# Morphological Characterisation of Solid Pharmaceutical Products using X-ray tomography

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## Aims

The measurement of morphological descriptors is widely applied in the pharmaceutical industry to evaluate (intermediate) solid forms in terms of their critical quality attributes that influence product-handling in the manufacturing process or to allow a prediction of the performance of the final dosage form. Previous publications have demonstrated the use of micro-focused tomography to analyze formulations and relate the product performance to structure and sample homogeneity[1].
The aim of this study was to assess the use of a commercial nano-focused x-ray tomography system to non-invasively investigate the three-dimensional structure of various solid pharmaceutical products. Special emphasis was given to sizing, the quantification of internal voids and the characterization of formulated samples.

## Method

A Skyscanner 2211 x-ray tomograph (NanoCT, Bruker, Kontich, Belgium) was utilized to assess its capabilities for the analysis of solid pharmaceutical products. The samples were scanned in microfocus with an image pixel size of 0.8 µm – 4.2 µm, frame averaging of 4 – 8 and a rotation step size of 0.1 – 0.2. Additionally, cross-section analysis was carried out using a customized image-processing script in Matlab (MathWorks). Scanning electron microscopy was employed to visually validate the structural characteristics of selected samples using a SU6600 (Hitachi, Japan). Samples were gold coated with a ACE200 low vacuum sputter coater (Leica, Germany).

## Results

Particles obtained from droplet drying experiments (sizes 0.5 mm – 2 mm) were analysed by x-ray tomography to visualize the three-dimensional structure of the solids and characterize the particles in terms of internal voids, (primary) particle sizes and particle sphericity.

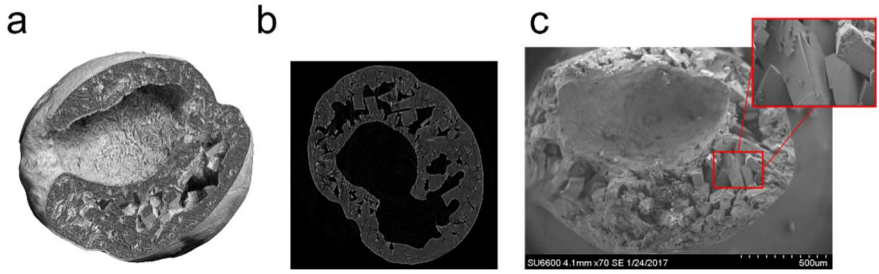


Figure 1: (a) Visualisation of a lactose particle (1.86 mm mean diameter) with a hollow solid crust. (b) Selected cross-section showing large inner void and block-shaped crystals. (c) Images from SEM analysis confirm particle structure as visualised by CT analysis.

The images in Figure 1 show a volume rendered model and a selected cross-section of a lactose particle (Figure 1, a - b) that can be initially used to qualitatively assess particle properties. Moreover, a SEM image (Figure 1, c) was acquired to validate these observations and shows a high correlation in the visual appearance of the sample morphology.

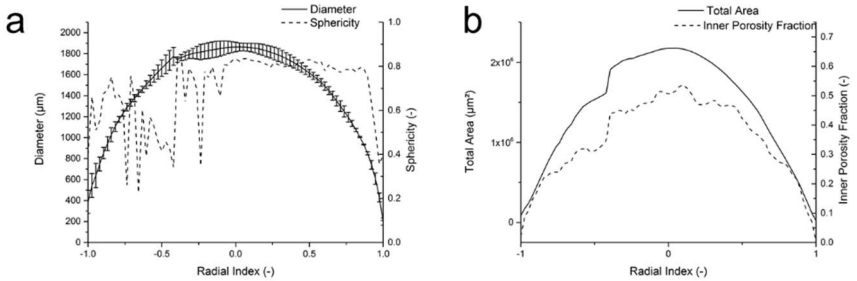


Figure 2: Results of a cross-section analysis of a lactose particle displaying (a) particle dimeter and sphericity as well as (b) total cross-section area and inner porosity fraction.

The results of a cross-section analysis are displayed in Figure 2. The graphs indicate a partially anisotropic particle structure demonstrated by large fluctuations in the particle sphericity value at a negative radial index (Figure 2, a) and an increasing fraction of the inner porosity towards the particle center (Figure 2, b). These particle properties have direct implications on the particle performance in the down-stream formulation process.

Nanotomogprahy was used to evaluate the manufacturing process of an injection moulded tablet (Figure 3, a – c) and a 3D-printed tablet (Figure 3, d), respectively. The visualizations of these formulated solid dosage forms were used for process development to improve the structural characteristics as well as the homogeneity of the final product. As visualized in Figure 3, c, the injection moulded tablet shows a high inhomogeneity in its x-ray attenuation with areas of higher apparent density. These differences in the sample homogeneity could be related to changes in its chemical composition during the manufacturing process.

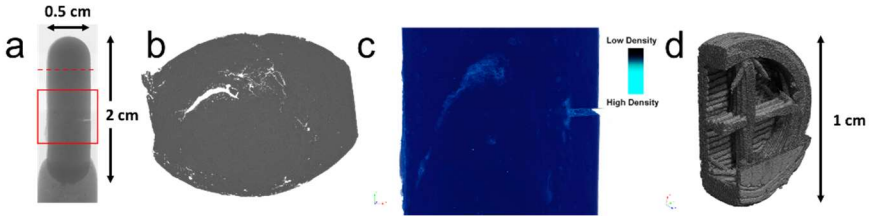


Figure 3**:** (a) Single scan of an injection moulded tablet, (b) cross-section identifying void areas within the injection moulded tablet tablet and (c) volume rendered model illustrating chemically inhomogeneous regions. (d) visualization of a 3D-printed tablet.

The results of a cross-section analysis are shown in **Figure** 4. The analysis was used to quantify the internal porosity within a subset of 226 cross-sections. The results show unevenly distributed porosity fractions which could influence the final performance of this oral dosage form. The total area of each cross-section remains mostly stable, however, indicated a deformation around cross-section No. 90.

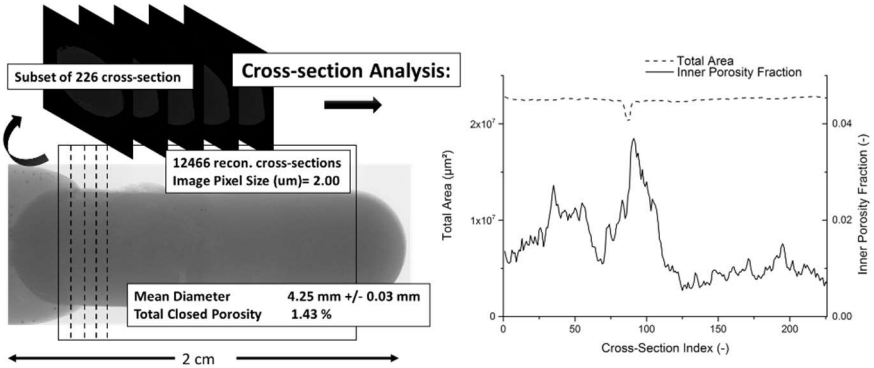


Figure 4**:** Cross-section analysis of a subset of 226 cross-sections to extract relevant structural data such as the 2D area fraction of detected closed porosity and the progress of the tablet size along its main axis.

## Conclusion

Nano-focused x-ray tomography was successfully employed to characterize solid pharmaceutical products in terms of their structural characteristics and solid phase homogeneity. The results can be directly employed to evaluate and improve production processes and enable a prediction of the (final) solid product performance. Future work will focus on extraction of quantitative data to inform rapid product and process development.

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