

New Developments in Characterization and Process Scale Up

Andrew Clark PhD



CRS 2023 ANNUAL MEETING & EXPOSITION

JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE

Correlating microstructure to performance of PLGA microspheres using X-ray microscopy and AI-based image analysis

Andrew Clark PhD



Booth 311

A.G. Clark, R. Wang, J. Lomeo, Y. Wang, A. Zhu, M. Shen, Q. Bao, D.J. Burgess, B. Qin, S. Zhang, "Investigating structural attributes of drug encapsulated microspheres with quantitative X-ray imaging," *JCR*, 258, (2023), 626-635
(<https://doi.org/10.1016/j.jconrel.2023.05.019>)

CONTROLLED RELEASE SOCIETY
CRS2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 **Paris Hotel » Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE

Journal of Controlled Release 358 (2023) 626-635
Contents lists available at ScienceDirect
Journal of Controlled Release
journal homepage: www.elsevier.com/locate/jconrel

ELSEVIER

Investigating structural attributes of drug encapsulated microspheres with quantitative X-ray imaging

Andrew G. Clark^a, Ruiteng Wang^a, Josh Lomeo^a, Yan Wang^a, Aiden Zhu^a, Mike Shen^a, Quanying Bao^a, Diane J. Burgess^b, Bin Qin^a, Shawn Zhang^a

^a Right Indent LLC, 100 West Cummings Park, Suite 300, Woburn, MA 01888, USA
^b Division of Nonprescription Drug and Combination Product Evaluation, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, MD, USA

ARTICLE INFO
Keywords: PLGA Microsphere development Structural uniformity Microsphere diameter X-ray microscopy AI image analysis

ABSTRACT
The intra-sphere and inter-sphere structural attributes of controlled release microsphere drug products can greatly impact their release profile and clinical performance. In developing a robust and efficient method to characterize these attributes, we have used quantitative X-ray microscopy (QXR) and artificial intelligence (AI)-based image analysis. Eight microsphere loaded poly(lactide-co-glycolide) (PLGA) microspheres batches were produced with controlled variation in manufacturing parameters, leading to differences in the size and distribution of microspheres. The size and distribution of the individual microspheres sample from each batch were imaged using high resolution non-invasive XRM, fluorescence microscopy, and electron microscopy. The size and distribution of the individual microspheres sample from each batch were used to calculate the mean diameter and standard deviation of the microspheres. The signal intensity within the eight batches was nearly identical, the range of microsphere diameters, indicating high structural similarity of spheres within the same batch. Overall, the mean diameter of the individual microspheres sample from each batch was not significantly different from the mean diameter of the individual microspheres sample from the other batches. The non-uniformity arising from differences in the underlying microstructures associated with different manufacturing conditions was assessed using QXR. The QXR images were used to calculate the mean diameter resolution focused on beam scanning electron microscopy (FB-SEM) and the *in vitro* release performance for the batches. The potential for this method for rapid at-line and offline product quality assurance, quality control, and quality assurance is discussed.

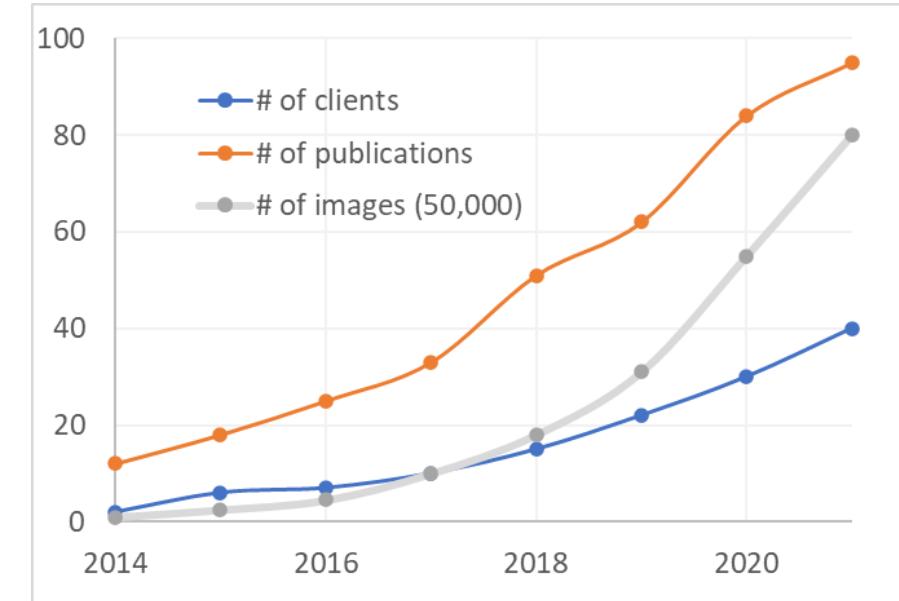
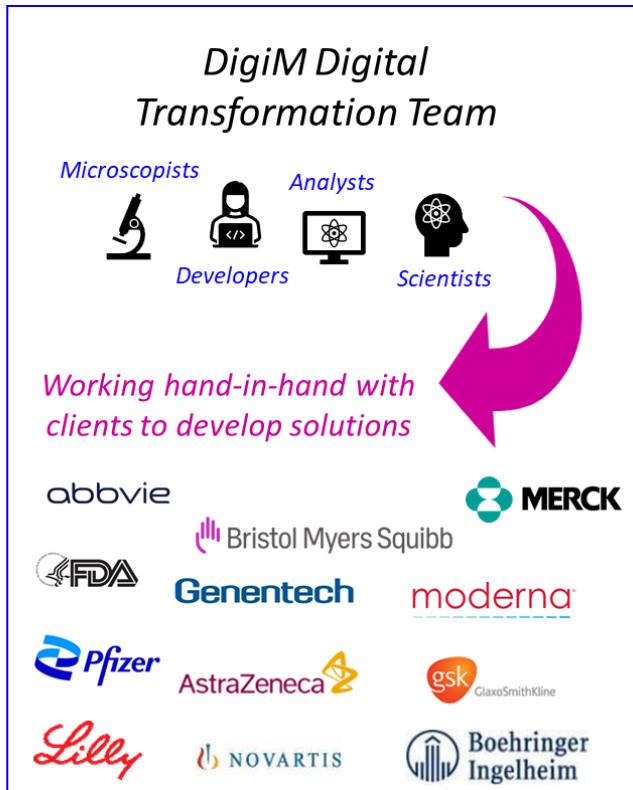
1. Introduction
Poly(lactide-co-glycolic acid) (PLGA) is a popular polymer for controlled release (CR) drug products in its pharmaceutical and biomedical applications [1-3]. Over the past 30 years there have been ~20 PLGA-based CR products approved for use by the FDA in the US. Over half of the aforementioned PLGA products are CR microspheres, where the drug is entrapped within a spherical polymeric matrix of particles [4]. PLGA microspheres are a well-known platform for CR products owing to their ability to encapsulate a wide range of drugs (including proteins, peptides, and small molecules, e.g., insulin, g., using a syringe), as well as sustained release for long periods of time [7]. Despite the advantages of the PLGA microsphere platform, there is a paucity of PLGA microsphere drug products on the market. The difficulty in reliably relating the measured critical quality attributes (CQA) to formulation, process conditions, and performance presents a significant barrier to the development of new and generic PLGA microspheres.

