Particle Analysis within Drug Products: Novel Methods in Quantification using 3D Microscopy

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PURPOSE

3D Characterization of API Particles in Drug Products

Characterizing the **shape**, **size**, and **spatial distribution** of active pharmaceutical ingredients (API) within a drug product are essential towards understanding and optimizing performance. In particular, particle analysis can help identify root causes of **performance and stability differences** across **processes** and **formulations**. While techniques such as laser diffraction can measure particle properties in bulk, there is a striking lack of techniques to analyze particles **within a product or intermediate.**

High-resolution imaging with **AI analytics** offers an attractive solution to overcome these obstacles.

The application of these techniques are presented in two case studies:

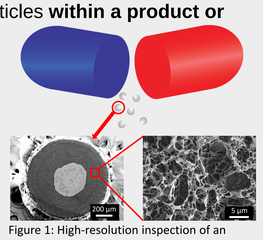
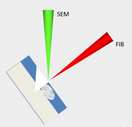


Figure 1: High-resolution inspection of an encapsulated particle within a capsule product.

1. **Intra-batch capsule performance differences**
2. **Spray dried particle process development**

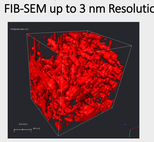
METHODS

X-Ray Microscopy up to 0.5 µm Resolution



FIB-SEM up to 3 nm Resolution

Artificial Intelligence Image Analysis



Advanced Quantification and Simulation

High resolution imaging techniques including non-invasive X-ray microscopy (XRM or XRCT) and focused ion beam scanning electron microscopy (FIB-SEM) were used to evaluate particle characteristics in 3D. A suite of Artificial Intelligence-based analysis was then employed to perform quantitative analysis of particle size, distribution, and morphology.

RESULTS INTRA-BATCH CAPSULE PERFORMANCE DIFFERENCES

3D XRM Imaging and AI-based Analytics

In this project, our client observed performance differences for capsules produced at different times on the manufacturing line. To determine the root cause, we applied high resolution 3D XRM imaging and image analytics. XRM provided visualization of the API particles across the capsule volume. From the XRM scan, we applied AI segmentation to identify each particle, then analyzed the sizes and spatial distribution of particles.

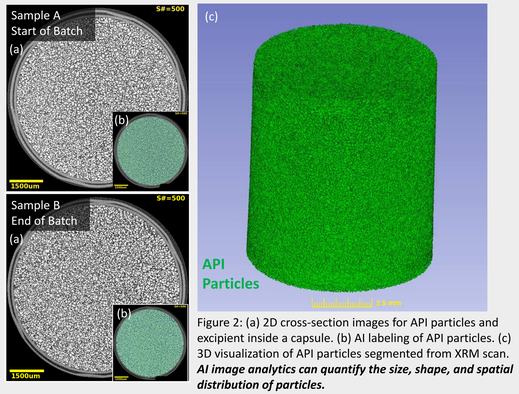


Figure 2: (a) 2D cross-section images for API particles and excipient inside a capsule. (b) AI labeling of API particles. (c) 3D visualization of API particles segmented from XRM scan. ***AI image analytics can quantify the size, shape, and spatial distribution of particles.***

Untangling the Source of Performance Differences

- Sample A dissolved notably faster than Sample B.
- AI analytics found that the particle size was comparable between samples.
- Despite similar particle size, the spatial distribution and volume of API particles was remarkably different.
  - Sample A's API volume is notably higher than Sample B.
  - Particles are evenly distributed in Sample A, while Sample B shows large variations along the capsule length and across the diameter.
- The volume and spatial distribution can be correlated to a faster dissolution network forming through the API particles of Sample A.

