand <sup>1</sup> , K. Roberts <sup>7</sup> , P.J. Withen <sup>104</sup> , D. Marnane <sup>104</sup>
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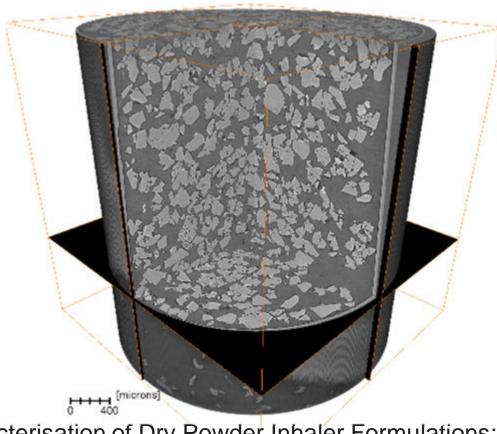
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3D Characterisation of Dry Powder Inhaler Formulations: Developing X-ray Micro Computed Tomography Approaches Gajjar, P. et al *Eur. J. Pharm. Biopharm.* 

Open Access: DOI <u>10.1016/j.ejpb.2020.02.013</u>





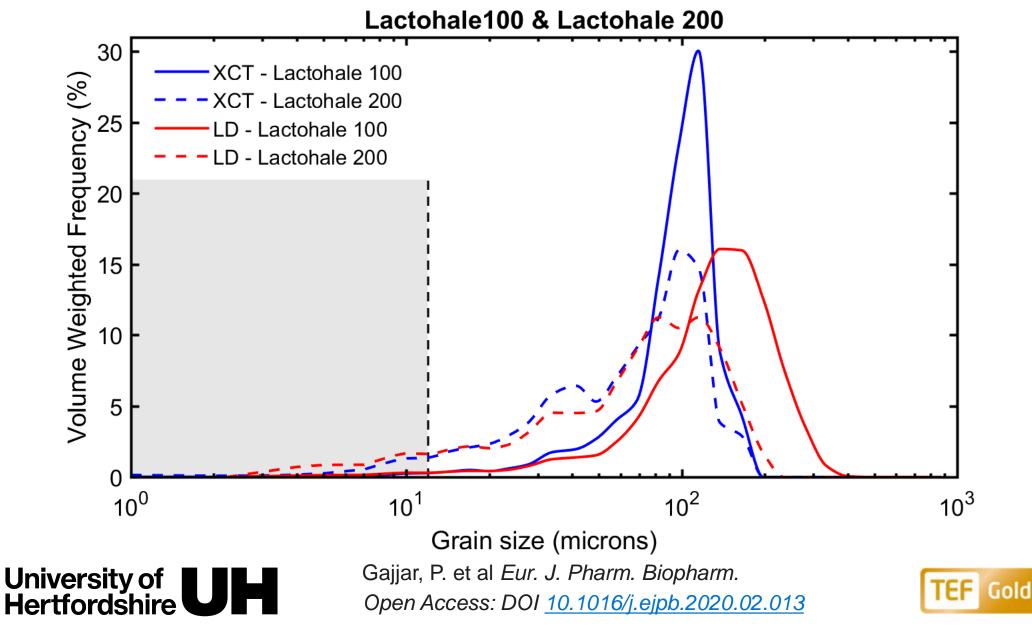


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X-ray tomographical insight into inhalation lactose

Non-destructive determination of particle size distributions



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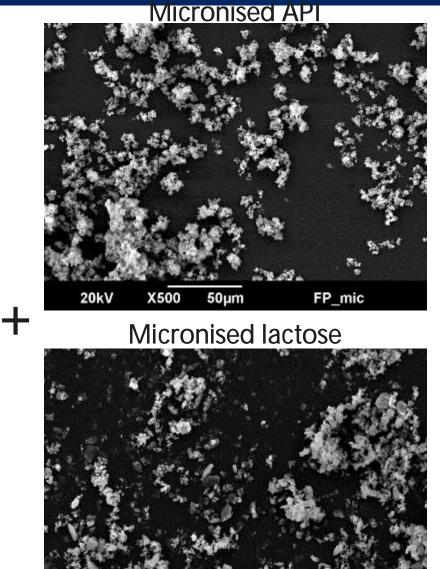