Recognizing the critical role that microstructure can play in the performance of complex drug products (e.g., topical and parenteral microencapsulated studies in part of biocompatibility assessment when assessing the safety of a drug product [8]), the pharmaceutical industry, i.e., the pharmaceutical industry, has conducted extensive studies to correlate the structural attributes of the microspheres to the performance of the drug products on the market. The difficulty in reliably relating the measured critical quality attributes (CQA) to formulation, process conditions, and performance presents a significant barrier to the development of new and generic PLGA microspheres.

^a Corresponding author.
E-mail address: clark@rightindent.com (S. Zhang).

What does **DigiM** do?

Technology leader for characterization-based solutions in drug development



- Founded in 2014
- HQ in Woburn, MA

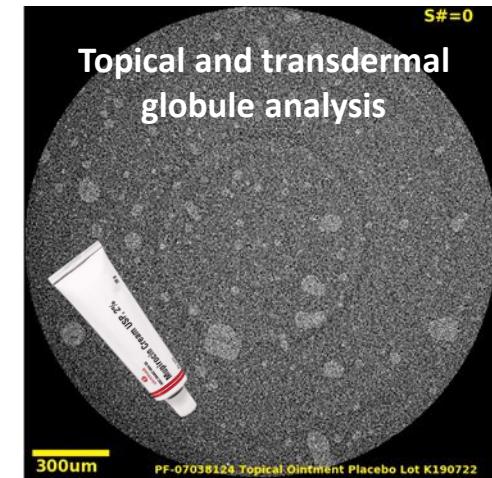
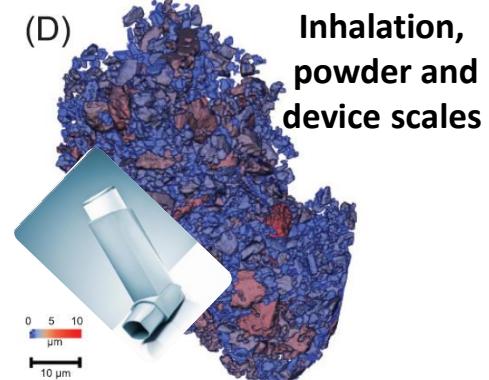
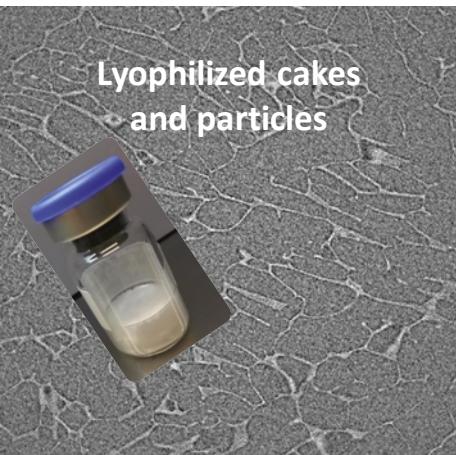
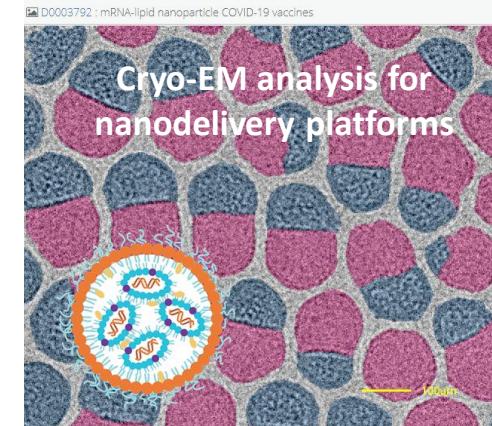
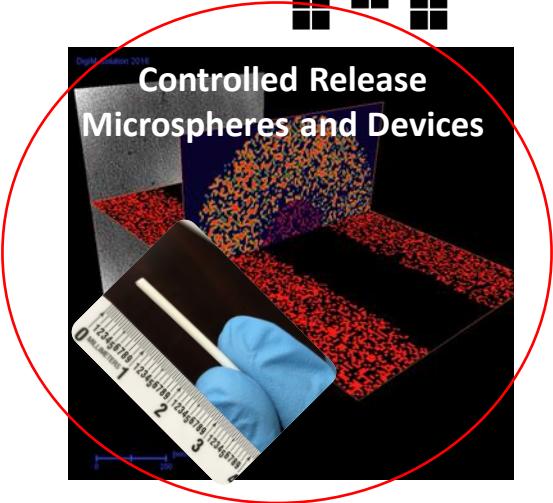
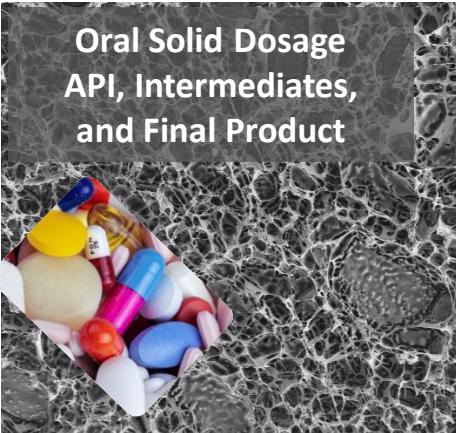
CONTROLLED RELEASE SOCIETY

CRS 2023 ANNUAL MEETING & EXPOSITION

JULY 24-28, 2023 **Paris Hotel » Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE

What does **DigiM**™ do?



Stop by booth 311
and poster 654 for
more info!



