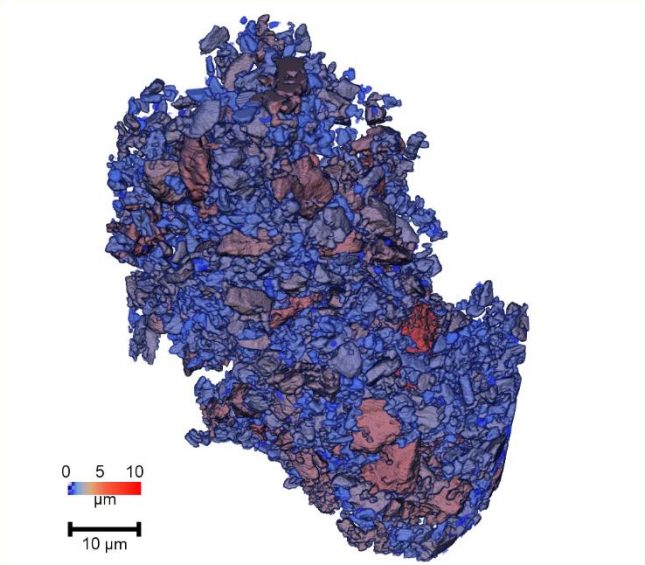
X-ray Microscopy for Inhalation Formulations

Parmesh Gajjar

Henry Moseley X-ray Imaging Facility, The University of Manchester

parmesh.gajjar@manchester.ac.uk

Hrishikesh Bale
Vivian Barron
Tim Burnett
Xizhong Chen
James Elliott
Robert Hammond
Allistair McBride
Darragh Murnane
Hien Nguyen
Kevin Roberts
Ioanna Danai Styliari
Ben Tordoff
Philip Withers



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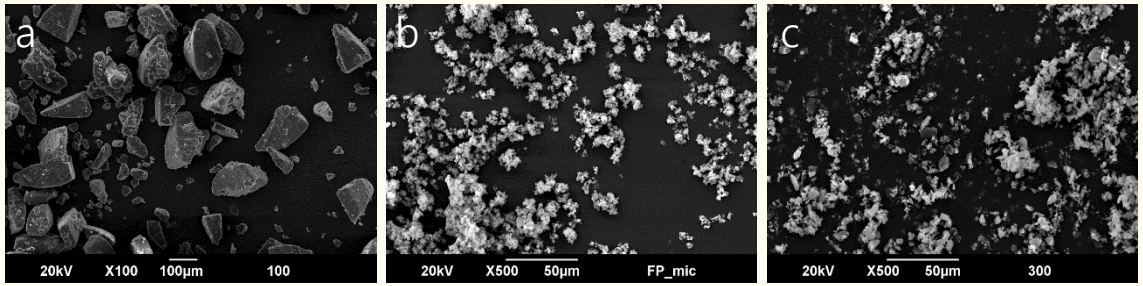
X-ray microscopy for inhalation formulations

- Recent development of x-ray magnification optics allows higher resolution and improved contrast compared to traditional x-ray computed tomography (XCT) systems
- These instruments are known as x-ray microscopes (XRM)
- A typical dry powder inhalation formulation consists of a mixture of large carrier lactose, micronized drug and micronized lactose
- Aim of this part of INFORM2020 project was to use XRM to examine the microstructure of these different parts of a dry powder inhalation formulation

The inside of a Zeiss Xradia Versa X-ray Laboratory Microscope



Main parts of a dry powder inhaler formulation: (a) Carrier lactose; (b) Micronised Drug and (c) Micronised Lactose

Characterising carrier lactose using XRM

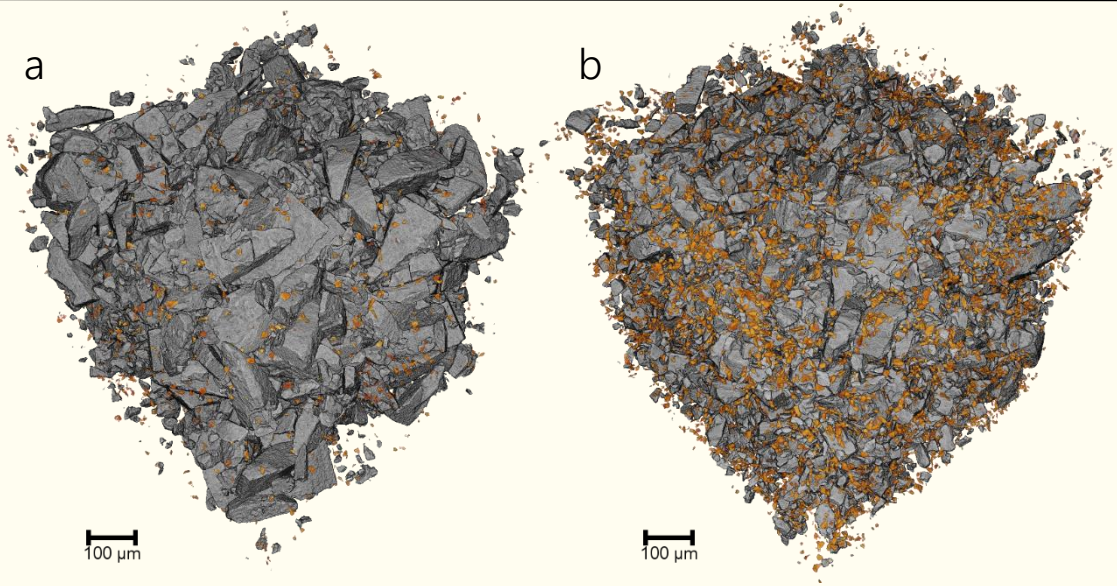
- Microscale XRM (Zeiss Xradia Versa) has been used to characterise both tabletting and inhalation grade lactose