## Deconstructing powder agglomerates and formulation components





## Characterisation of typical DPI formulated products Formulation components in 2 dimensions



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Darragh Murnane | Future Formulation IV | Deconstructing Powder Agglomerates |

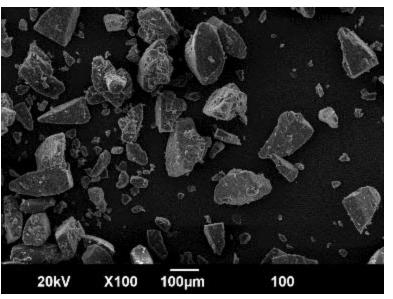
20kV

X500

50µm

300

### Lactose (Carrier)





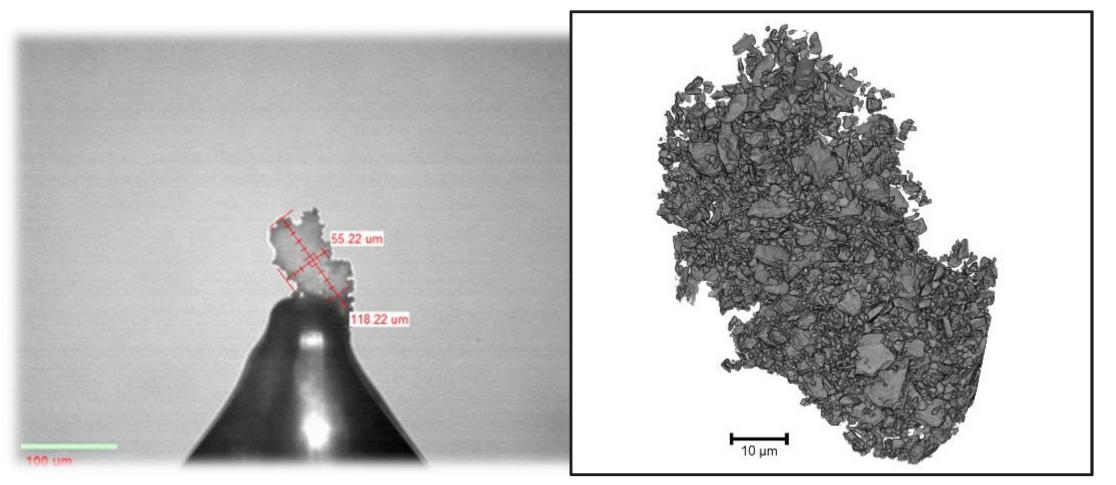
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## Nano-scale XRM with Zeiss Ultra



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## 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







#### Engineering and Nano-scale measurements of micronized lactose **Physical Sciences Research Council** Non-destructive determination of agglomerate properties Eq Diameter (microns) 0 2 3 5 6 10 ZEINN 14 12 Number Weighted Frequency (%) 10 8 2 10 µm 0 Accurate determination of porosity: 2 5 6 9 0 3 8 10

LH300: 71.1%  $\pm$  0.7%

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



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Eq Diameter (microns)

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Deconstructing agglomerates in inhalation powders Realistic inhalation blends

Excipient: Lactohale 100

- Drug: Micronised Fluticasone Propionate
- Mixing: Picomix® high shear mixer module, 1000 rpm, 2 min
  - Ratio: 10% w/w of API

