

Characterisation of powder microstructure inside blisters using 3D X-ray Imaging

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Introduction

- ▶ **Microstructure** has emerged as one of the important characteristics of inhaled products to be assessed in bioequivalence assessments, with integral links to properties, processing and performance.
- ▶ The microstructure of the aerosol affects deposition, dissolution and PK, and can be characterised using methods such as MDRS and RPSD. The FDA recommends MDRS for aerosol characterisation in several product specific guidance documents^[1,2].
- ▶ Characterising the microstructure of DPI formulations **pre-actuation** is important for the role that powder structure plays in air-permeability and particle dispersion during fluidisation. **Heterogeneity** in pre-actuated microstructure may also lead to differences in aerosol microstructure.
- ▶ Current methods such as MDRS, SEM-EDX and TOF-SIMS are all surface methods, and cannot determine microstructure below 10 microns of a surface (e.g. through a capsule wall). These methods are all destructive as they disrupt the bulk powder bed within blisters and capsules. Thus, further **complimentary** techniques are required to provide pre-actuated microstructural assessment.
- ▶ **X-ray Computed Tomography** has shown **potential** in characterising pre-actuated microstructure^[3-5], but all existing work has required filling powders into Kapton tube sample holders (Fig. 1) and thus is destructive.

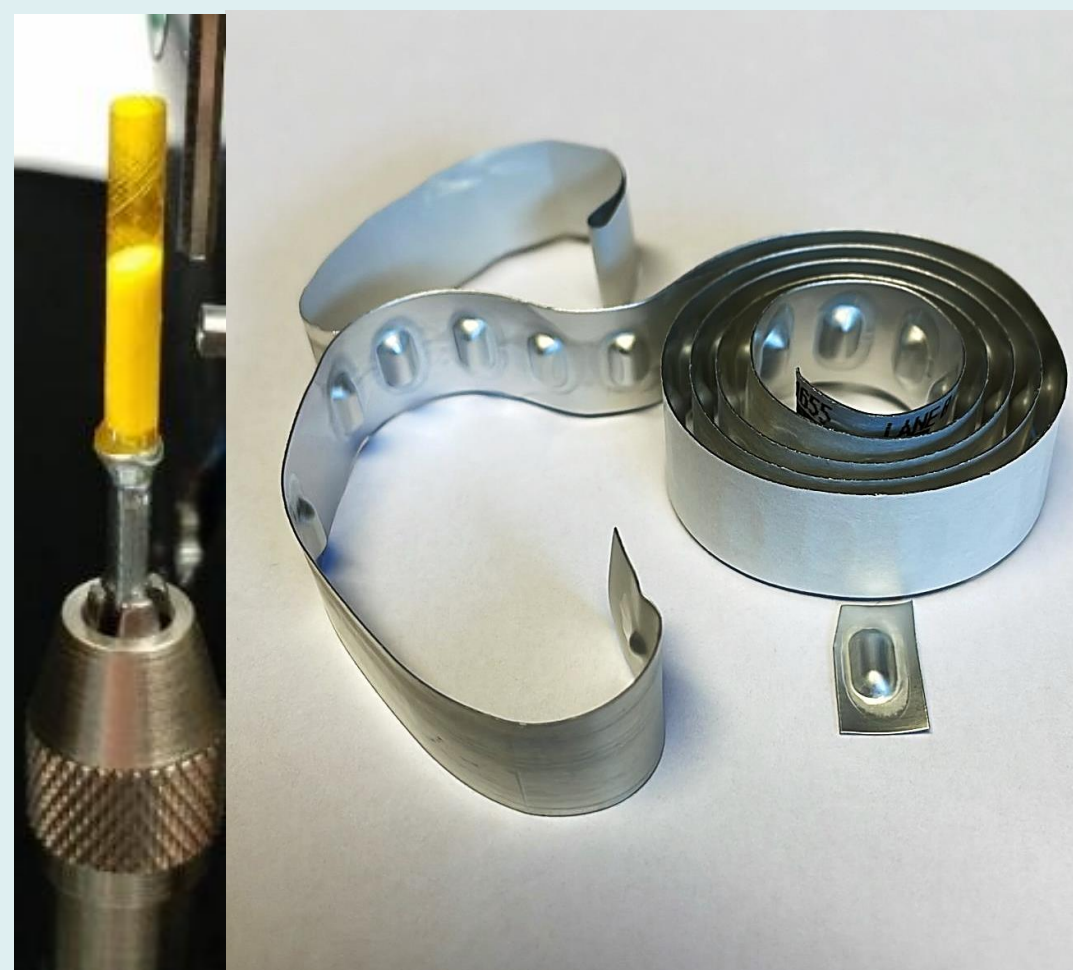


Figure 1: Current work using XCT has used samples filled into Kapton tube holders (left), and is thus destructive. Can XCT non-destructively image inside blisters (right)?

