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Unlocking secrets of inhalation blends through X-ray Computed Tomography and Microscopy

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Introduction

Although demonstrating bioequivalence (BE) of inhalation products is necessary for the development of generic alternatives and to support post-approval formulation or manufacturing process changes, the FDA's concept of microstructural equivalence (Q3) is problematic for dry powder inhalers (DPIs) as microstructural changes induced upon aerosolization will differ according to the DPI device and the patient's aerosolization efficiency. Thus, there is an acute need to understand the detailed microstructure of pre- and post-aerosolised powder formulations. In this work, we show how advanced 3D X-ray computed tomography (XCT, also known as X-ray microscopy, XRM) techniques can provide unique microstructural insight of pre-aerosolized material. Micro-scale XCT/XRM is shown to be able to visualise lactose fines (< 12 μm) within a powder bed and quantify their number. It is also shown how XCT/XRM can discriminate between excipient and drug particles in a powder formulation. These advanced XCT/XRM techniques could help provide valuable microstructural information that links Q3 and BE.

Assessing Q3 Structural Equivalence

There remains a gap in linking the pre-aerosolised formulation with the performance of the inhaled product and some critical questions still remain unanswered: What does the microstructure of the formulation really look like? How does processing change this microstructure? And how do microstructural differences in the formulation manifest in the final aerosolisation performance?

The potential of X-ray CT (XCT) to provide unique 3D microstructural insight for pharmaceutical formulations has been a question asked by many [1,2]. However, the small particle sizes in inhalation blends have been a major challenge. Laboratory x-ray microscopes (XRM) can be utilised as multiscale characterisation tools for inhalation powders, providing information on meso-, micro- and nano-scales [3]. In this work, we show how new XRM techniques can help unlock further microstructural features of inhalation blends.

Spatial distribution of fines

The addition of fine lactose particles increases the cohesiveness of a bulk lactose powder and thus reduces the flowability [4,5]. Using XRM for DPI formulations, we were able to visualise the spatial positions of fine particles in Lactohale 100 (LH100) and Lactohale 200 (LH200). Figure 1 shows 3D data, with particles less than 12 μm in size coloured orange and those larger than 12 μm in grey. Furthermore, it was also possible to quantify the number of fines in each sample. Whilst LH200 has more than 7 times as many

fines compared to LH100, the high spatial variation in the number of fines could be an explanation for the inconsistent entrainment behavior. Further work is underway to quantify the number of fines across a range of powders and link this to other physical properties.

Revealing multiple species in inhalation blends

The key component of a DPI is the API, and its de-agglomeration from the carrier particles. This can be traced back to the spatial interactions of drug and excipient for which XRM could be a useful exploratory tool due its intrinsic three-dimensional nature. A blend of Capsulac60 and terbutaline-sulphate (TBS) in a 9:1 mass ratio was prepared. Although Capsulac60 is a tabletting grade, it was chosen as a model powder in the blend due to its larger size. The blend was imaged on a Zeiss Xradia Versa 620 micro-CT instrument. The Versa system produces in-line phase contrast due to the highly coherent source, and thus the final volume contains some absorption contrast along with Fresnel fringes.

Figure 2A shows cross sectional slice through the 3D volume. X-ray absorption is proportional to material density, with the molar mass of air, TBS and lactose monohydrate producing different grayscale contrast. However, Figure 2B shows a zoomed in section of the cross sectional slice with several example small particles circled, whose grayscale value is brighter than the surrounding lactose, due to the phase fringe produced due to propagation. Thus, from the raw reconstructed volume alone, it is extremely challenging to distinguish between the lactose and TBS that are both low Z materials with only small density differences.

After post-processing the data with a phase-retrieval algorithm, there are distinct grayscale values allowing particles of each species to be identified. Figure 2C shows Capsulac60 and TBS colored differently, with the proportion of TBS calculated to be 8.1%. It is possible to verify the segmentation by obtaining size-distributions of the two phases, as shown in Figure 2D. The size distribution of the TBS phase is less than 75 μm, whilst that of Capsulac60 is between 100-400 μm. Although the size range is broadly similar, the distribution located from the blend has a bimodal distribution. Examining the morphology of the two phases, the Capsulac60 particles have the characteristic tomahawk shape, sometimes with particles aggregated together as shown in Figure 2E. By contrast, the identified TBS particles have a plate-like morphology as shown in Figure 2F. Further work is currently underway to improve the particle separation and extend to inhalation blends.

Conclusions

X-ray computed tomography with phase-contrast modality can provide unique insight into the microstructure of inhaled formulations. Micro-scale XRM allows individual drug and excipient particles to be identified within a powder sample. Unique to XRM is that it is non-destructive potentially opening doors to production line assessment of formulations within blisters and capsules. Further work is certainly needed, but promising early signs are that XRM could potentially unlock the assessment of microstructure of inhaled formulations and provide a bridge between Q3 and BE studies.