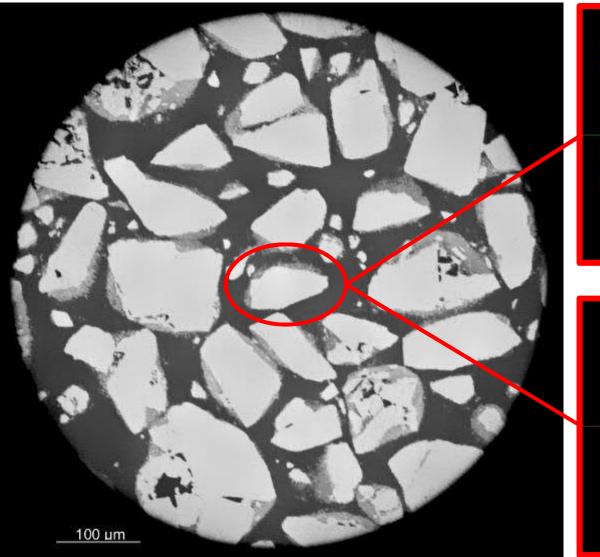




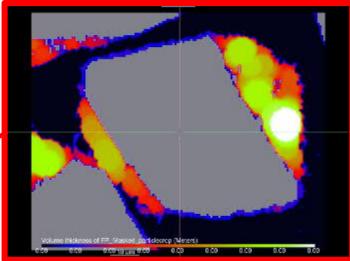
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# Deconstructing agglomerates in inhalation powders

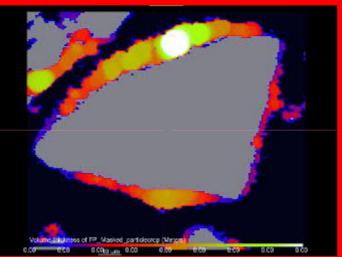


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Differential coating on different facets

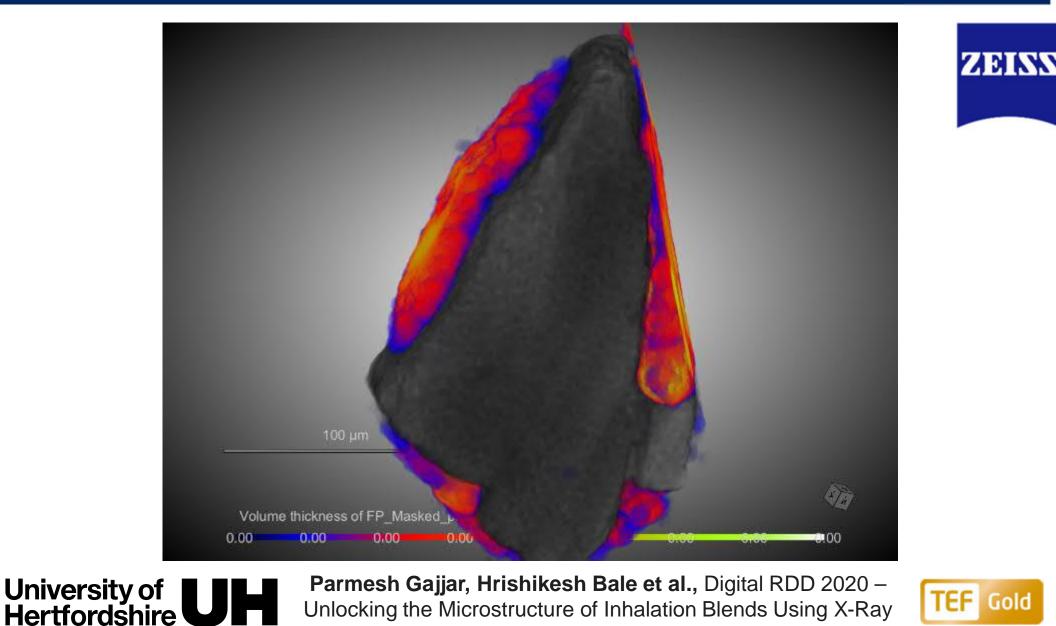


(Slightly different slices of same particle in zoomed in section shown)