▶ In this poster, we explore how **X-ray Computed Tomography (XCT)** can **non-destructively** characterise powder microstructure **within blisters**.

Methods

- ▶ An Ellipta Placebo blister was scanned using on settings in Table 1.

Instrument	Mode / Scans	Voltage	Power	Binning	Pixel size	Projections	Exposure
Zeiss Xradia Versa 520 XRM	Stitch / 2	80 kV	7W	2X	4.27 μm	1601	0.5 sec

Table 1: Ellipta placebo scan settings

- ▶ Particulate phase identification through automatic Otsu-thresholding algorithm. Particulate phase area (hereafter particulate area) and blister area calculated for each virtual horizontal slice through the blister. Analysis total height was 6.64 mm.
- ▶ Post-processing and profile visualisation using the stats language R (version 4.3.3).
- ▶ The fill height was determined from the bulk powder phase volume within the blister. The particulate fraction at each height was calculated as the ratio of the particulate area to the blister internal area in each horizontal slice. The powder fraction calculated as D/B (Fig 2), whilst the particulate fraction was calculated as C/D (Fig 2).
- ▶ A Seretide 250 blister along with a generic equivalent were scanned using the ID19 beamline at ESRF at 0.33 μm pixel size. The resultant datasets were analysed using a previously reported method^[3] to visualise the thickness of the micronized phase.

Figure 2: Powder metric calculations: (A) Grayscale cross sectional slice through blister; (B) Blister volume; (C) Segmented particulate phase; (D) Powder volume and air volume.

