Laboratory Diffraction Contrast Tomography (LabDCT): A new technique for measuring crystal habit and formulation structure

Laboratory Diffraction Contrast Tomography (LabDCT): A New Technique for Measuring Crystal Habit and Formulation Structure

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INTRODUCTION

Both formulation and device have a strong influence on the aerodynamic performance of test and reference inhalation products undergoing bioequivalence testing. In many cases it is necessary to consider the crystal habit [1, 2]. Single crystal X-ray diffraction (SCXRD) and powder X-ray diffraction (PXRD) are two methods routinely used to determine the crystal structure from single crystals and powder populations, respectively. However, given a known crystal structure, there are no existing methods for determining crystallographic information of individual particles within a population.

LABORATORY DIFFRACTION CONTRAST TOMOGRAPHY (LabDCT)

In this work, we introduce LabDCT – a new technique to provide 3D crystallographic information (crystal habit) of bulk powders. Diffraction contrast tomography takes advantage of the fact that a polycrystalline sample both absorbs and diffracts an incident X-ray beam. LabDCT involves collecting a conventional absorption-contrast scan, where transmitted X-rays are captured to acquire the physical morphology of the sample [3]. Diffraction data is additionally acquired which provides crystallographic information. As shown in Figure 1, an aperture is placed between the X-ray source and the sample, and a beamstop is placed between the sample and the detector. With this optical set-up the individual crystal planes give rise to line-like spots on the detector as shown in Figure 1. Similar to conventional absorption tomography, a series of diffraction images are acquired as the sample is rotated through 360°. Information from both datasets is combined using the proprietary reconstruction software GrainMapper3D™ (Xnovo Technology ApS, Denmark) to calculate the crystallographic orientation and morphology of the individual crystals [4].

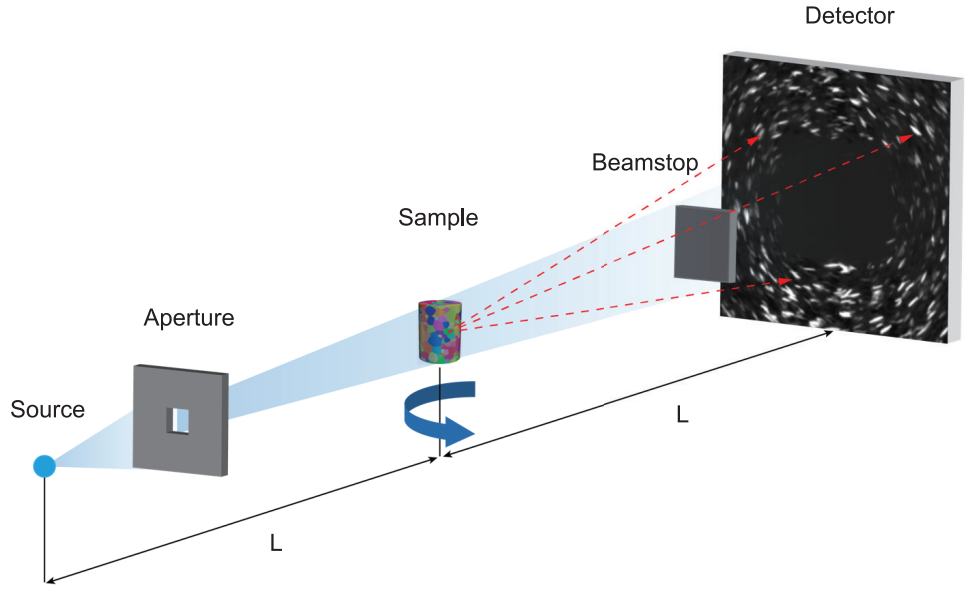

Figure 1. **The laboratory geometry used for acquiring diffraction data in a LabDCT setup. Figure reproduced from Oddershede *et al.* [5] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).**

LabDCT has grown into a popular technique in the metal and mineralogy communities, e.g. the microstructural evolution of copper particles during sintering [6]. Organic compounds are more challenging due to a dominance of more asymmetric crystal structures [7] and weaker diffraction patterns. Here we present the first results for LabDCT of lactose monohydrate, an asymmetrical monoclinic organic crystal.

METHOD

A recrystallized α-lactose monohydrate powder was used for calibration. A solution with 31.95 g of α-lactose monohydrate dissolved in 50 g water was cooled from 70°C to 20°C at a slow cooling rate of 0.05°C/min, then kept at 20°C until the onset of nucleation. Around five days after nucleation, the crystals were isolated and dried at room temperature before sieving (mesh size 425 μm). To facilitate LabDCT, a single crystal and a cluster of crystals were separately glued to the end of a toothpick. The toothpick was chosen to avoid metal streak artifacts [8]. Measurement was performed on a Zeiss Xradia 520 Versa X-ray microscope equipped with the LabDCT module (Carl Zeiss Microscopy, California, USA). The absorption contrast tomography scan was performed using a source voltage of 50 kV and a current of 80 μA, collecting 3000 projections. Each projection had an exposure time of 1.5 s. The diffraction contrast scan was performed using a source voltage of 110 kV and a current of 90 μA, collecting 360 projections. Here the exposure time for each projection was 120 s. For both scans a camera binning factor of two was used.