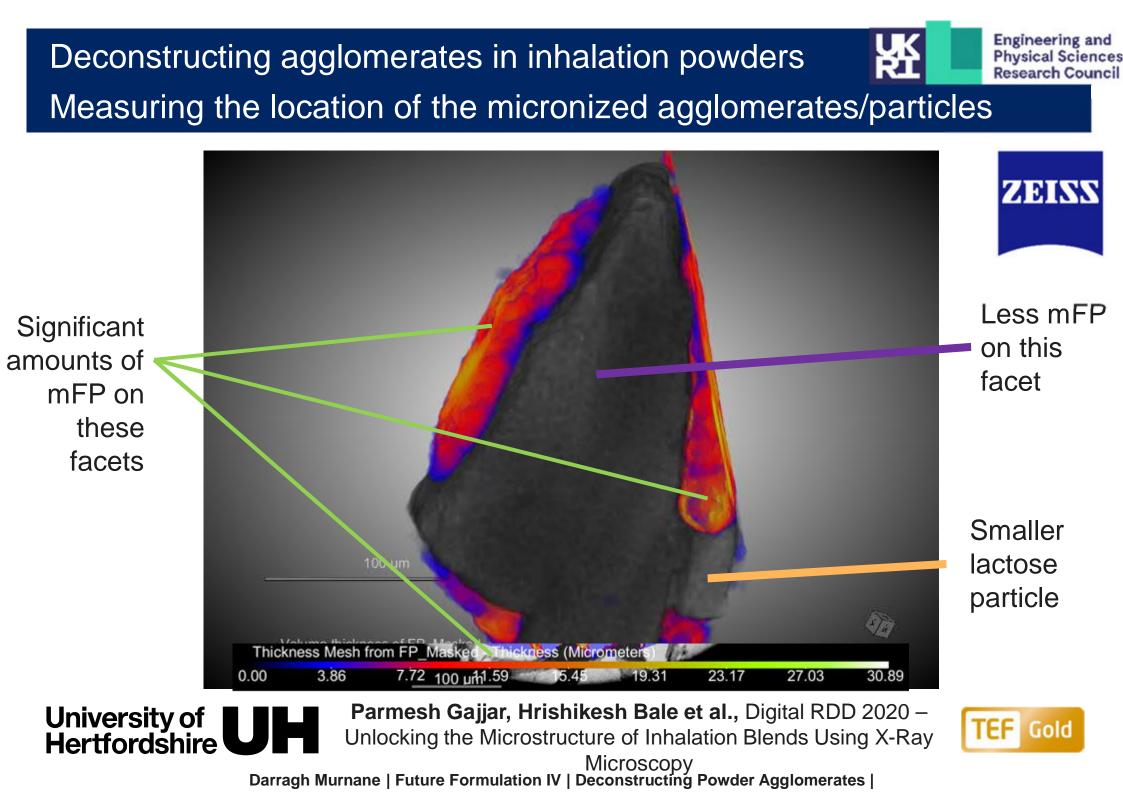
Parmesh Gajjar, Hrishikesh Bale et al., Digital RDD 2020 – Unlocking the Microstructure of Inhalation Blends Using X-Ray Microscopy Darragh Murnane | Future Formulation IV | Deconstructing Powder Agglomerates |

Engineering and Deconstructing agglomerates in inhalation powders **Physical Sciences Research Council** 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 Darragh Murnane | Future Formulation IV | Deconstructing Powder Agglomerates |