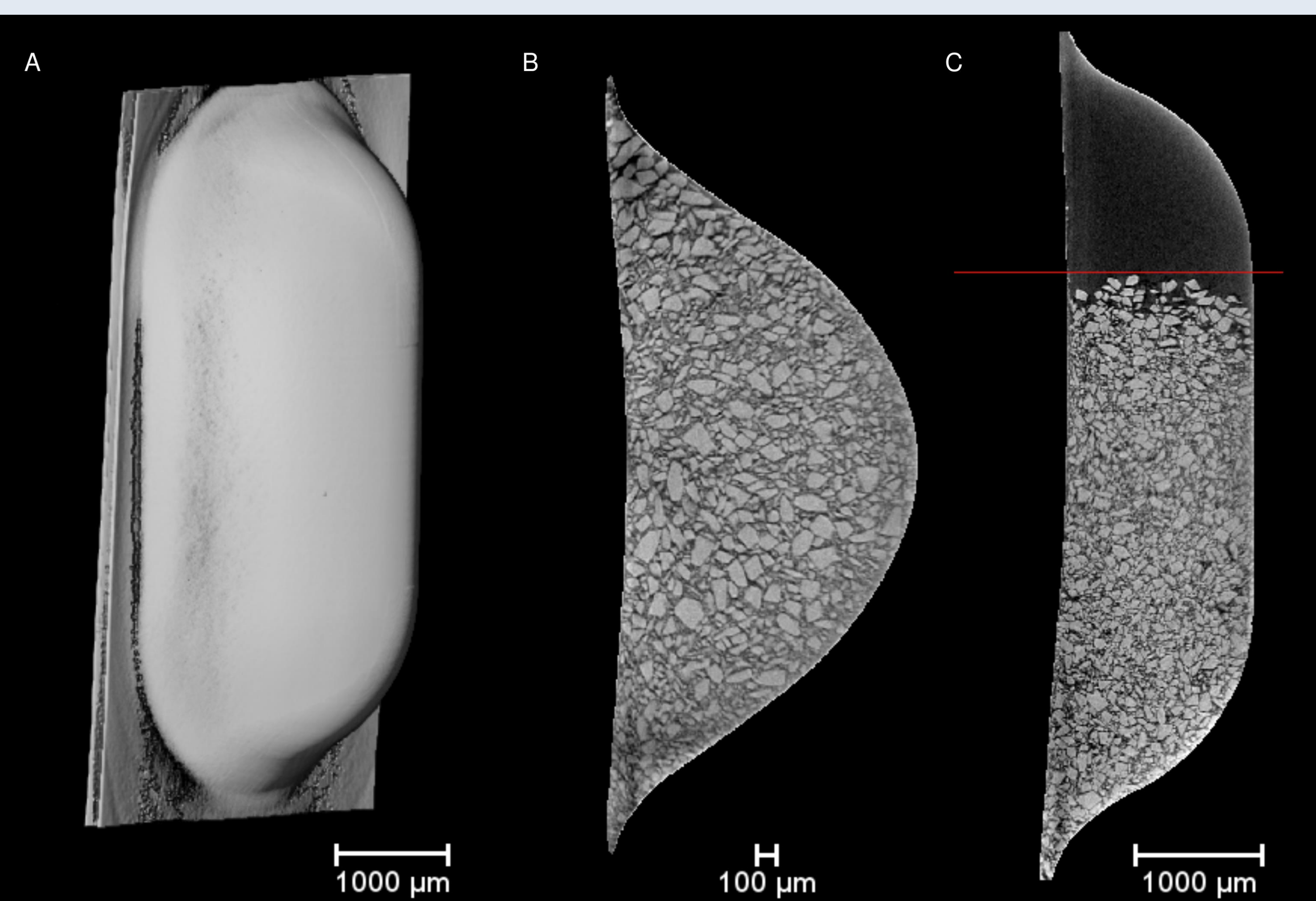
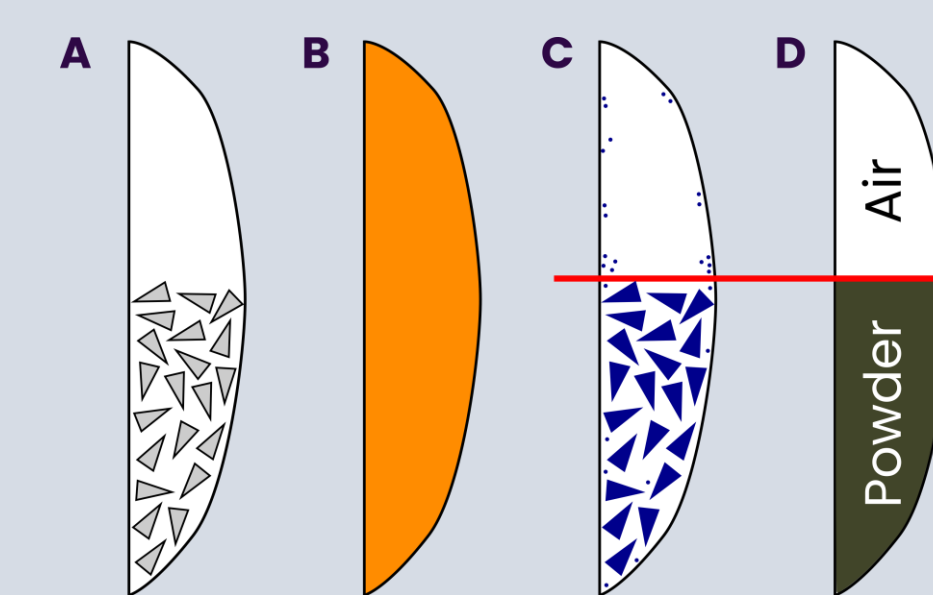


Figure 3: 3D Visualisations of Ellipta Placebo blister: (A) 3D Visualisation; (B) Central lateral cross-sectional slice; (C) Central vertical cross-sectional slice.