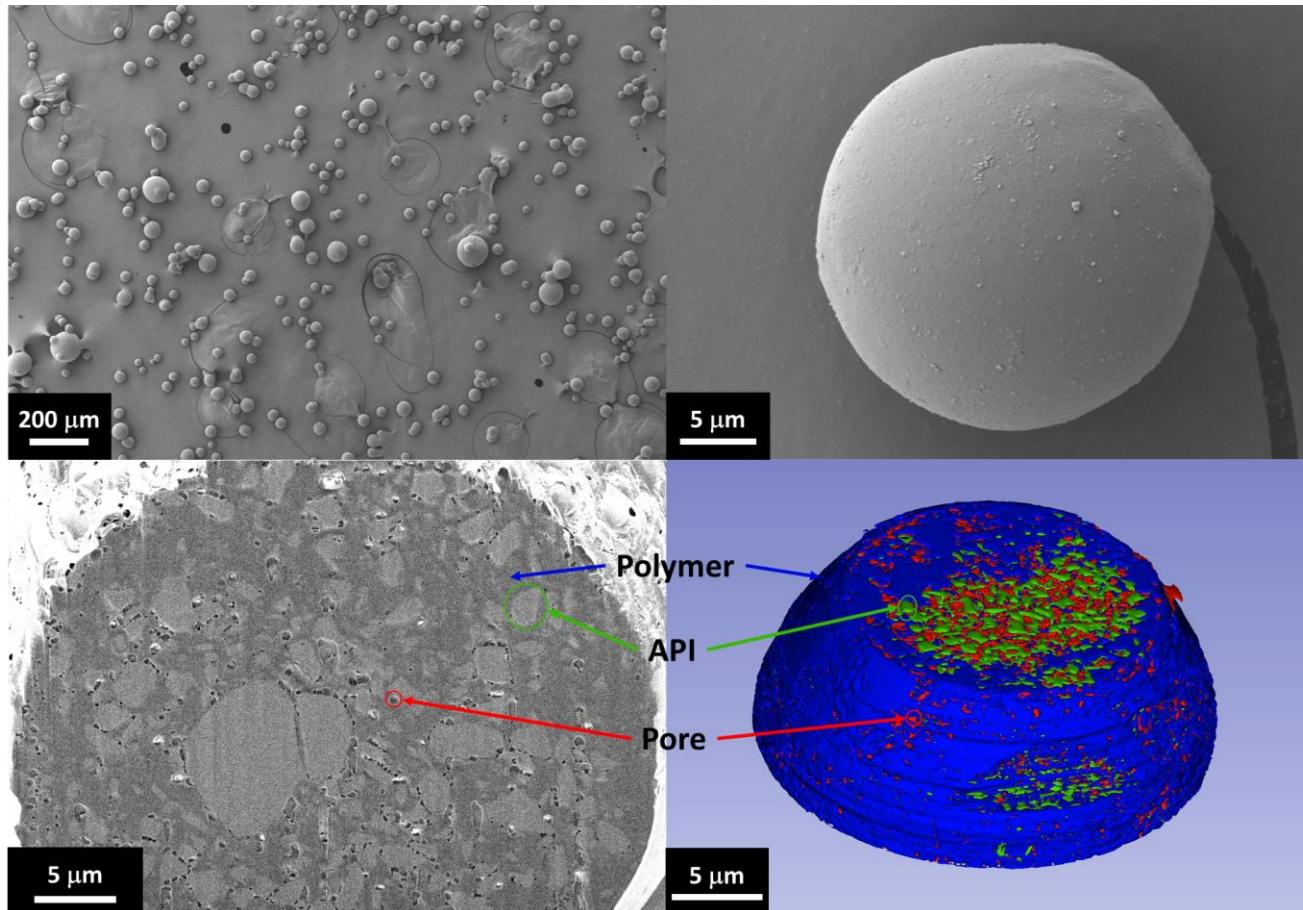
CONTROLLED RELEASE SOCIETY

CRS 2023 ANNUAL MEETING & EXPOSITION

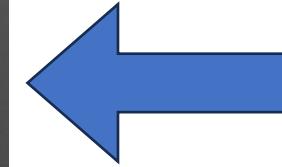
JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE

Traditional microsphere quality attributes are difficult to correlate to final product performance



Clark et al. JCR (2023)



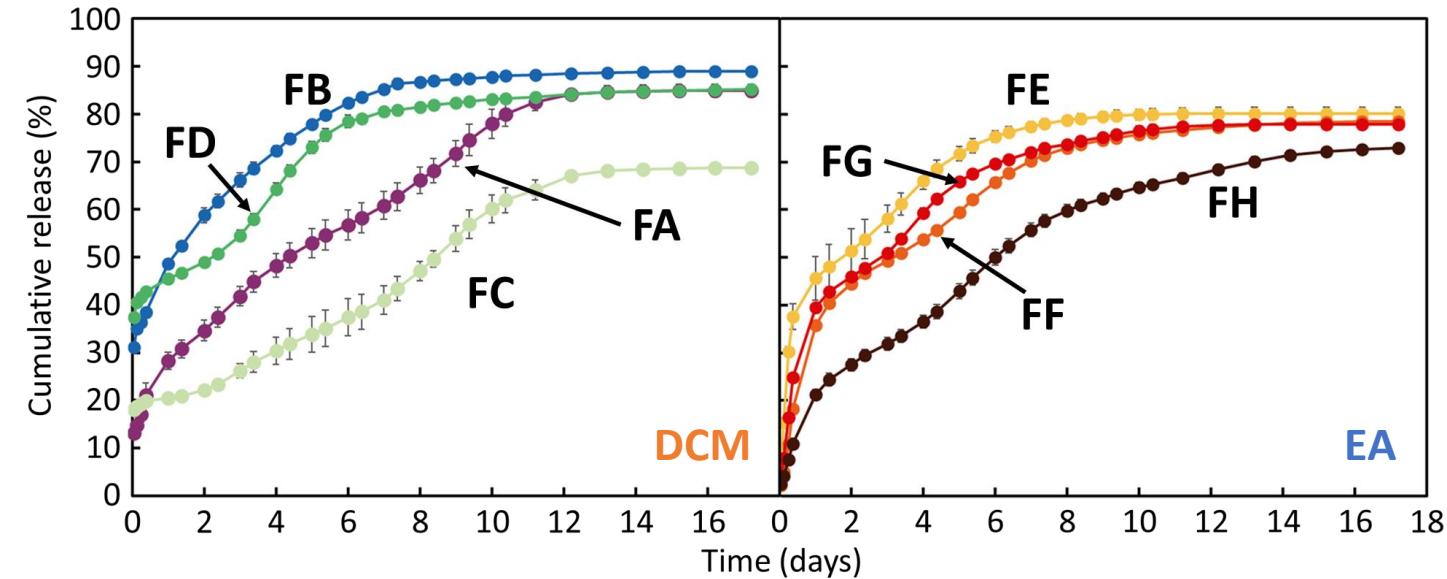
Bulk characterization assays might not inform on the final performance of a microsphere product.