- Work recently published in European Journal of Pharmaceutics and Biopharmaceutics

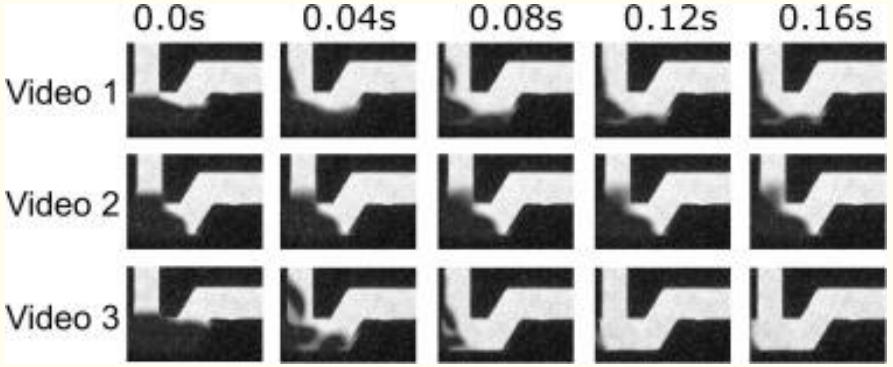
  3D Characterisation of Dry Powder Inhaler Formulations: Developing X-ray Micro Computed Tomography Approaches
  Gajjar, P. et al *Eur. J. Pharm. Biopharm.* (2020)
  Open Access: DOI 10.1016/j.ejpb.2020.02.013

- It is possible to visualise and quantify the number of fine lactose particles <12 µm, with LH100 and LH200 containing 9426 ± 559 particles per mm^3 and 66458 ± 6033 particles per mm^3 respectively.

- High variation in LH200 may explain chaotic behaviour previously seen in experiments.



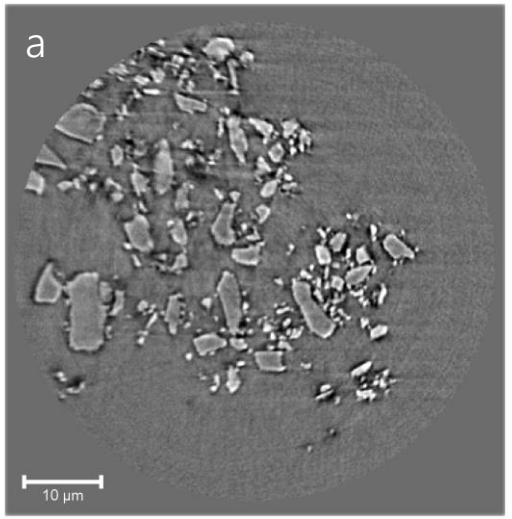
Visualisation of fine lactose present in (a) LH100 and (b) LH200



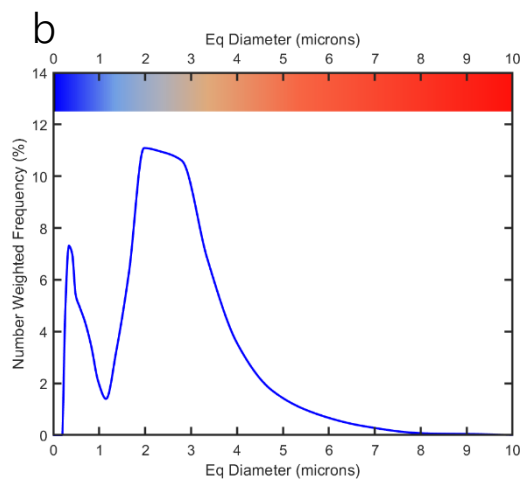
Chaotic behaviour of LH200 from DOI:10.1016/j.ijpharm.2018.10.021 showing variable behaviour between runs

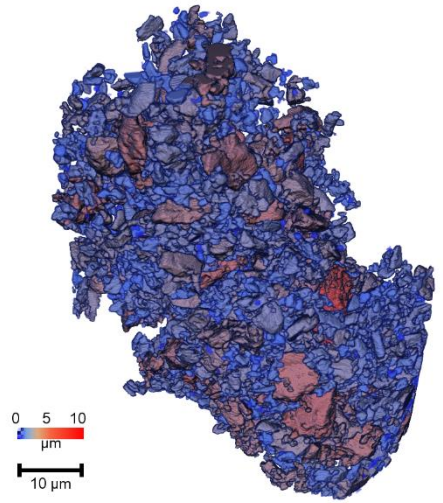
Microstructure of single lactose agglomerates