Results

- ▶ **Visualisations** of the blister are shown in Figure 3, with a 3D visualisation of the entire blister (A) and central cross-sectional slices in lateral (B) and vertical (C) directions. These show a range of particle sizes, however lower scan resolution compared to previous work^[3,6] does not allow determination of full size distributions.
- ▶ **Particle packing** is homogenous across the blister, with powder occupying lower 75% of the blister up to the fill-height (red horizontal line), with head-space above.
- ▶ **Quantitative profiles** are shown in Figure 4, showing relationship between blister internal area (dark blue) and particulate area (orange) in Fig 4A, and the particulate fraction in Fig. 4B. Small amount of particulate area above fill height is due to image noise incorrectly identified as particulate phase, and together with reducing blister volume, causes increase in particulate fraction towards the top of the blister.
- ▶ **Calculated statistics** are given in Table 2. Although exact components of placebo formulation are unknown, the air (void) fraction is similar to that previously calculated for other inhalation lactose grades^[6].

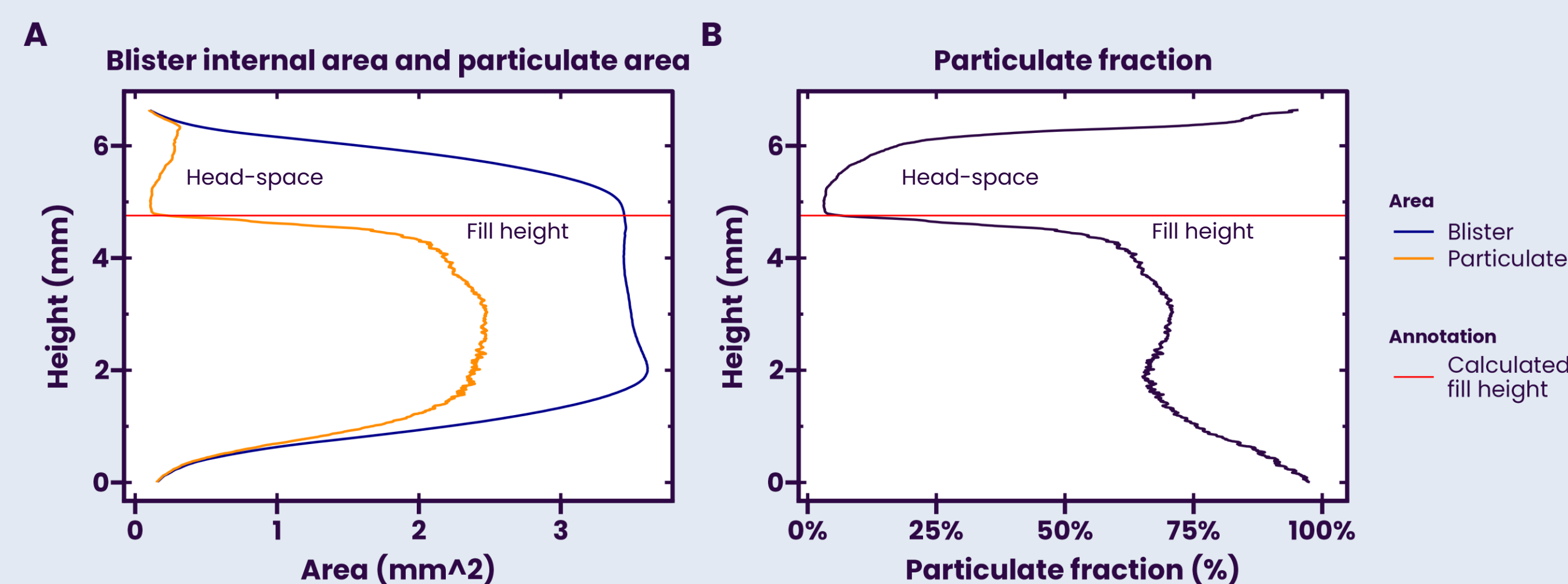


Figure 4: Quantitative analysis of (A) blister area and particulate area; (B) Particulate fraction within the blister.

Total Blister Volume (mm^3)	Total Particulate Volume (mm^3)	Fill Height (mm)	Head-space (mm)	Head-space (%)	Total Powder Fraction [D/B]	Particulate Fraction [C/D]	Air Fraction
17.7	9.31	4.76	1.88	23	0.773	0.654	0.356

Table 2: Calculated powder metrics for Ellipta Placebo blister.

