New Developments in Characterization and Process Scale Up

Andrew Clark PhD

CONTROLLED RELEASE SOCIETY
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

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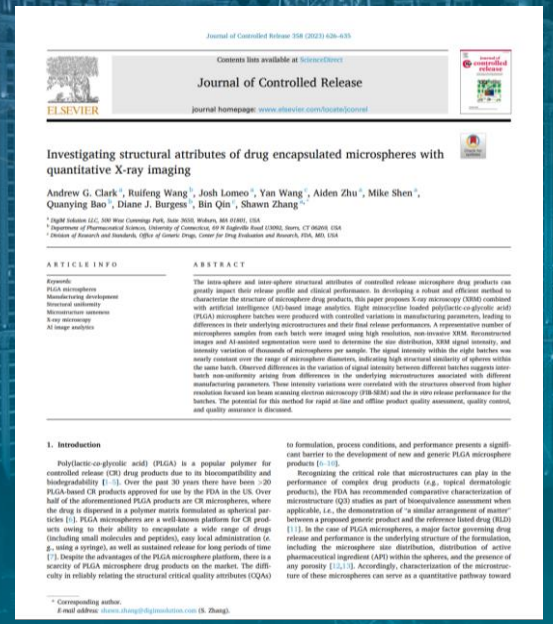
UCONN
UNIVERSITY OF CONNECTICUT

Digi M™

FDA

Booth 311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Investigating structural attributes of drug encapsulated microspheres with quantitative X-ray imaging

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ARTICLE INFO

ABSTRACT

1. Introduction

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*
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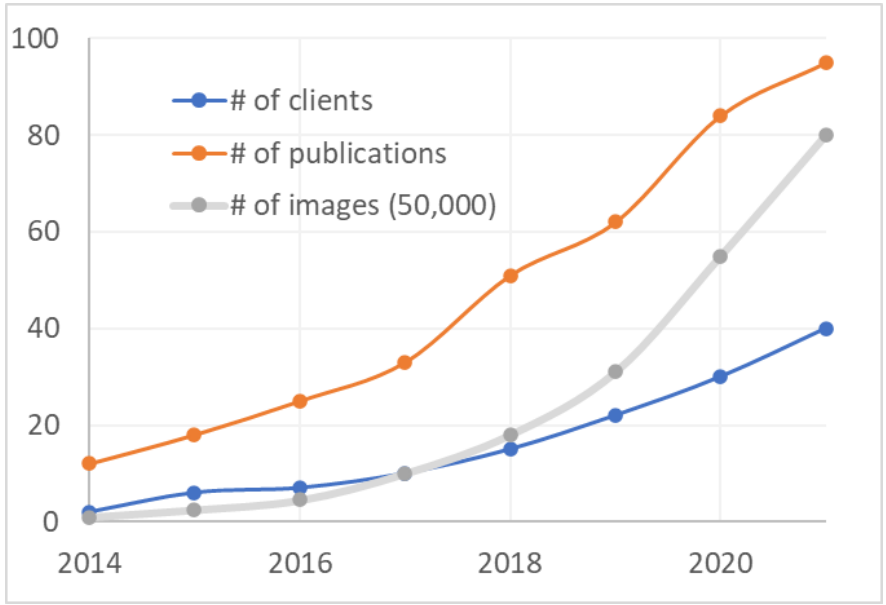
THE FUTURE OF DELIVERY SCIENCE

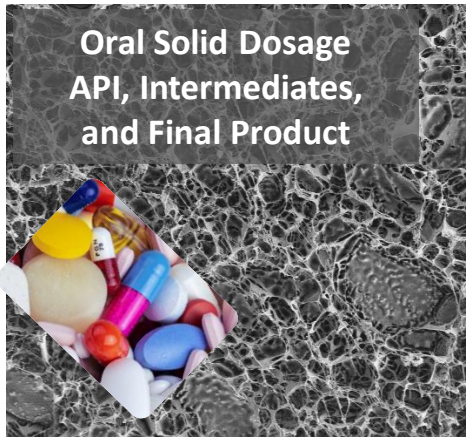
What does DigiM™ do?