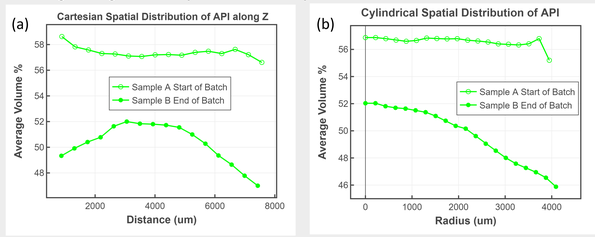


Figure 3: (a) Spatial distribution of API particles along the length of the capsule volume. (b) Spatial distribution of API particles across the diameter of the capsule volume. ***The spatial distribution of API particles can be directly tied to performance differences and the formation of a dissolution network.***

RESULTS SPRAY DRIED PARTICLE PROCESS DEVELOPMENT[1]

Background

Spray drying is a technique often applied to produce **amorphous solid dispersions (ASD),** which increase the performance of poorly water-soluble drugs. Properties of the **spray dried (SD) particle** can change depending on the composition and the conditions of the spray drying technique. In addition, the particle characterization is critical to understanding tableting performance. In this study, XRM and FIB-SEM were used to study **particle morphology** at various **spray-drying temperatures.**

Particle Morphology

Three different morphologies were observed with XRCT and FIB-SEM imaging:

- Hollow, spherical particles with a smooth surface and thin wall.
- Collapsed spheres or raisin-like particles.
- Fine solid particles/fragments.

These particles were observed in three batches manufactured at different temperatures.

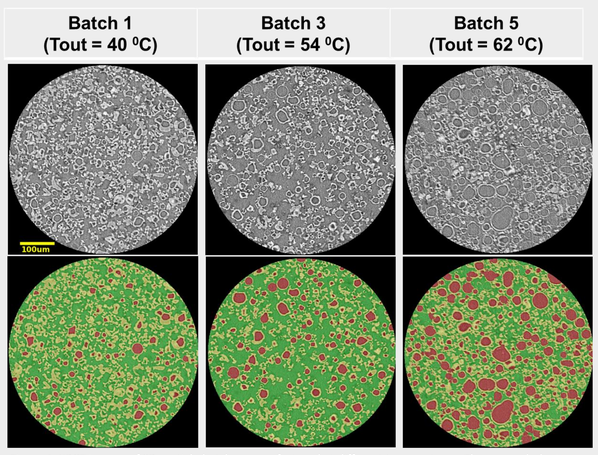


Figure 4: XRCT images of SD particle batches manufactured at different temperatures. Three morphologies are observed, with the amount of each depending on the SD conditions. The AI-segmented images are in the second row, where yellow = solid, red = void inside hollow particle, and green = exterior air.

Process Temperature Correlation with Morphology

XRM imaging revealed a direct correlation of the spray drying temperature and particle morphology.

- The number of hollow particles increased as the temperature of spray drying increased.
- Particle wall thickness decreased as the temperature increased.
- Observed morphologies can be correlated with tableting compression performance and further process optimization.

Figure 6 displays a comparative plot of particle diameter vs wall thickness. This morphology analysis at high-resolution, for thousands of particles, is unique to XRCT and AI image analytics.

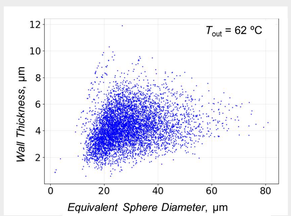


Figure 6: Plot displaying the relationship of particle size with wall thickness for a SD batch produced at T_{out} of 62°C.

CONCLUSIONS

High resolution imaging and AI analytics can uniquely quantify particle characteristics within drug products and intermediates. This analysis, including size, morphology, and distribution, can greatly assist in troubleshooting, root cause analysis, process development, and formulation decisions.

Intra-batch Capsule Performance Differences

- End of batch Capsules had less uniform drug distribution.
- The distribution and connectivity of API particles, characterized from XRM, can be directly correlated to dissolution differences.

Spray Dried Particle Process Development

- Using image-based analysis to characterize spray dried particles by imaging the internal microstructure revealed three distinct morphologies:
  - Spherical particles with thin walls and a center large void space.
  - Raisin-like particle with thicker shell and reduced void space.
  - Fine solid particles without internal voids.
- Spray drying at higher temperatures resulted in more spherical hollow particles with smooth surfaces and thinner walls. At a lower temperature, it produced more raisin-like particles with thicker walls.
- Particle analysis can be applied for further upstream process control and an understanding of downstream tableting performance.

DigiM™ Microstructure Characterization

1. Characterization of Spray Dried Particles Through Microstructural Imaging. *Journal of Pharmaceutical Sciences*. August 2020. **With Merck**. https://doi.org/10.1016/j.xphs.2020.07.032

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