- Nanoscale XRM (Zeiss Xradia Ultra) with a resolution of 150 nm allows microstructure of micronized agglomerates to be assessed. Here a LH300 agglomerate is analysed.
- Porosity within the agglomerate can be calculated as 72.1 % ± 0.7 %.
- Individual particles within the agglomerate can be separated. A intra-agglomerate size distribution is bimodal with a small peak around 0.5 µm and a second peak around 2.5 µm.



(a) Single virtual cross sectional slice through agglomerate

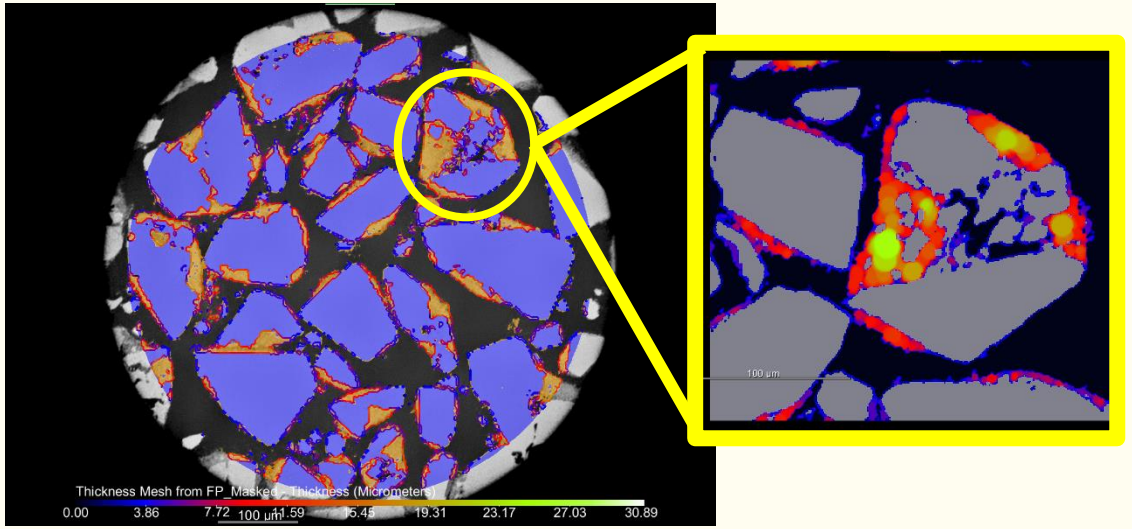




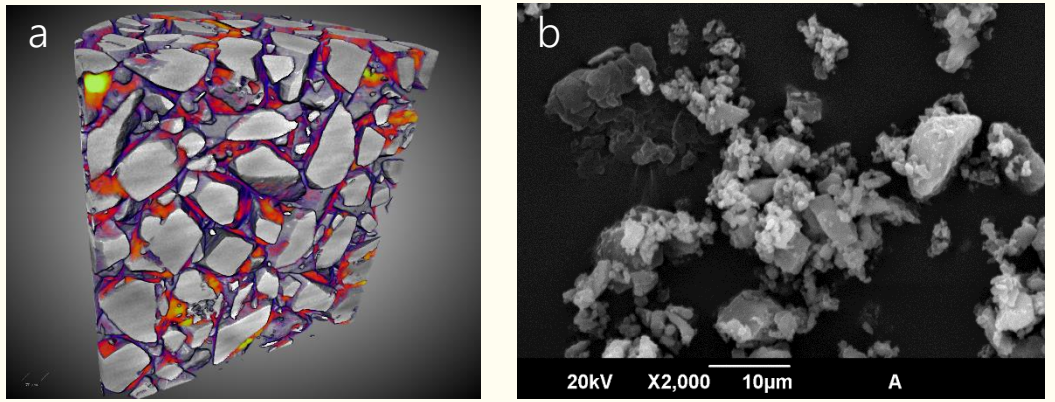
(c) Size distribution for particles within agglomerate; (d) 3D visualisation with particles coloured by size.

Microstructure of blends

- Microscale XRM (Zeiss Xradia Versa) has been used to characterise drug-carrier blends and identify the different compounds
- This allows individual structures to be examined such as drug-carrier agglomerates, or drug adhesion to carrier facets.
- 3D information provided by XRM allows unique insight into the microstructure compared to currently employed techniques such as scanning electron microscopy (SEM).



Microstructure of an inhalation blend, with lactose coloured blue and drug orange. Inset shows a drug-lactose agglomerate with lactose coloured grey and drug coloured by thickness of layer.



(a) 3D visualisation of blend compared with current standard method of using an SEM (b).

Thanks to …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