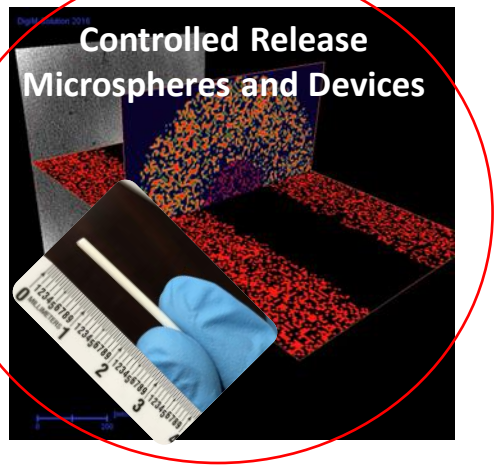
Technology leader for characterization-based solutions in drug development

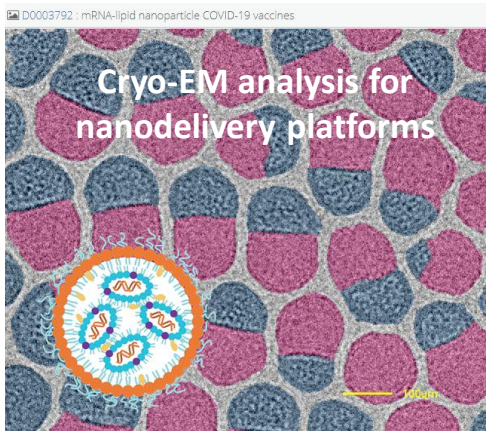


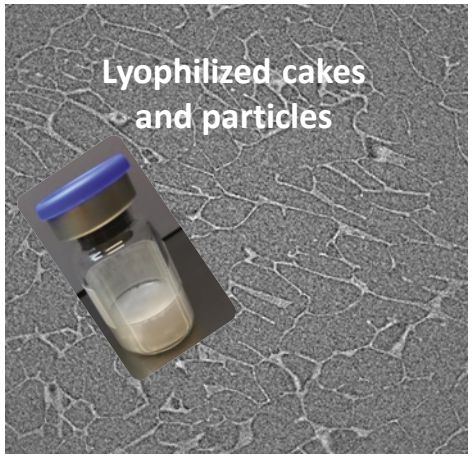
- Founded in 2014
- HQ in Woburn, MA

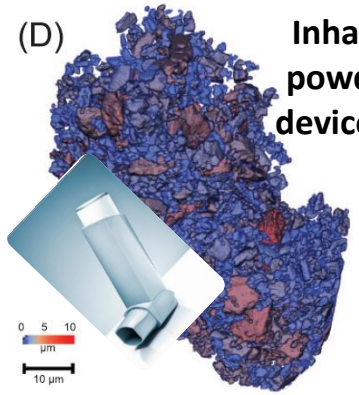
What does DigiM™ do?

