Drug Particle Characterization Inside Long-Acting Intrauterine Systems with 3D Imaging Analytics

Yuri Qin[1], Quanying Bao[2], Yan Wang[3], Aiden Zhu[1], Diane Burgess[2], Liping Zhou[1], Shawn Zhang[1]

[1]DigiM Solution LLC, 67 South Bedford Street, Suite 400 West, Burlington, MA 01803, USA

[2]University of Connecticut, School of Pharmacy, Storrs, CT 06269, USA

[3]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

Contact Information: Shawn.Zhang@digimsolution.com

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PURPOSE

Advantages of long-acting drug delivery systems

- More sophisticated control to achieve desired release profiles and release characteristics
- Improved patient centricity
- Reduced systemic toxicity

Challenges and Solution

- Due to the nature of such systems, the product development phase can be long even if an accelerated *in vitro* release method is applied.
- In this work, a new high-resolution micro-image-based characterization approach has been applied with the goal of seeking a fundamental understanding of the micro-scale physical and structural arrangement of different material phases in the complex long-acting controlled release system and how the microstructure impacts the device performance.

OBJECTIVES

- Elucidate distribution of active pharmaceutical ingredient (API) inside an Intrauterine System (IUS) sample.
- Quantitatively compare a test IUS formulation to a commercially available sample for microstructure similarity assessment.
- Compare pre-release and post-release samples.

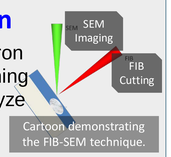
METHODS

IUS Preparation

A qualitatively and quantitatively similar levonorgestrel (LNG) intrauterine system (IUS) was prepared[1] and compared side-by-side with the commercially available Mirena IUS device. Post-dissolution samples were collected under stressed *in vitro* release conditions.[2]

Image-based Characterization

Focused Ion Beam – Scanning Electron Microscopy (FIB-SEM), a thin sectioning imaging technique, was used to analyze both the in-house and Mirena IUS samples.

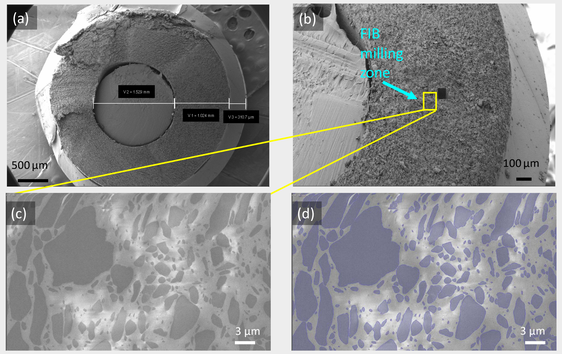


For each IUS sample, one device prior to release and one device post completed release were studied. The collected images were quantitatively analyzed with an artificial intelligence (AI)-based image analytics.

RESULTS

Pre-release API dispersion inside IUS

Figure 1. FIB-SEM Imaging Analytics Workflow



(a) an overview image of IUS cross section prepared with a razor blade,
(b) a magnified view of cross section, with area prepared by FIB for SEM imaging,
(c) magnified view of API particles dispersed in polymer,
(d) AI segmentation labels API particles separately from polymer, which can be used to quantify features (Table 1). The suspected phase compositions were confirmed with energy dispersive X-ray spectroscopy (EDS).

Figure 2. EDS Confirms Phase Separation

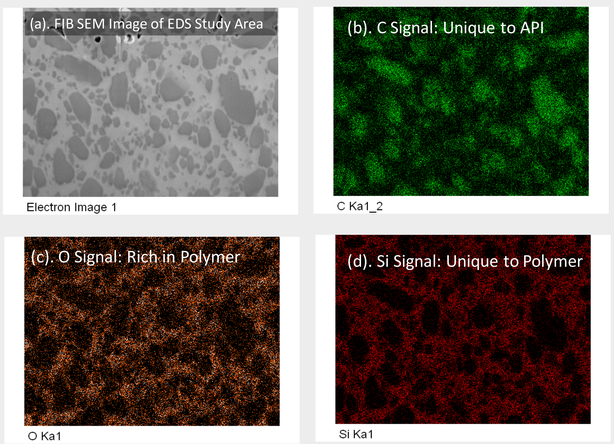
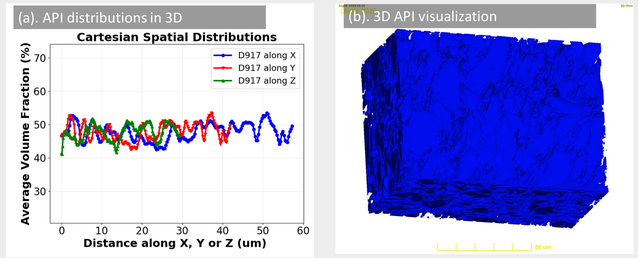


Figure 3. 3D API dispersion uniformity



In-House vs Commercial Product

Figure 4. FIB-SEM images of API in two samples

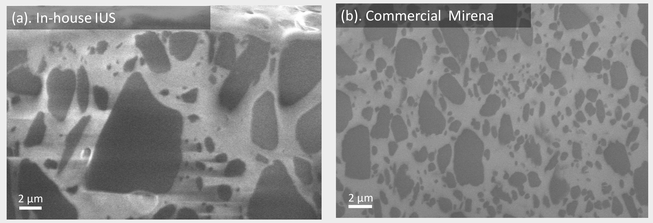


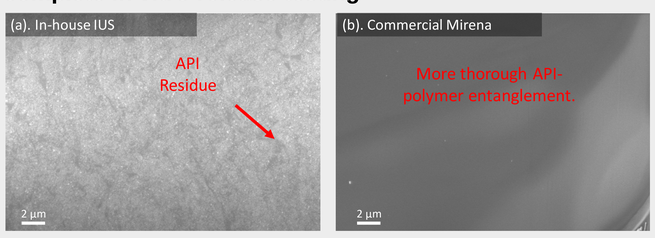
Table 1. API particle size distribution

Sample	API Particle Size, µm			Volume Fraction of API
	D10	D50	D90	
In House IUS; pre-release	2.13	5.05	8.58	48%
Mirena; pre-release	0.74	1.08	1.42	51%

Larger API particles observed

Post-release comparison

Figure 5. FIB-SEM images of IUS microstructures after complete *in vitro* release testing



CONCLUSION

- FIB-SEM micro-images and image analytics quantified clear microstructural differences between the in-house and commercial IUS devices.
- The microstructural differences, including the size distribution of API particles and polymer behavior, correlated well with *in vitro* observations and performance differences.
- FIB-SEM imaging and imaging analytics can offer an alternative approach for evaluating the microstructure properties of complex drug products. The application of these techniques to correlate microstructure with performance is being evaluated.
- Imaging analytics, including quantification of microstructures and simulation of transport properties, can help advance the development of long-acting and controlled-release dosage forms.

ACKNOWLEDGEMENTS

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1. Bao Q, Gu B, Price CF, Zou Y, Wang Y, Kozak D, Choi S, Burgess DJ. "Manufacturing and characterization of long-acting levonorgestrel intrauterine systems", *Int J Pharm*, 2018; 550: 447-454.

2. Bao Q, Zou Y, Wang Y, Kozak D, Choi S, Burgess DJ. "Drug release testing of long-acting intrauterine systems", *J Control Release*, 2019; 316: 349-358.

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