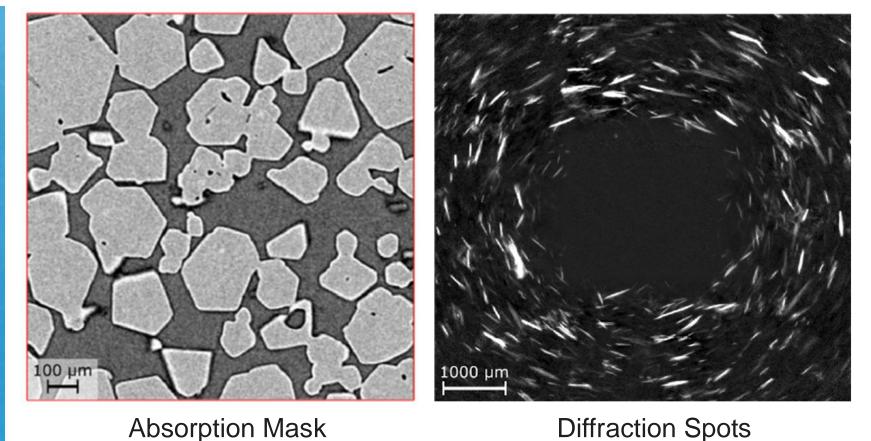


## Is it possible to identify to which particle surfaces the drug particles adhere in a formulation?





# Direct measurement of powder crystallography



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



University of Hertfordshire





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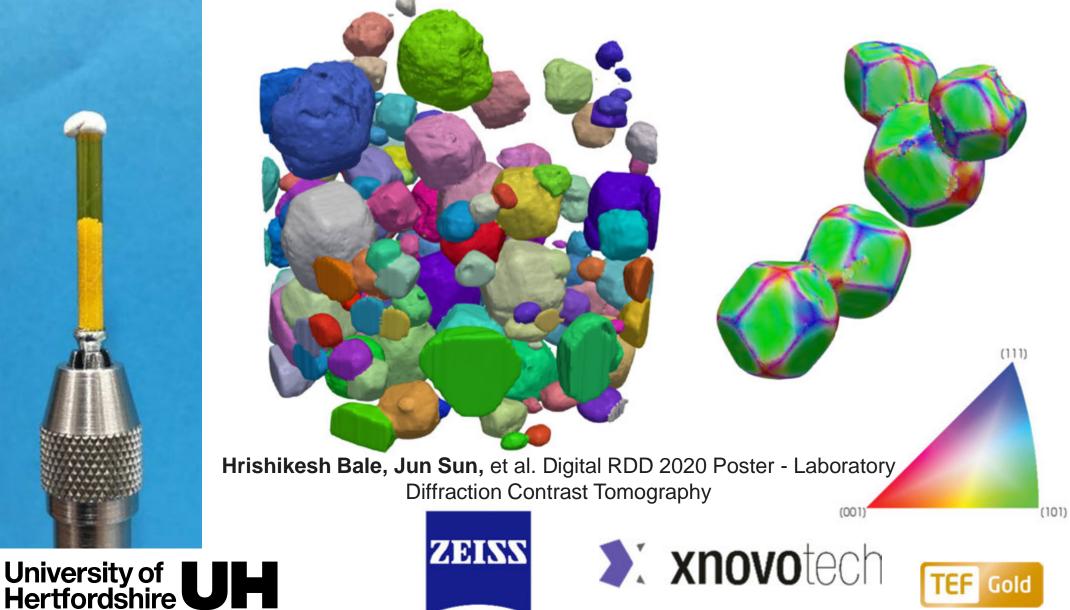
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## Laboratory diffraction contrast tomography Hexamine as a model power

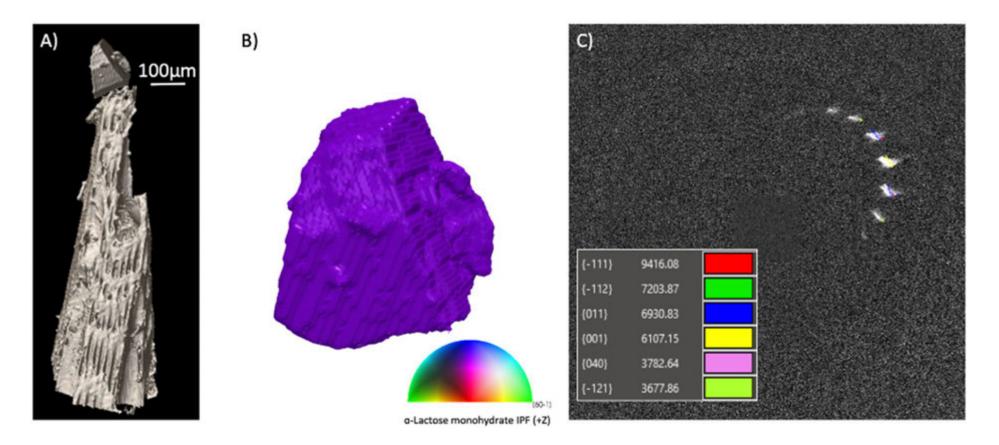


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## Laboratory diffraction contrast tomography α-Lactose Monohydrate