Microstructure characterization of the internal sphere structure CAN be correlated to final product performance.

How can we ensure a statistically representative number of microspheres are considered in structural characterizations?

Eight in-house microsphere batches were manufactured with variations in processing parameters that promote in vitro release variations

PLGA solvent:	Silicone oil	Stirring speed	
		350 cSt	1000 cSt
		350 rpm	Formulation A Formulation B
Dichloromethane		600 rpm	Formulation C Formulation D
PLGA solvent:	Silicone oil	350 cSt	1000 cSt
		350 rpm	Formulation E2 Formulation F
		600 rpm	Formulation G Formulation H



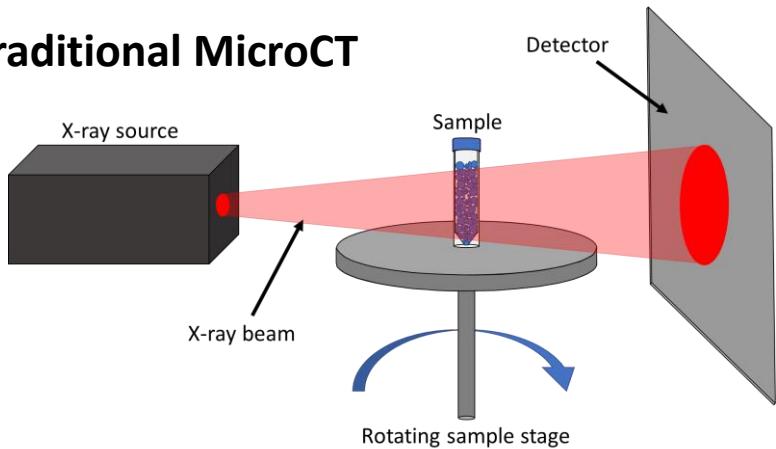
Imaging Modalities - XRM: X-Ray Microscopy

Non-destructive tomography

Family of Computed Tomography Techniques

- Medical CT
- Traditional MicroCT
- Advanced MicroCT | XRM

Traditional MicroCT



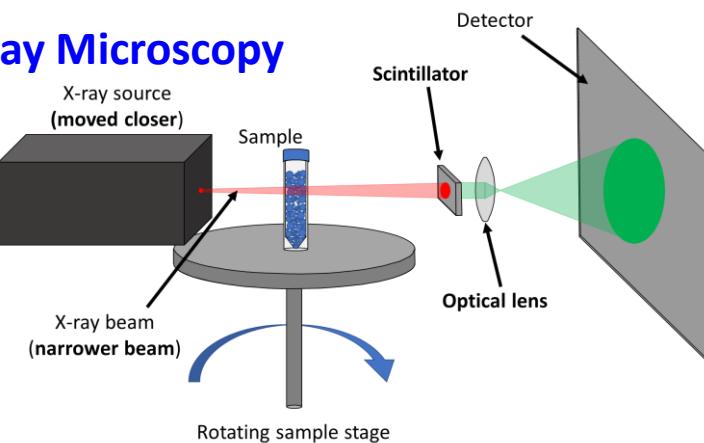
Advantages of XRM over traditional X-ray MicroCT:

- Local tomography at distance
- One order of magnitude increase in resolution

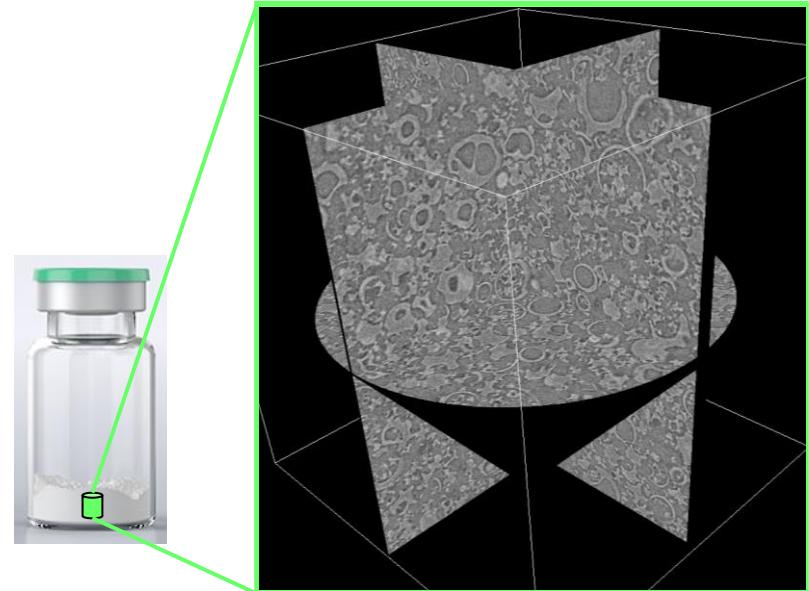
XRM Resolution

- Large sample, 5-50 μm
- Small sample, 0.34-5 μm

X-ray Microscopy



3D movie of a spray dried particle x-ray microscopy scan



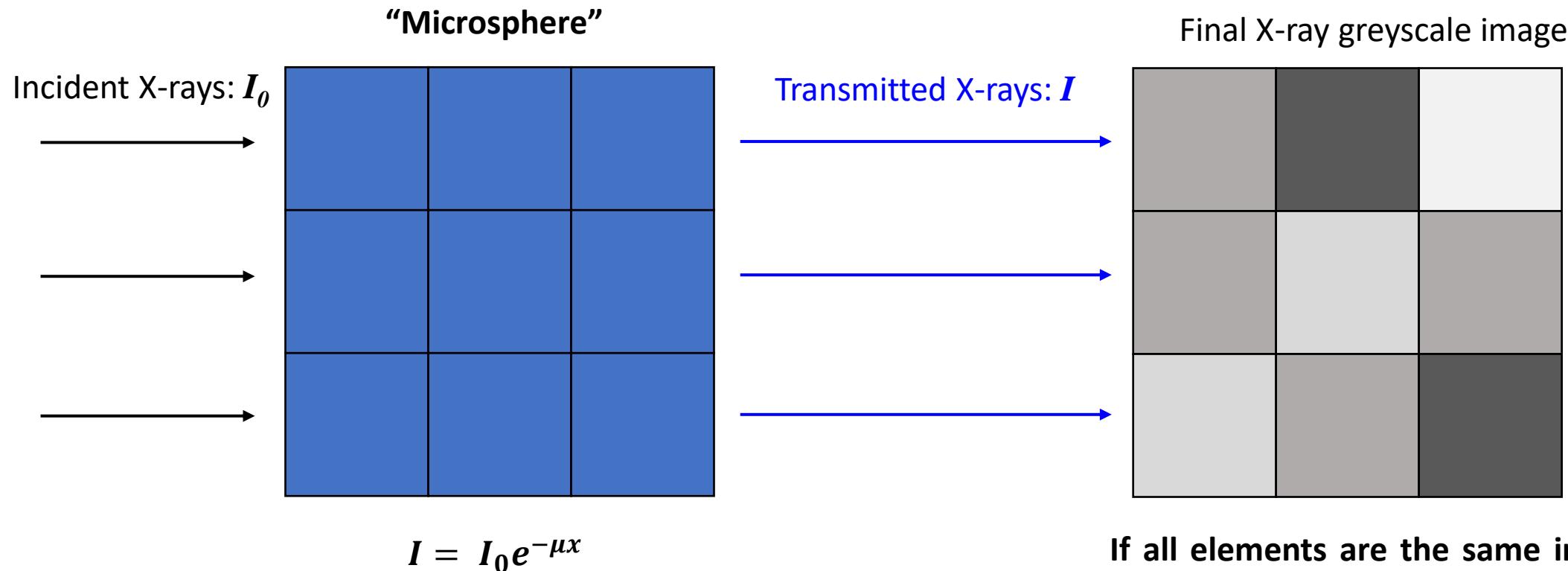
CONTROLLED RELEASE SOCIETY

CRS 2023 ANNUAL MEETING & EXPOSITION

JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE

XRM signal/pixel intensity is dependent on a material's microstructure

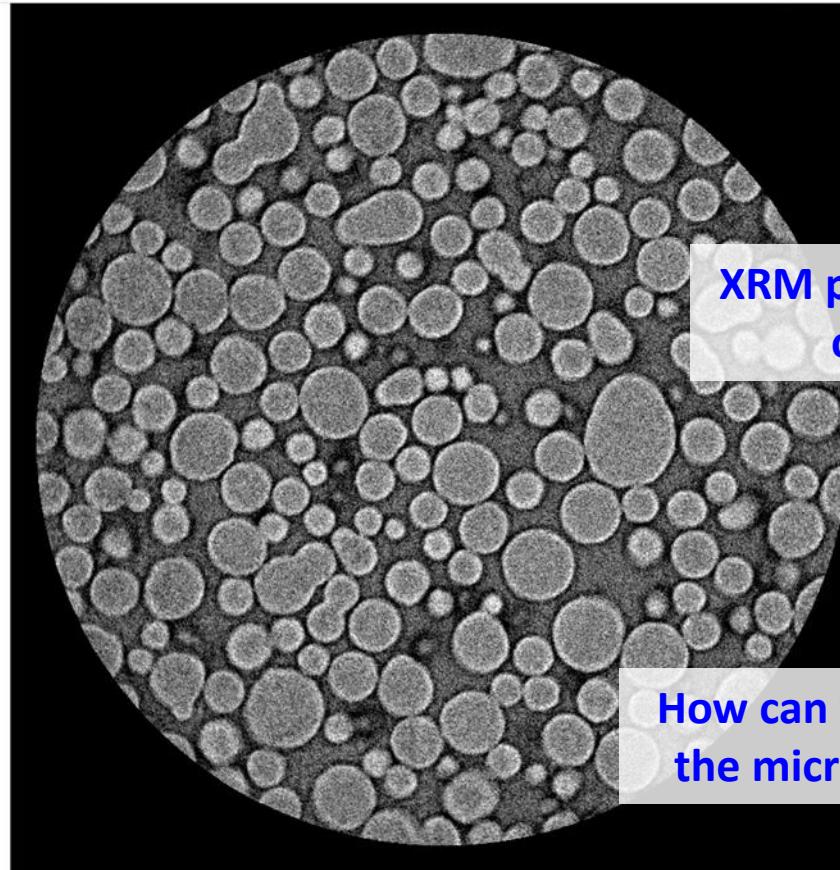


If all elements are the same in each pixel, then the pixel intensity will be dependent only on the density of the material within that pixel

XRM allows for the imaging of a statistically representative amount of microspheres

D0001397: Lot C030621-FB
Slice 0000
02/28/2022 16:51

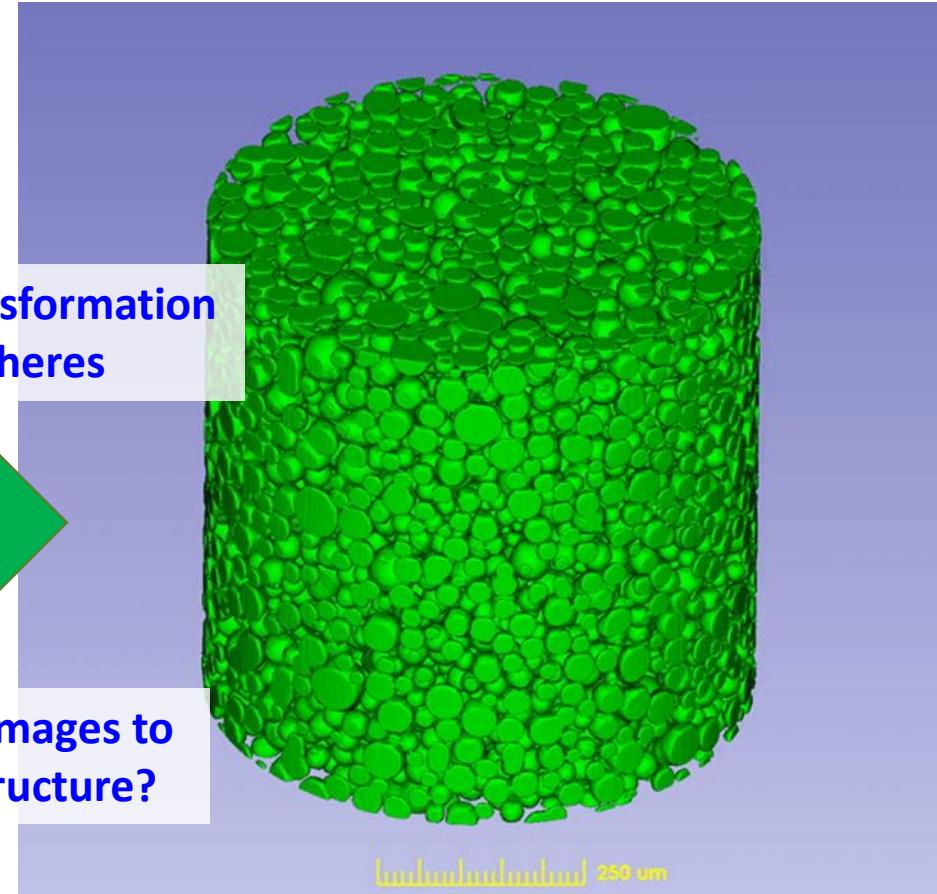
90.0um



XRM provides digital transformation of 1000s of microspheres



How can we correlate XRM images to the microsphere internal structure?



