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Application of X-ray Micro-Tomography to Study the Morphology and Porosity of Pharmaceutical Granules

Leon Farber* , Gabriel Tardos and James N. Michaels***

* Merck and Co., Inc, West Point, PA 19486
** The City College of the City University of New York, Department of Chemical Engineering, NY

Optical or scanning electron microscopy is widely used to provide detailed images of specimen cross-sections. However, the information obtained is two dimensional and can not always be translated into a three-dimensional body. Sample preparation is always required. This is a time and labor intensive process that may also introduce artifacts. The problem is further compounded when a series of slices have to be taken to obtain three-dimensional information. In that case, either too much work is required to prepare thin slices and acquire images of all of them or the distance between slices is too coarse to fully recreate the three-dimensional body without losing too much information.

X-ray computed tomography (XRCT) is a technique that uses X-ray shadow images to reconstruct the internal microstructure of objects non-destructively. The technique is known as CAT-scan in medicine. Recent development of powerful yet miniaturized dedicated X-ray sources resulted in production of compact tabletop X-ray systems with the resolution of several microns. This advances the technique into "microscopy" category and makes it feasible to apply this technique for characterization of a wide range of materials in laboratory settings. We report in this paper on application of a micro-tomography system for studying the microstructure of pharmaceutical granules (agglomerates made of individual particles).

Granules for this study were fabricated from Mannitol using either a very low- or high shear granulation (A and B-C, respectively). Individual granules from each granulation were analyzed with a Skyscan 1072 high-resolution X-ray microtomograph (Skyscan, Belgium) equipped with 1024X1024 CCD detector that provides a resolution of up to 4 microns. Samples were scanned in the zero-to-180 degree interval using a 0.9 Deg. scan step. Typical acquisition time was about 1 hour. Median filtration and geometrical correction were applied during acquisition. Cross-sectional pixel size was 11 and 3.42 microns for samples A and B-C, respectively. Cross-sectional and 3-D images were reconstructed using the Skyscan software package.

Figure 1 shows a typical side view, a vertical slice and three representative horizontal cross-sections of granule A . Each cross-section represents an 11 micron-thick slice of the material. The pore structure in the granule is clearly revealed. The pores are not uniformly distributed through the granule: a large void space exists in the central part of the granule. Figure 2 shows representative cross-sections of granules B and C produced under "low" and "high " shearing conditions. Both samples are porous, although the amount of porosity and pore connectivity is different. Tomographic images reveal that the pore network of individual granules in granule B is comprised of relatively large cavities connected by narrower yet quite wide pore necks. In contrast, the pores appear occluded in sample C. However, complementary analysis involving mercury porosimetry established that the pores are interconnected by channels of about 0.1 micron in diameter which is below the resolution of the micro-tomograph. Thus, the major structural difference between granules

is a lower void space and reduction in the pore-neck diameter; the cavity size is relatively insensitive to shear in the granulator. Additionally, comparison of pore size distributions determined from tomographic images and mercury porosimetry indicates that mercury intrusion measures the pore-neck size distribution, while tomography reveals the true pore sizes ca. 4 μm or larger (the instrument resolution). The total void volume determined from the reconstructed images (52, 58 and 12.5 % for granules A, B and C, respectively) agrees well with mercury porosimetry data. We conclude, that X-ray microtomography is a very useful and effective "microscopy" tool that has a great potential for microstructure analysis, being informative, non-destructive and relatively fast.