Discussion & Future Vision

- ▶ This work shows that XCT can be used to **non-destructively** analyse powder **within blisters**, providing information on overall powder-bed packing.
- ▶ A key question is whether XCT has sufficient resolution to examine formulations containing API, and whether it has sufficient discriminatory ability to distinguish between formulations?
- ▶ Figure 5 shows visualisations of Seretide 250, and one of its generic equivalents, where critically, both have been imaged within blisters.
- ▶ This is an exciting development, opening pathways to extend quantitative XCT analysis of blends^[3-5] to **non-destructively** examine formulations **within blisters** and capsules, crucially without the need for any sample preparation.
- ▶ XCT shows potential as a key technique to monitor quality variations and heterogeneity in pre-actuated formulations, and thus detect batch failure.

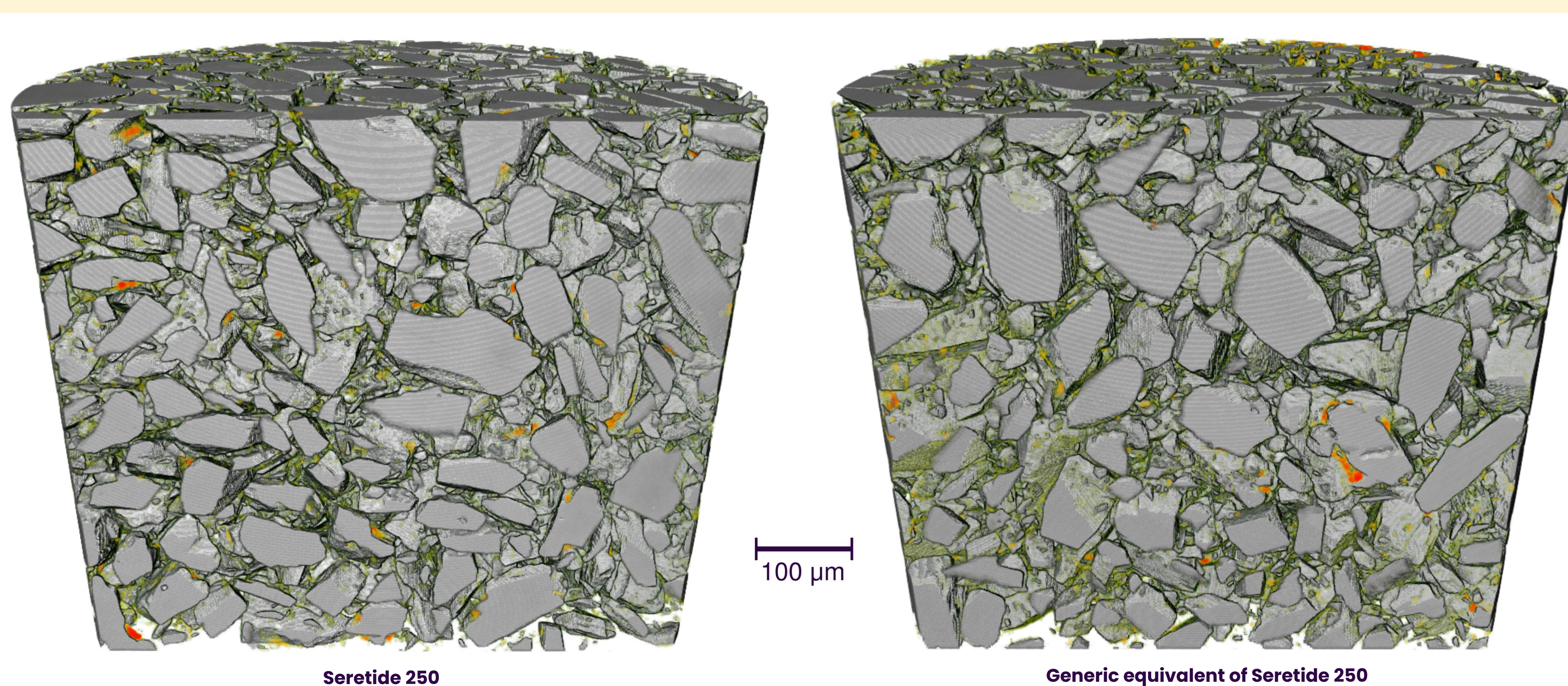


Figure 5: 3D Visualisations of Seretide 250 and a generic equivalent of Seretide 250, imaged within the blister. The thickness of the micronized-phase is coloured.

References

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