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Quantitative Characterization of Crystallization in Amorphous Solid Dispersion Drug Tablets Using X-Ray Micro-Computed Tomography

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One approach to improve solubility and bioavailability of poorly soluble active pharmaceutical ingredients (API) is to formulate the API in an amorphous state as an amorphous solid dispersion (ASD). Amorphous compounds, while kinetically more soluble, are thermodynamically less stable than their crystalline form. Polymer stabilizing material is often employed to prevent crystallization 0. Manufacturing of ASD based drug products involves complex mechanical and thermal transformations necessary to render the API in a kinetically stabilized amorphous state. However, detection and monitoring crystallization, either from residual crystalline API or crystallization of amorphous API, is extremely important in assessing the effectiveness of the formulation design and process.

Based on the qualitative insight obtained from two-dimensional correlative imaging techniques 0, this work quantified API crystallinity using three-dimensional (3D) X-Ray Micro-Computed Tomography (MicroCT). Three modeled tablet samples composed of 20% indomethacin in copovidone (PVPVA) with similar drug loading and different levels of crystallinity (Table 1) were imaged with various resolutions and contrast techniques. The massive amount of image data was processed with an artificial intelligence based image segmentation engine 0. A suite of quantitative matrices were computed for not only the ASD domains and crystal API particles, but also pore space and pure polymer domains.

MicroCT imaging at 2μm was identified as the optimal spatial resolution and representative elementary sampling volume (Figures 1a, 1b, 1c). Upon the failure of conventional threshold and gradient-based segmentation methods, an artificial intelligence image segmentation engine successfully segmented all four material phases (Figure 1d and 1e), which allowed various quantifications such as domain size distributions of pores (Figure 3a), crystalline API (Figure 3b), as well as quantitative characteristics of volumes and surface areas for all four material domains.

Clearly the accurate material phase models allow quantification of crystalline API domains and compaction related porosity. This data can provide insight into the effectiveness of rendering the API in an amorphous state as well as the kinetic stabilization of the formulation. The data also has the potential to predict drug release performance by combining these models with image-based computational physics, to measure effective diffusivity coefficient, disintegration pattern, as well as various designed release behavior. Upon continued improvements, such approaches can potentially result in drug product development efficiencies with respect to development time, material costs as well as reducing the burden of animal and/or clinical screening studies [4].

References:

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[4] Joseph Neilly and Gerald Danzer are employees of AbbVie and may own AbbVie stock. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

