XRT: Extraction of Quantitative Structural Descriptors from Solid Pharmaceutical Products

Frederik J. S. Doerr* [1,2], Alastair J. Florence[1,2]

[1] EPSRC Future Research Hub for Continuous Manufacturing and Advanced Crystallisation, University of Strathclyde, Glasgow, United Kingdom
[2] Strathclyde Institute of Pharmacy & Biomedical Sciences (SIPBS), University of Strathclyde, Glasgow, G4 0RE, UK
* e-mail address: frederik.doerr@strath.ac.uk

Aims

In this project we demonstrate the use of x-ray tomography for the quantification of structural descriptors from two selected solid pharmaceutical products: single formulated particles and a commercial Ibuprofen capsule. In particular, we demonstrate the application of image processing strategies for noise reduction, image segmentation and the extraction of quantitative structural descriptors. Information on the sample's solid state properties can be used to evaluate the manufacturing process and allows a prediction of the solid performance for subsequent processing steps or after administration to the patient.

Method

A Skyscanner 2211 x-ray tomograph (NanoCT, Bruker, Kontich, Belgium) was utilised to acquire the initial raw data. The samples were scanned in micro- or nanofocus with an image pixel size of 0.8 µm – 2.5 µm, frame averaging of 3 – 8 and a rotation step size of 0.2 deg. Image reconstruction was performed using NRecon and InstaRecon (Version 1.7.1.6, Bruker, Kontich, Belgium) after optimising parameters for post-alignment, beam hardening and ring artefacts. Subsequential 3D image segmentation and analysis was implemented in Matlab (R2017b, MathWorks, Natick, United States) to allow a quantitative data extraction for solid state properties including size, shape, and sample porosity descriptors.

Results

Single Particle Analysis:

The structure of particles obtained from droplet drying experiments were investigated using x-ray tomography. Parallelised 2D image processing of CT cross-sections for the quantitative data extraction after reconstruction was demonstrated previously[1] and was further extended to cover a full analysis of the 3D particle volume space. Information of the final particle morphology and its structural solid state properties can be further correlated to its subsequent performance undergoing mechanical stress and particle dissolution.

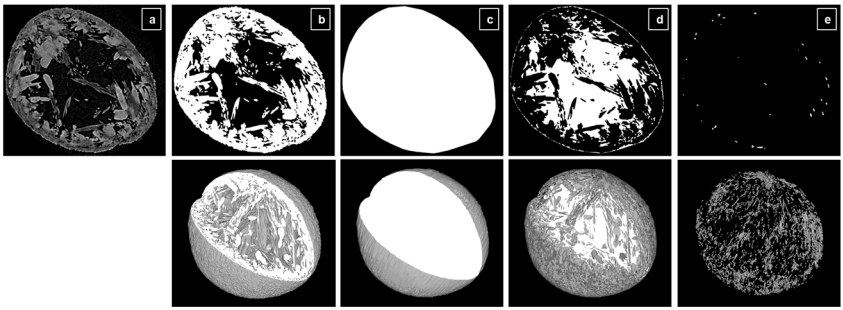

Figure 1: X-ray tomography of a single formulated particle obtained from droplet drying experiments: (a) 8-bit raw image, (b) binarised image after noise reduction, (c) image ROI, (d) open porosity and (e) closed porosity. Desired descriptors on particle volume, size, shape, porosity, and internal structure can be extracted using 3D image analysis.

Ibuprofen Capsule:

A commercial Ibuprofen capsule for controlled release was investigated using x-ray tomography. Key objectives were the measurement of the capsule's void volume and the evaluation of structural descriptors for its population of formulated drug-loaded pellets influencing drug dissolution and therefore, the performance of this oral dosage form after administration to a patient.
The extraction of structural descriptors from all pellets requires a successful volume separation of all touching objects which was accomplished using a marker-controlled watershed transformation.[2] Fig. 2 shows selected steps of the image processing workflow from raw data acquisition, to the automated separation of all touching objects and the in-depth structural characterisation for each individual pellet.

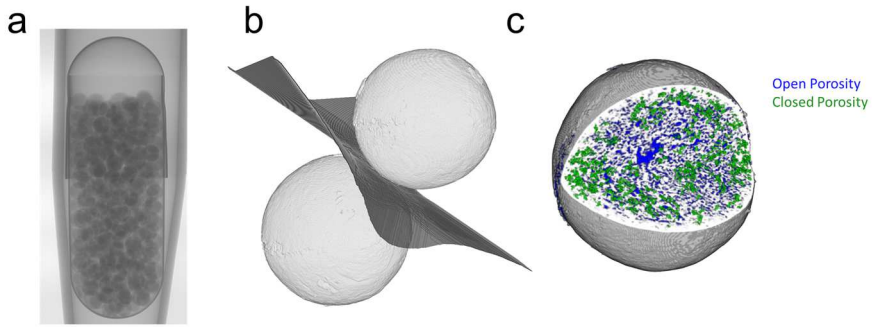

Figure 2: (a) Image of an Ibuprofen capsule with formulated drug-loaded pellets during data acquisition. (b) An example of two selected pellets with calculated marker-controlled 3D watershed segmentation lines for volume separation. (c) Successful volume separation allows the extraction of size, shape and porosity descriptors for each individual Ibuprofen pellet.

After successful volume separation, the structural properties of each pellet are extracted and can be used to identify broken pellets within the formulation as well as give an insight into the structural variation within the population of pellets.

Conclusion

X-ray tomography was successfully used to characterise a wide range of solid pharmaceutical samples. Beside sample visualisation, advanced 3D image-processing strategies have the potential to enable the extraction of quantitative descriptors for a broad range of morphological properties such as size, shape, porosity and solid phase uniformity. These quantitative descriptors can be used to inform rapid product and process development.

Acknowledgements

The authors would like to thank EPSRC and the Doctoral Training Centre in Continuous Manufacturing and Crystallisation (Grant Ref: EP/K503289/1) and the EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (Grant Ref EP/ EP/P006965/1) for funding this work. The authors would like to acknowledge that this work was carried out in the CMAC National Facility supported by UKRPIF (UK Research Partnership Fund) award from the Higher Education Funding Council for England (HEFCE) (Grant ref HH13054).

References:

1. Doerr F. J.S., Morphological Characterisation of Solid Pharmaceutical Products using X-ray tomography, 2017 Bruker microCT User Meeting, 2017
2. Meyer, F., “Topographic distance and watershed lines”, Signal Processing 38(1), 113–125, 1994