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









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





## Crystallographic structure particle property predictions α-Lactose Monohydrate

C12H22O11.H2O	Face {hkl}	E <sub>att</sub> (kcal/mol)	Dispersive SE (mJ/m <sup>2</sup> )	Total SE (mJ/m <sup>2</sup> )			
LACTOS11	{020} {001}	-13.64 -16.79	71.64 70.96	82.90 82.59			
a = 4.78; b = 21.54; c = 7.76	{01-1} {02-1}	-20.4 -23.87	83.81 80.82	96.73 92.64			
β=105.91 <sup>0</sup> ; V= 768.8	{031} {100}	-27.07 -20.67	77.87 55.39	89.54 63.83			
{0-31} Surface Energy (SE): 84.21 mJ/m <sup>2</sup> {100}: 59.1mJ/m <sup>2</sup>	{1-10} {10-1} {1-20}	-22.14 -20.37 -23.96	58.21 51.61 59.32	66.97 58.26 68.23			
{020}: 77.96 mJ/m <sup>2</sup>							
Calculated SE for LMH: 73.69 mJ/m <sup>2</sup> (Dispersive: 64 mJ/m <sup>2</sup> )							
Styliari, Nguyen et al. Digital RDD 2020 Poster - On Measuring the Specific Surface Area of inhalation-grade lactose powders							
University of UH Ramachandran, et al., Mol. Pharr	n., 2014	4. 12: 8-33;	(	TEF Gold			

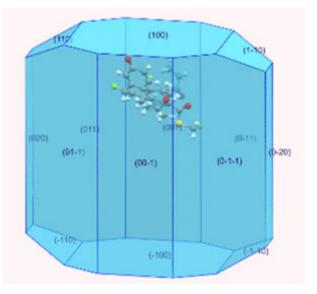
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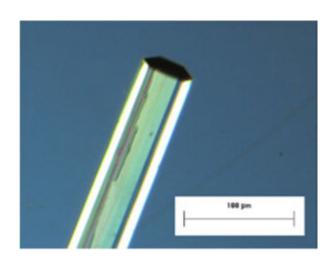
**Physical Sciences Research Council** 

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

## Crystallographic structure particle property predictions Fluticasone propionate





Face	Surface	Total SE		
{hkl}	Area (%)	(mJ/m <sup>2</sup> )		
{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





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Engineering and Crystallographic structure particle property predictions **Physical Sciences Research Council** Terbutaline Sulphate: Nguyen, et al., CrystEngComm. 2020 In Press iGC - Surface energy distrubitions {010} surface: {1-10} surface: 27.7 (mJ/m²) 150  $45.6 (mJ/m^2)$ Dispersive Polar Total Surface Energy (mJ/m<sup>2</sup>) 100 (0-10) (-100) {-100} surface: {001} surface: (001)50  $50.6 (mJ/m^2)$  $109 (mJ/m^2)$ 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 6 7 8 9 10 11 12 13 % of surface coverage **Dispersive SE Surface energy** Total SE (mJ/m<sup>2</sup>)  $(mJ/m^2)$ Surface energy (weighting % 28.27 48.2 surface area) **IGC Surface energy surface** 49.1 - 44.7103.3 - 92.1coverage [0.05-0.8]

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

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

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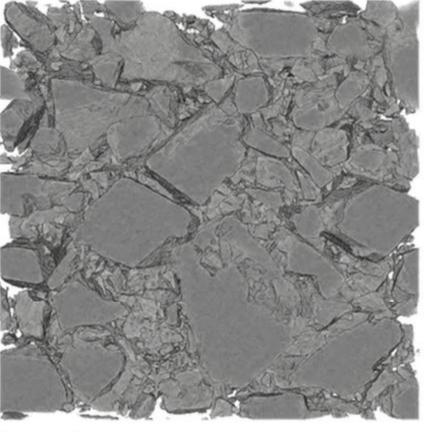