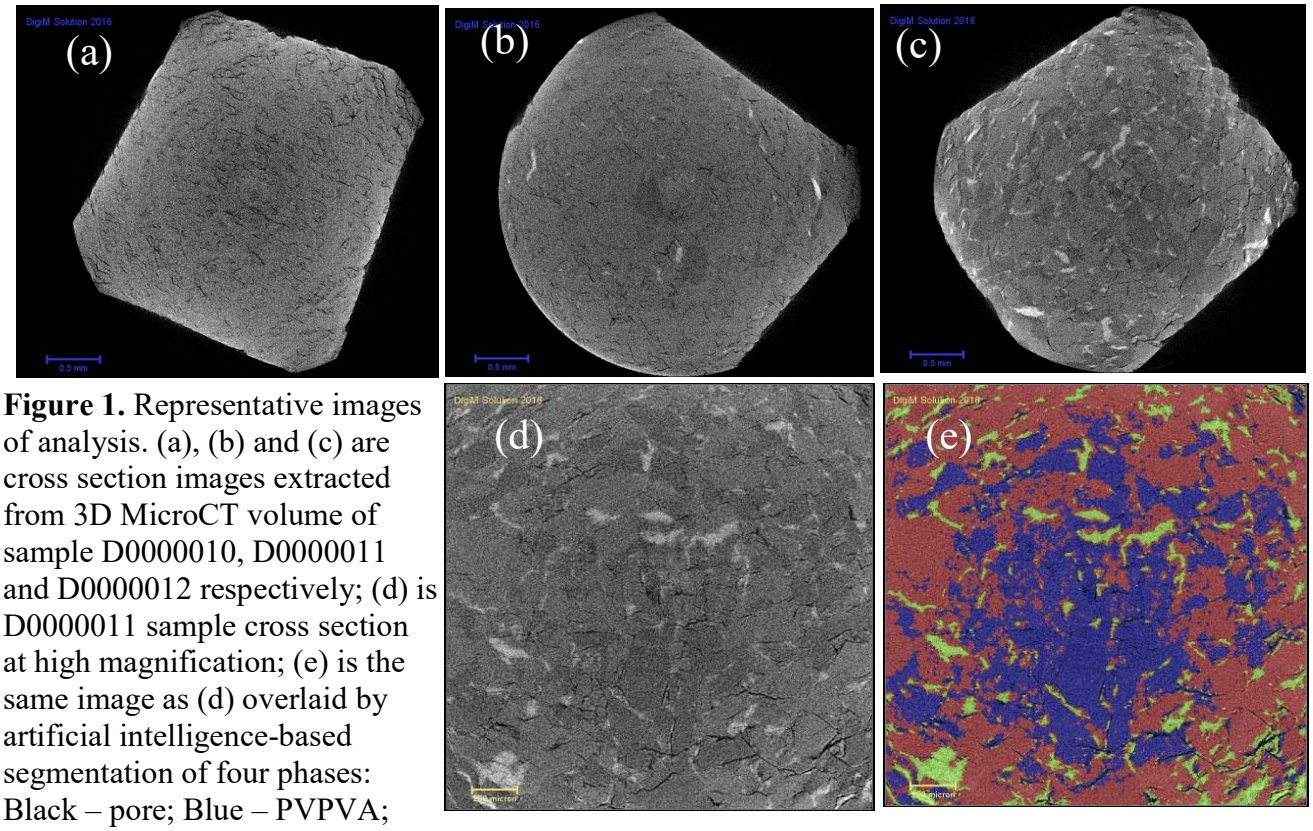

Figure 1. Representative images of analysis. (a), (b) and (c) are cross section images extracted from 3D MicroCT volume of sample D0000010, D0000011 and D0000012 respectively; (d) is D0000011 sample cross section at high magnification; (e) is the same image as (d) overlaid by artificial intelligence-based segmentation of four phases: Black – pore; Blue – PVPVA; Red – ASD; Green – Crystal API.

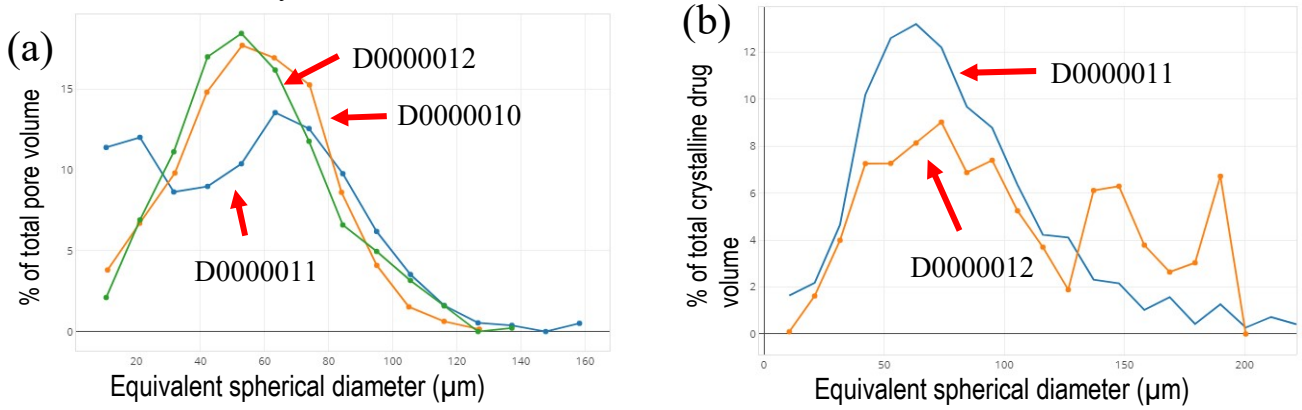

Figure 2. (a). Pore Size Distribution; (b). Crystalline API particle size distribution.

Analysis ID	Porosity	API	PVPVA	ASD
D0000012, 20% indomethacin, (10% crystalline, 10% amorphous)	2.62	10.08	40.3	47.2
D0000011, 20% indomethacin, (1% crystalline, 19% amorphous)	4.11	0.77	4.67	90.5
D0000010, 20% indomethacin, (0% crystalline, 20% amorphous)	4.76	0	0	95.24

Table. 1 Phase quantification of three samples.

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