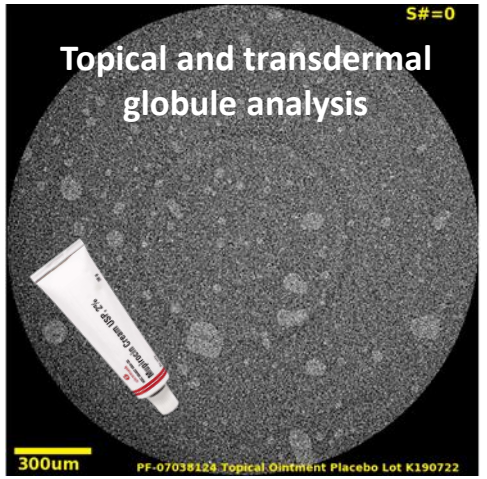






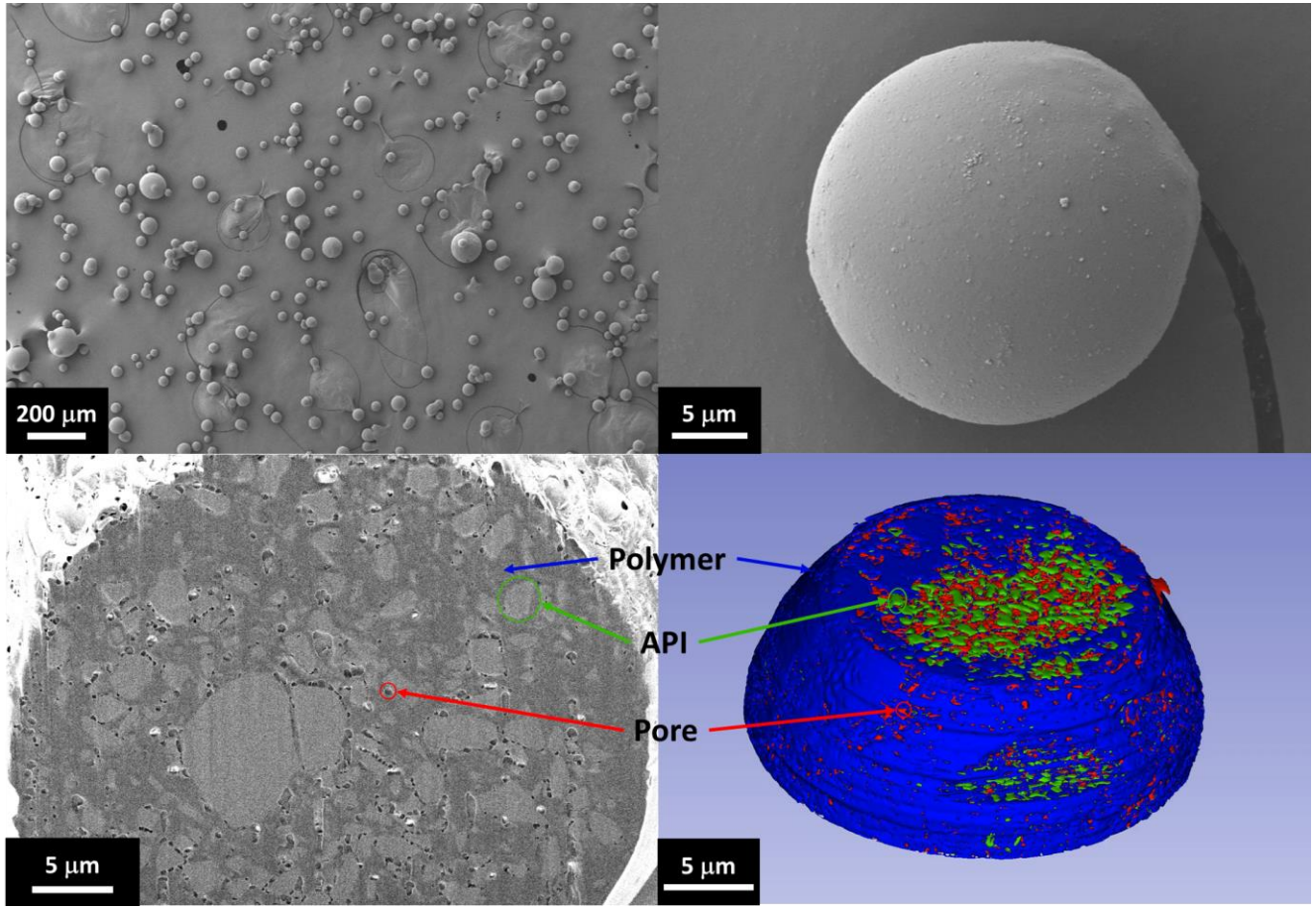






Stop by booth 311 and poster 654 for more info!

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.