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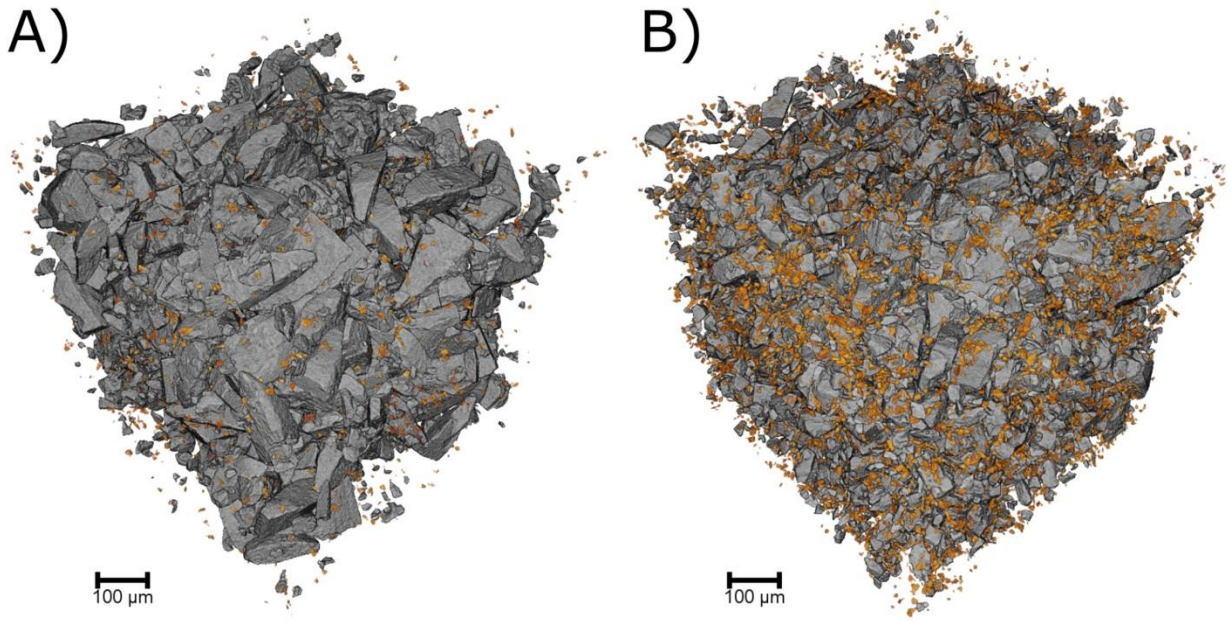

Figure 1. 3D Visualizations of (A) Lactohale 100 and (B) Lactohale 200, with particles smaller than 12 µm colored orange, and those larger than 12 µm in grey.

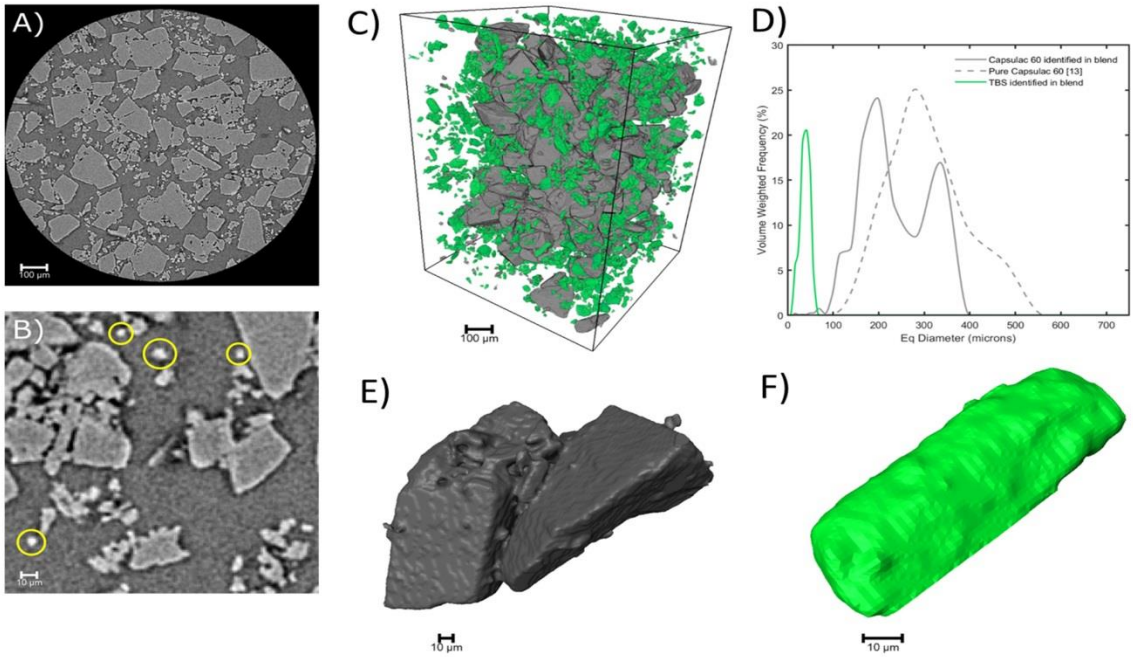

Figure 2. (A) Virtual horizontal cross sectional slice through the blend of Capsulac 60 and TBS. (B) A zoomed in section of the same slice with several particles highlighted than have uncharacteristically bright greyscale color. (C) 3D visualisation of Capsulac 60 – TBS blend, with Capsulac 60 coloured grey and

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TBS coloured green. (D) Size distribution of the two identified phases, with pure Capsulac 60 plotted alongside for comparison. (E) Typical Capsulac 60 morphology, showing the characteristic tomahawk shape arranged in an aggregate. (F) Typical plate-like TBS morphology.

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