### Reconstructing inhalation blends of powder agglomerates





Reconstructing agglomerative inhalation powders The power of multi-scale correlative x-ray microscopy









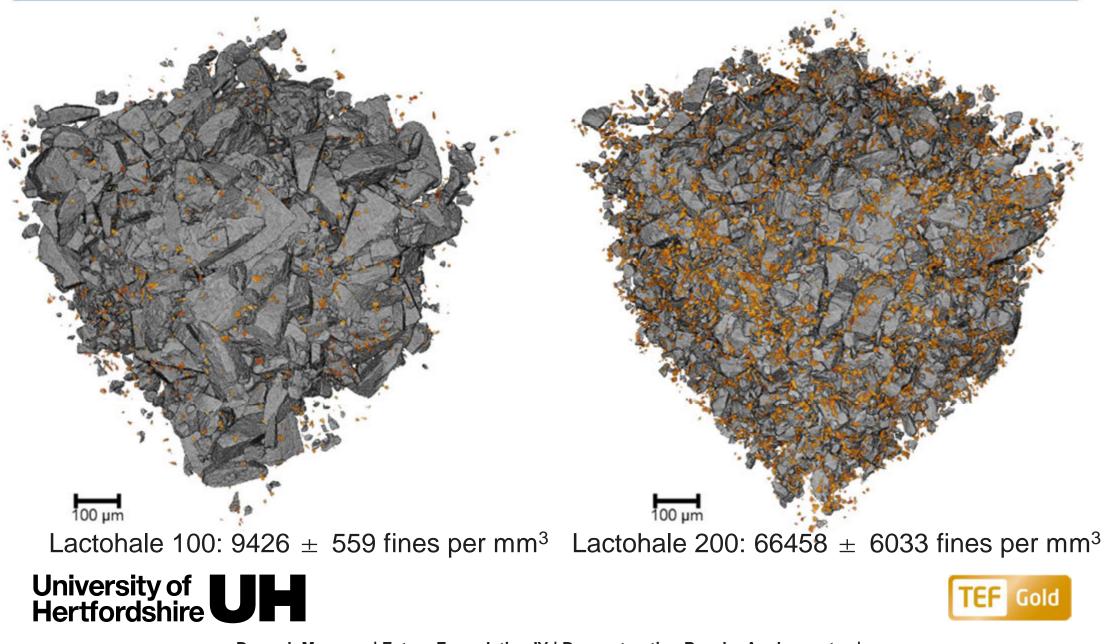
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## Reconstructing agglomerative inhalation powders Identification of powder microstructure and processing



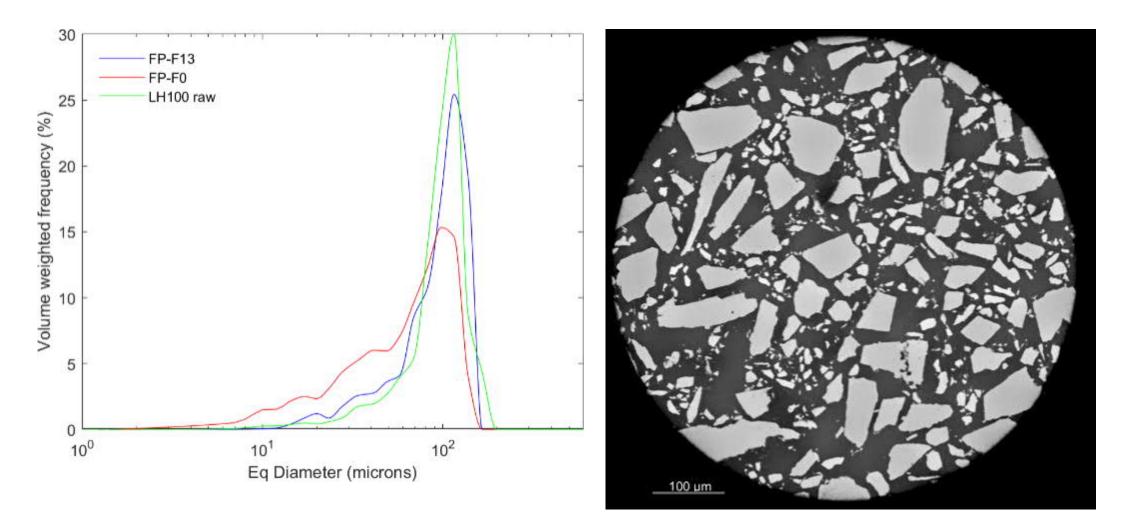
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# Reconstructing agglomerative inhalation powders