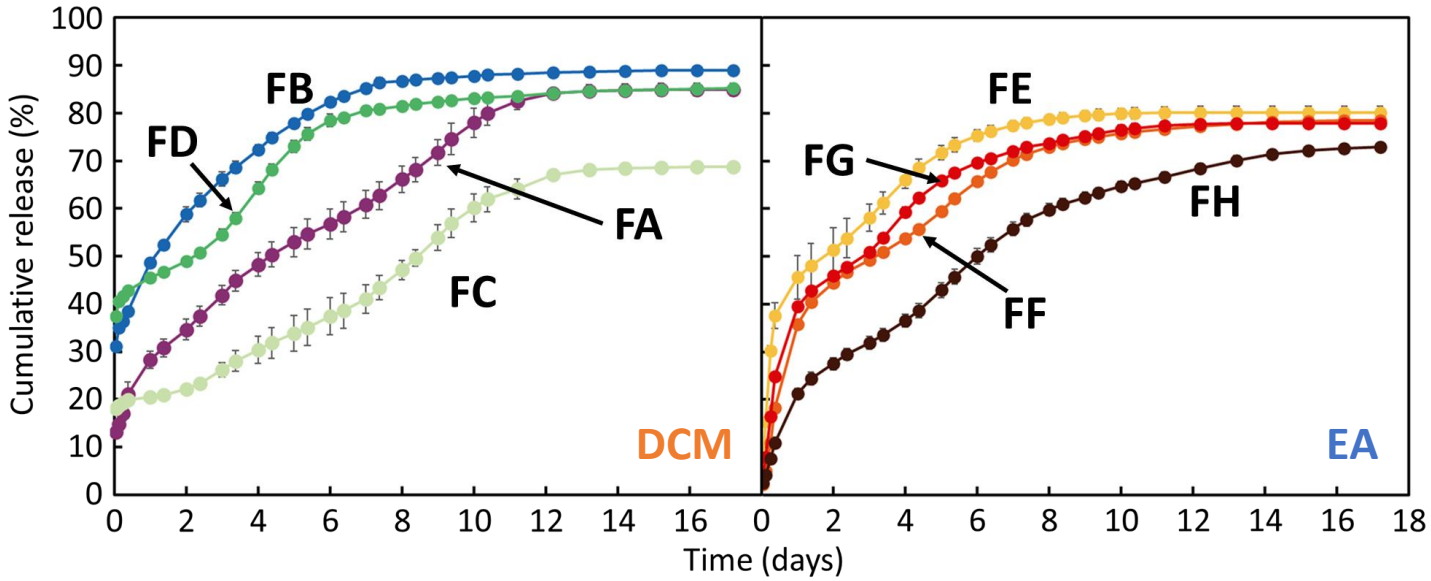
Microstructure characterization of the internal sphere structure CAN be correlated to final product performance.

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: Dichloromethane	Silicone oil / Stirring speed	350 cSt	1000 cSt
	350 rpm	Formulation A	Formulation B
	600 rpm	Formulation C	Formulation D

PLGA solvent: Ethyl Acetate	Silicone oil / Stirring speed	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