RESULTS AND DISCUSSION

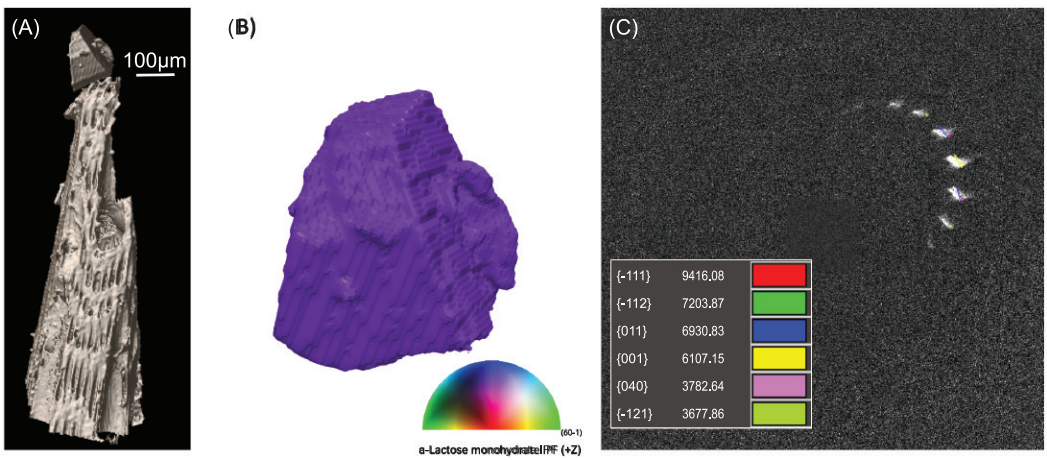

Figure 2. **LabDCT results for single lactose crystal. (A) Absorption contrast tomography showing entire sample; (B) Lactose crystal colored by its orientation with respect to the sample stage (inverse pole figure coloring, [9]); (C) Simulated diffraction spots originating from the first six families of crystal lattice planes with Miller Indices (hkl) [10] that have the largest diffracting ability (faint colored lines) overlaid on the acquired diffraction spots.**

Figure 2 shows the LabDCT results for the single crystal sample. The accuracy of the particle indexing can be seen in panel C which compares the actual diffraction spots against simulated spots for the crystal orientation shown in panel B. Figure 3 shows acquired data for a cluster of lactose particles. The large number of crystals creates a high number of diffraction spots, thus increasing the complexity of the diffraction pattern and work is underway to index each of the crystals in this sample.

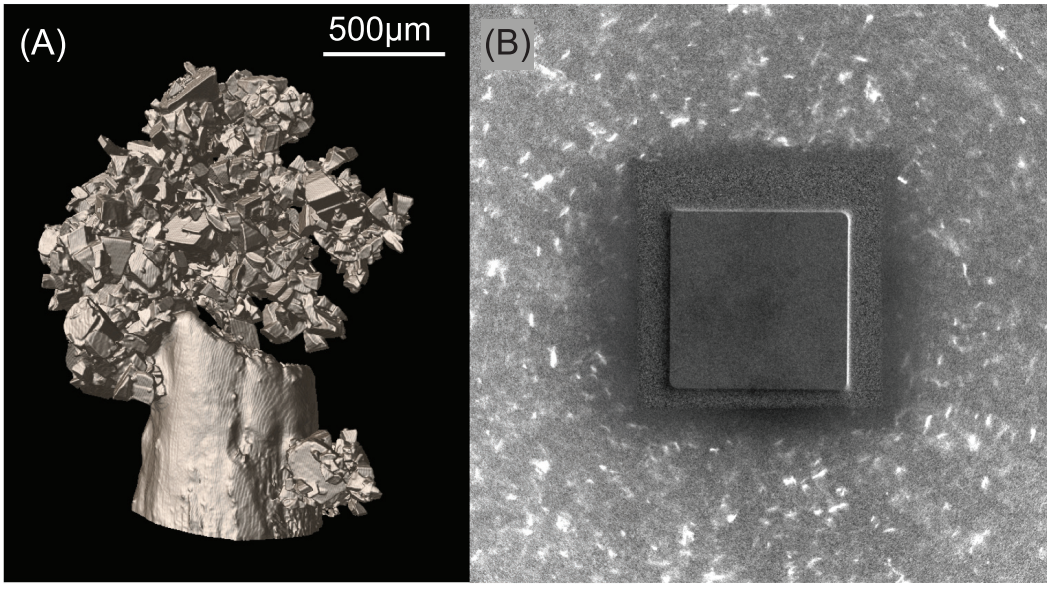

Figure 3. LabDCT for a cluster of lactose particles: (A) Absorption tomography showing the sample; (B) An example of the diffraction spots.

The advantage of LabDCT over SCXRD is the ability to provide individual crystal orientations for each crystal within a bulk powder sample. Pairing this with crystal structures predicted from molecular modelling [11] would allow the different facets of each crystal particle in a powder to be determined. When coupled with crystal modelling and visualization software, LabDCT could allow particle orientations and arrangements to be compared between test and reference products. In particular, this could allow separation energies and hence agglomeration forces to be compared.

CONCLUSIONS

LabDCT is a new technique that is potentially able to provide 3D crystallographic information on crystalline bulk powders of lactose monohydrate.

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