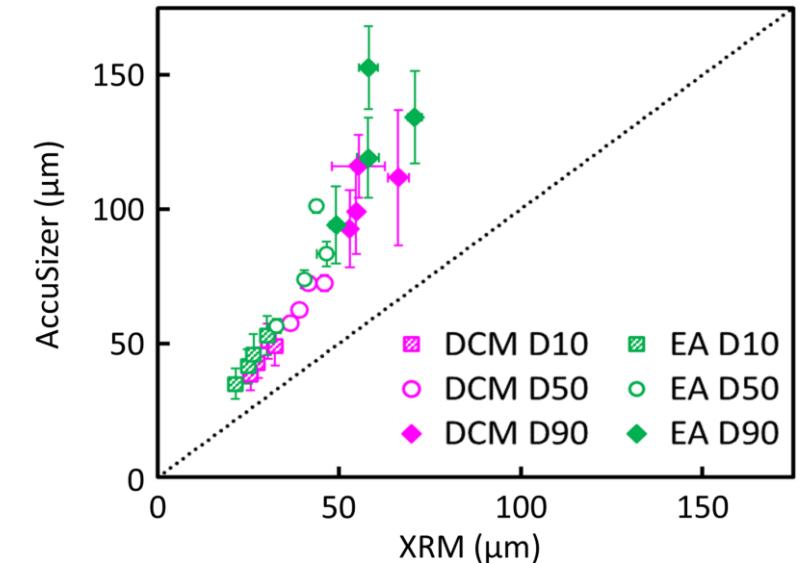
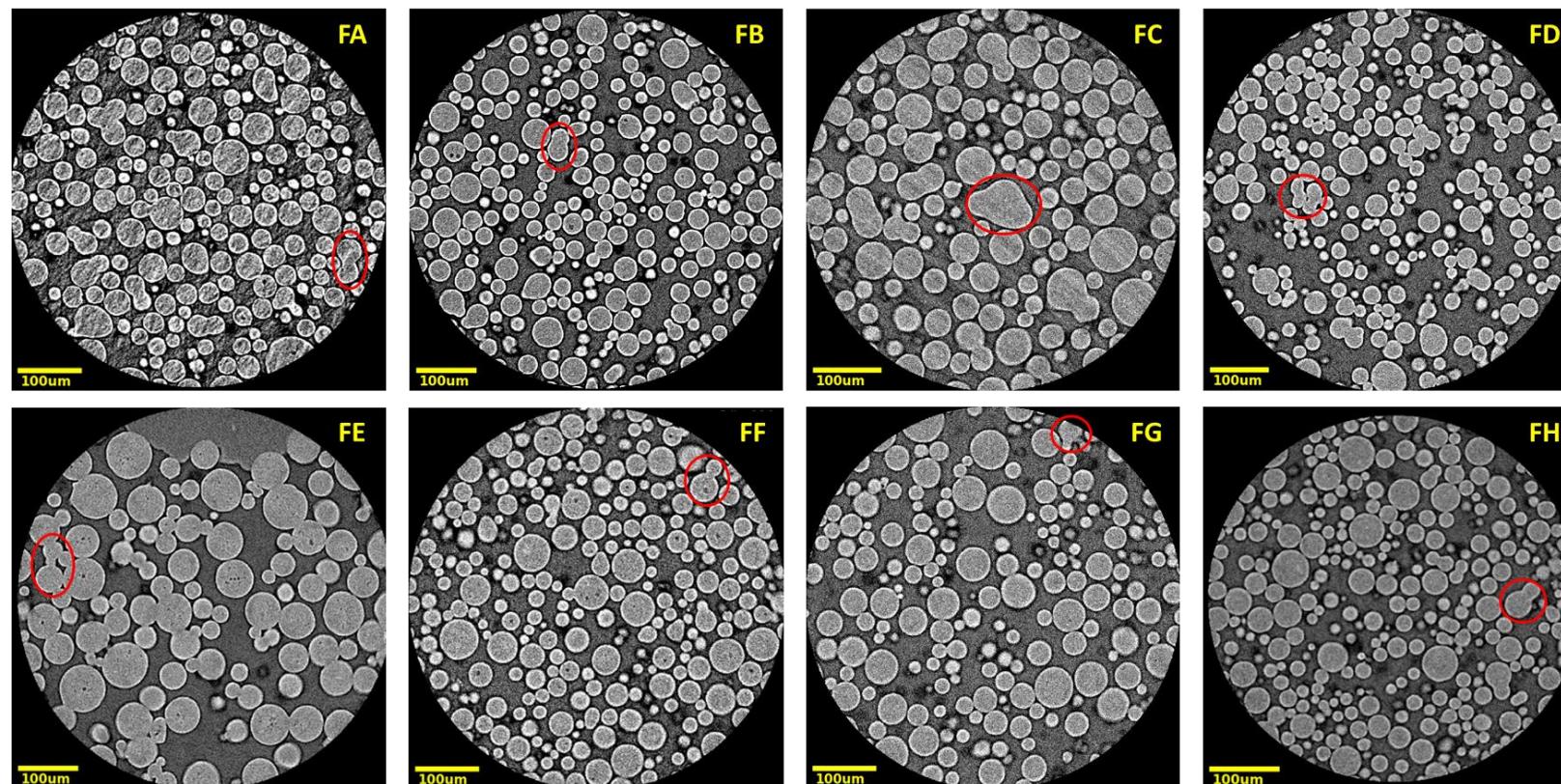
CONTROLLED RELEASE SOCIETY