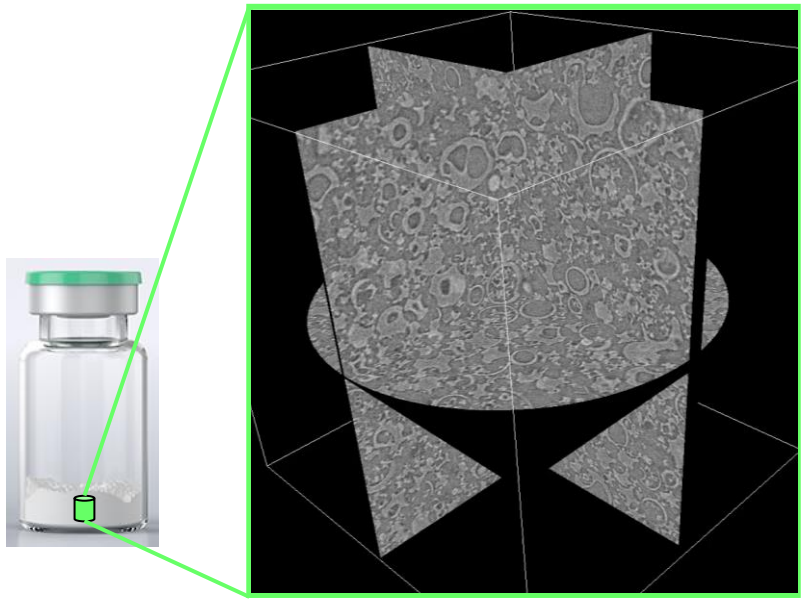
- Medical CT
- Traditional MicroCT
- Advanced MicroCT | XRM

Advantages of XRM over traditional X-ray MicroCT:

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

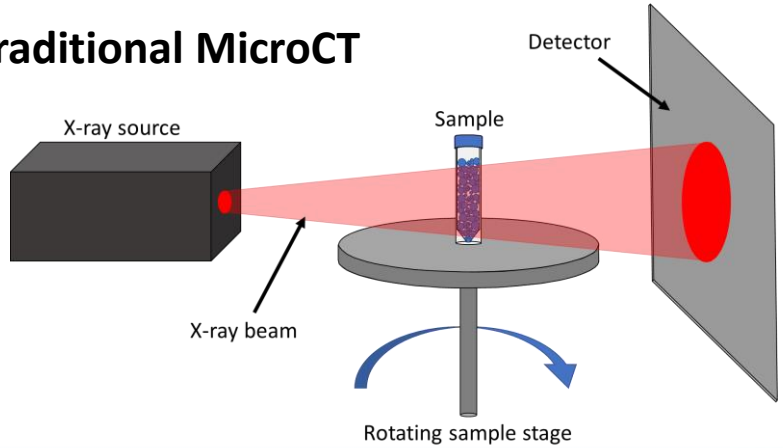
XRM Resolution

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

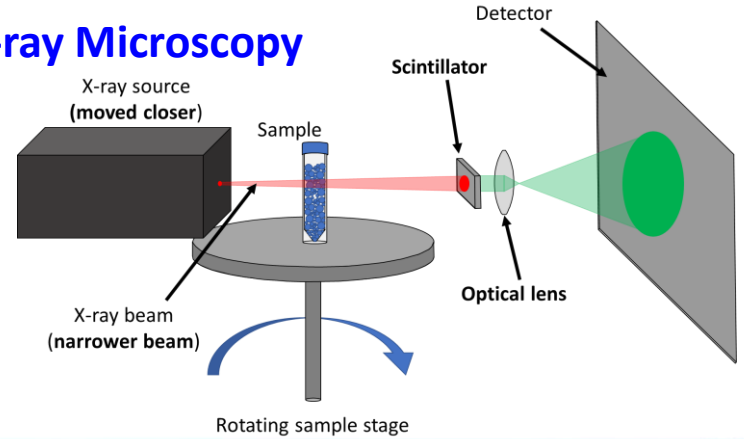


3D movie of a spray dried particle x-ray microscopy scan

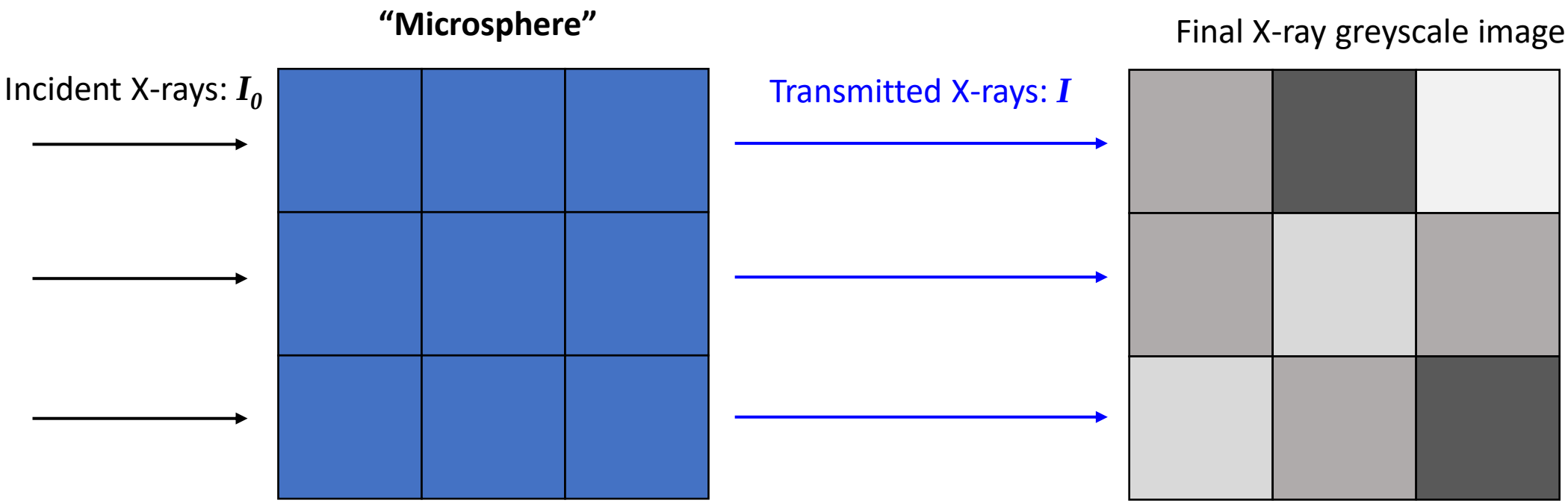
Traditional MicroCT



X-ray Microscopy



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

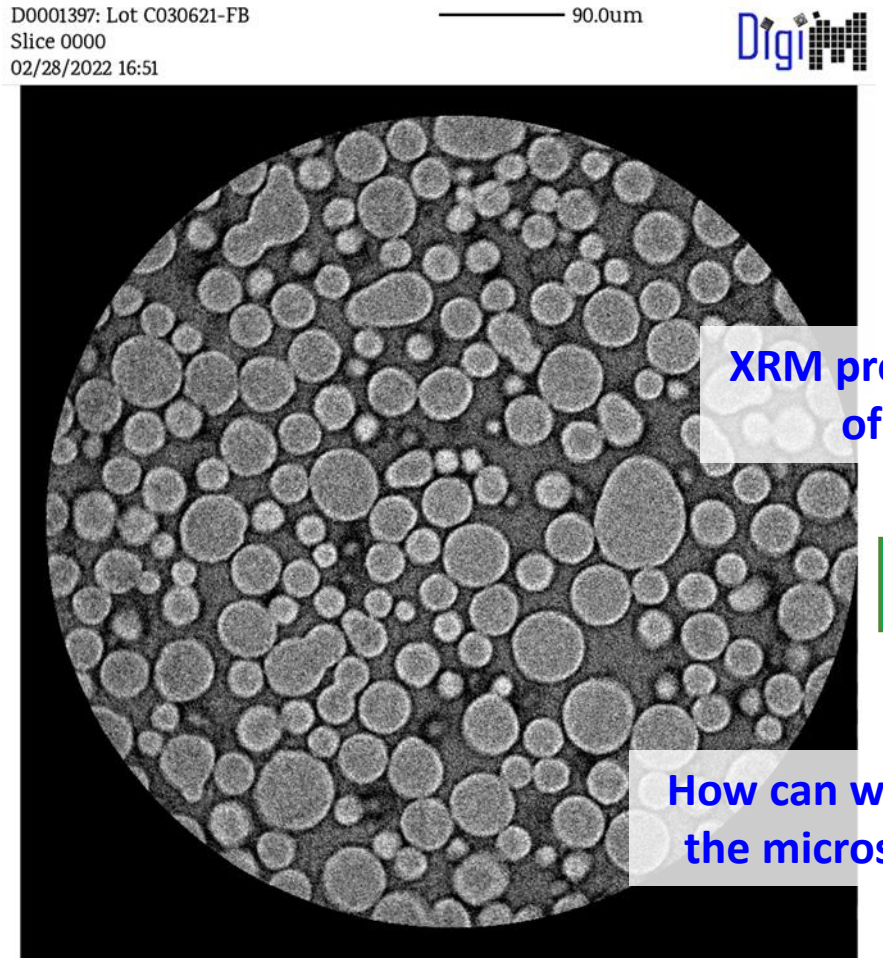