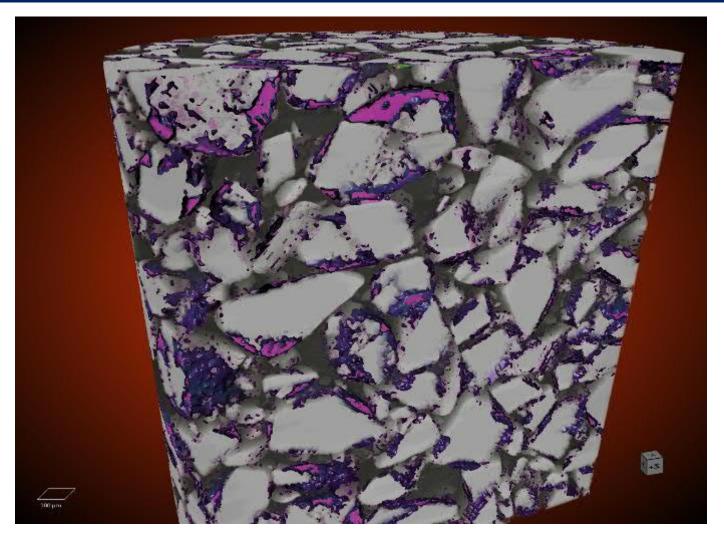




## Reconstructing agglomerated powder blends Is this what we mean by the Q3 microstructure?



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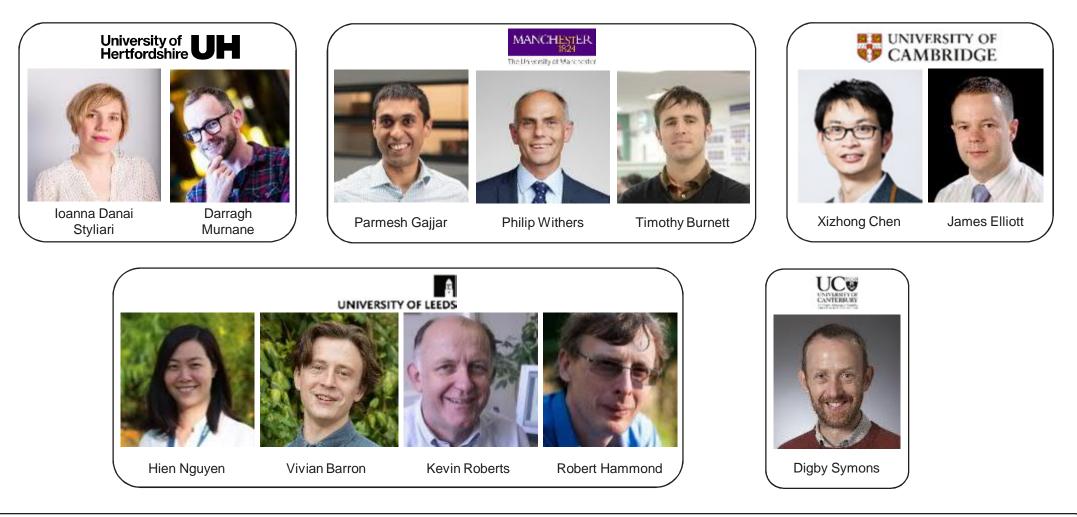


Lactohale 100 + Fluticasone Propionate (10% w/w ratio) University of Hertfordshire



## Acknowledgements





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