CRS 2023 ANNUAL MEETING & EXPOSITION

JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

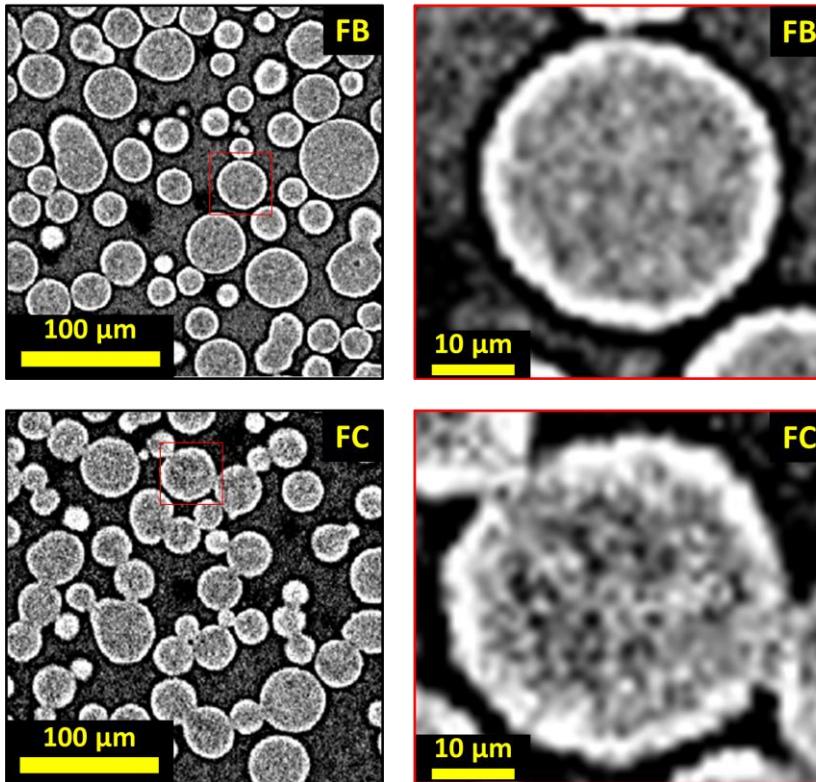
THE FUTURE OF DELIVERY SCIENCE

Initial XRM images show comparable microsphere morphologies and an alternative approach for PSD determination

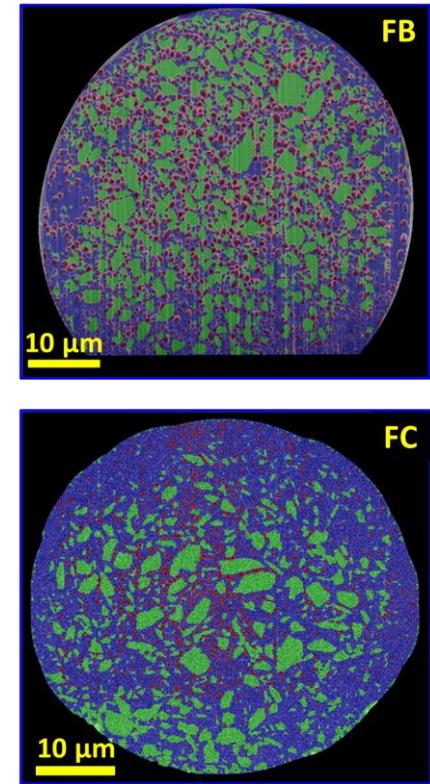
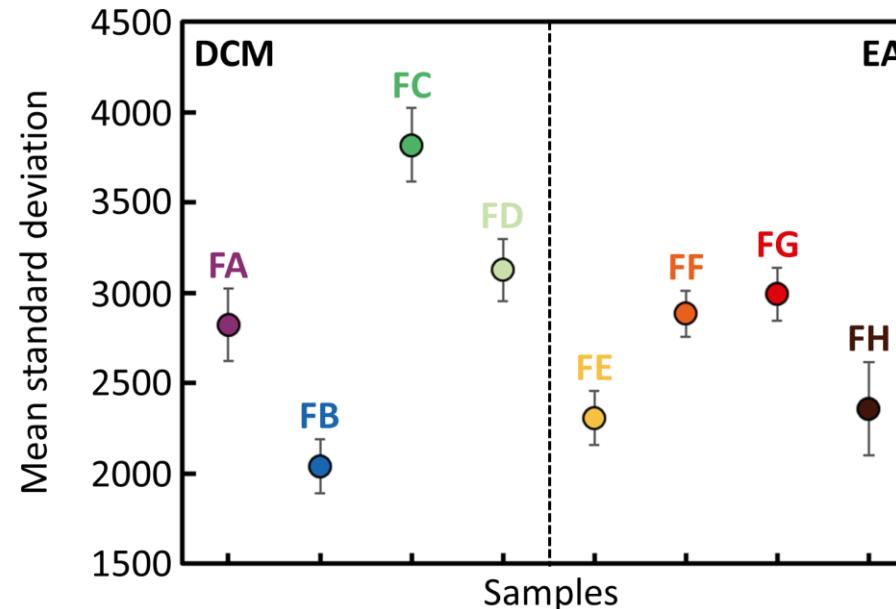


XRM allows for particle size distribution measurements that are less subject to agglomeration than in traditional light-based methods.

Different microsphere batches show distinct variations in pixel intensity that correspond to well to batches with confirmed structural differences