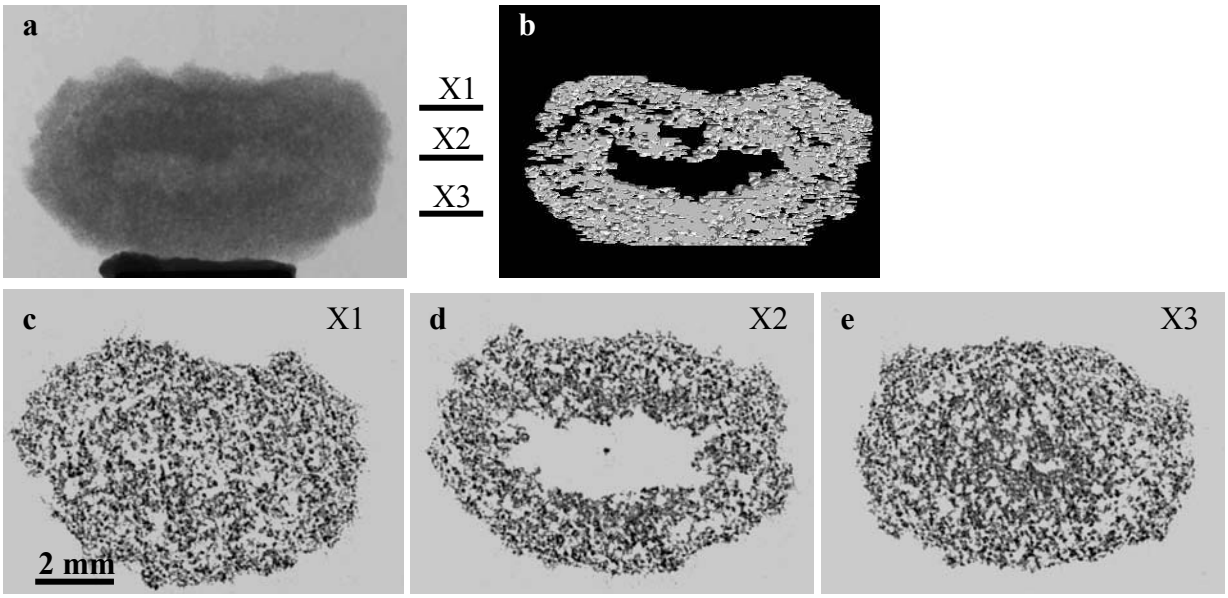

Figure 1. Granule A: a) typical side view X-ray image, b) vertical cross-sectional slice (3-d reconstruction, mannitol is gray), c-d) reconstructed 2-d horizontal slices X1-X3 (Mannitol is dark gray); slice thickness is 80μm in b) and 11μm in c)-e).

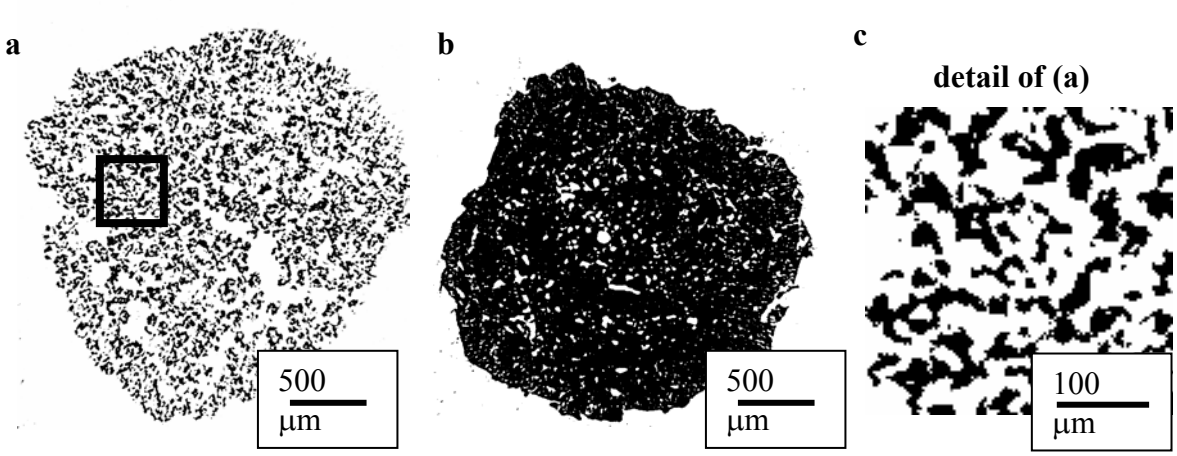

Figure 2. Typical reconstructed cross-sectional slices of a) granule B, b) granule C; c) enlargement of a boxed area in (a); in all figures: pixel size is 3.2 mm; slice thickness is 3.2 μm

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