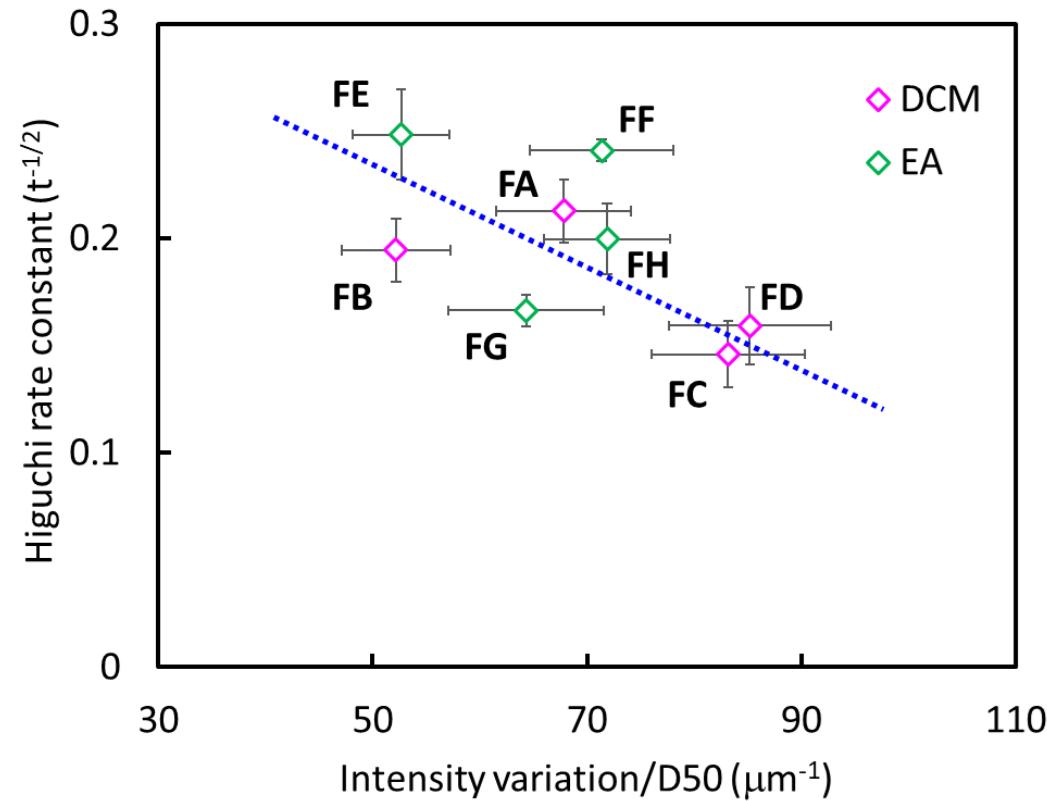
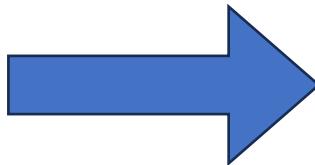
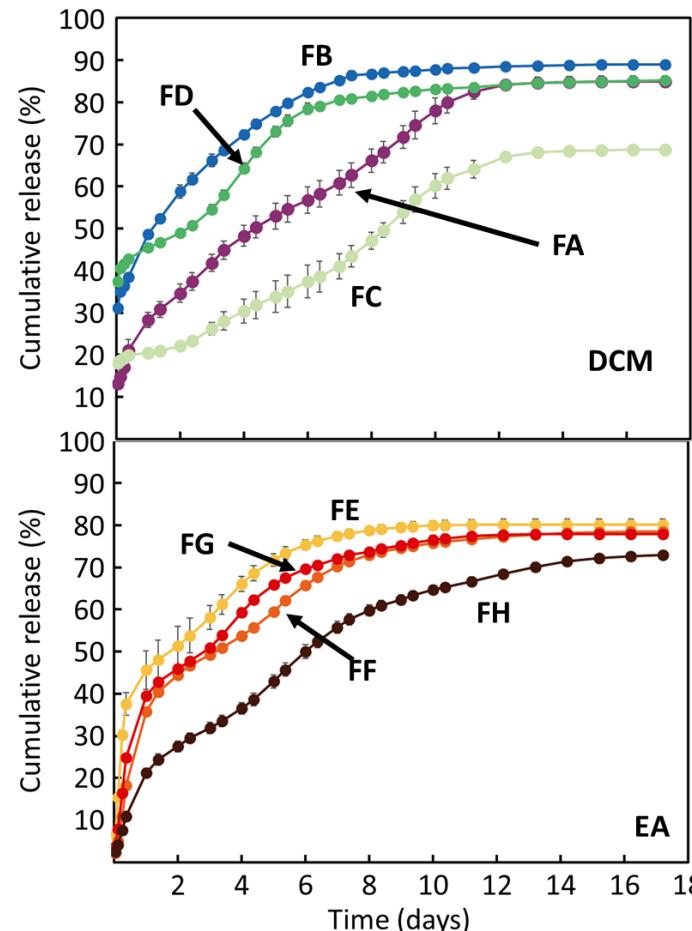


Variations in the microsphere pixel intensities per microsphere indicate variations in their structure



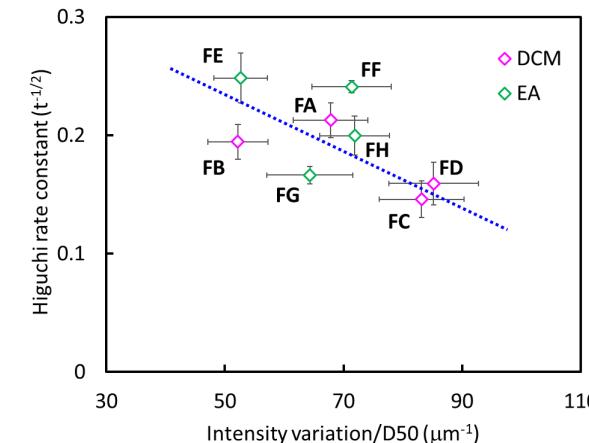
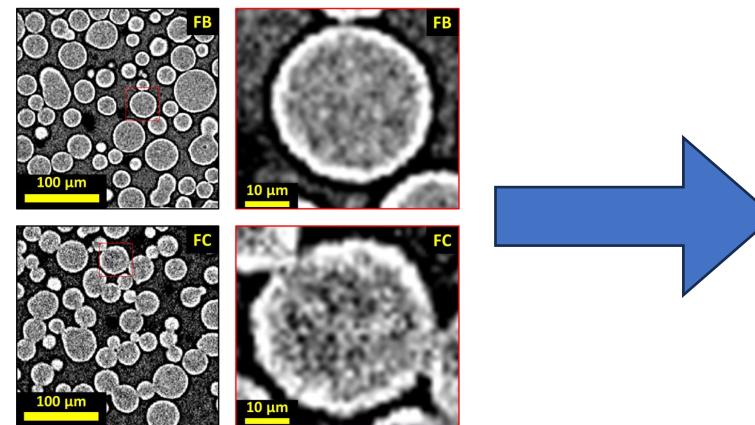
FIB-SEM characterized internal structure correlates to mean sphere intensity variations

XRM pixel variation is correlated with the Higuchi rate constant from the in vitro release rate indicating the impact of structure on release



Conclusions

- ❖ Microstructure characterization is a powerful tool to characterize and compare controlled release microspheres.
- ❖ XRM imaging combined with AI analytics can be leveraged to structurally characterize a statistically representative number of microsphere per batch, **including quantitative characterization of true material density (stop by poster 654 for details)**.
- ❖ Structural variations between microsphere batches as characterized via XRM can be correlated to downstream *in vitro* release performance.



Acknowledgements

BAA Contract xxx



DigiM Team
Burgess Lab
FDA Office of Generic Drugs



CONTROLLED RELEASE SOCIETY

CRS 2023 ANNUAL MEETING & EXPOSITION

JULY 24-28, 2023 **Paris Hotel** » **Las Vegas, NV, USA**

THE FUTURE OF DELIVERY SCIENCE