$$I = I_0 e^{-\mu x}$$

μ = attenuation coefficient, dependent on atomic number and number of absorbers
x = optical path length (constant in a CT experiment due to rotational symmetry)

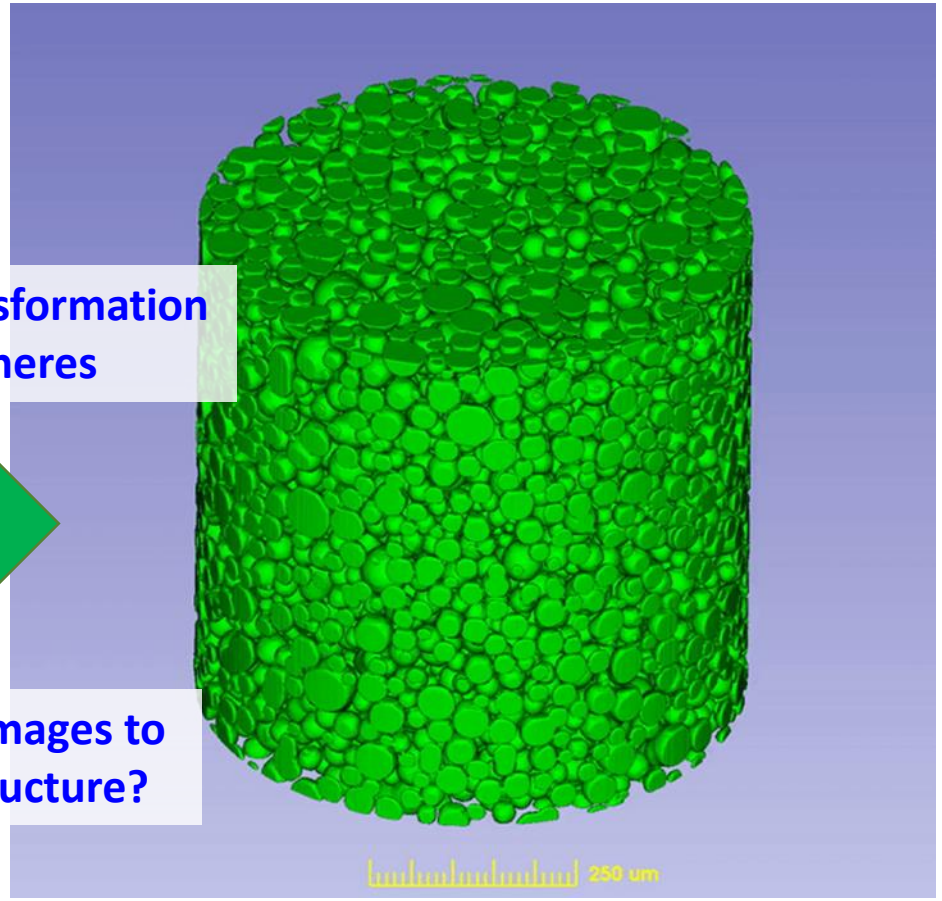
If all elements are the same in each pixel, then the pixel intensity will be dependent only on the density of the material within that pixel

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

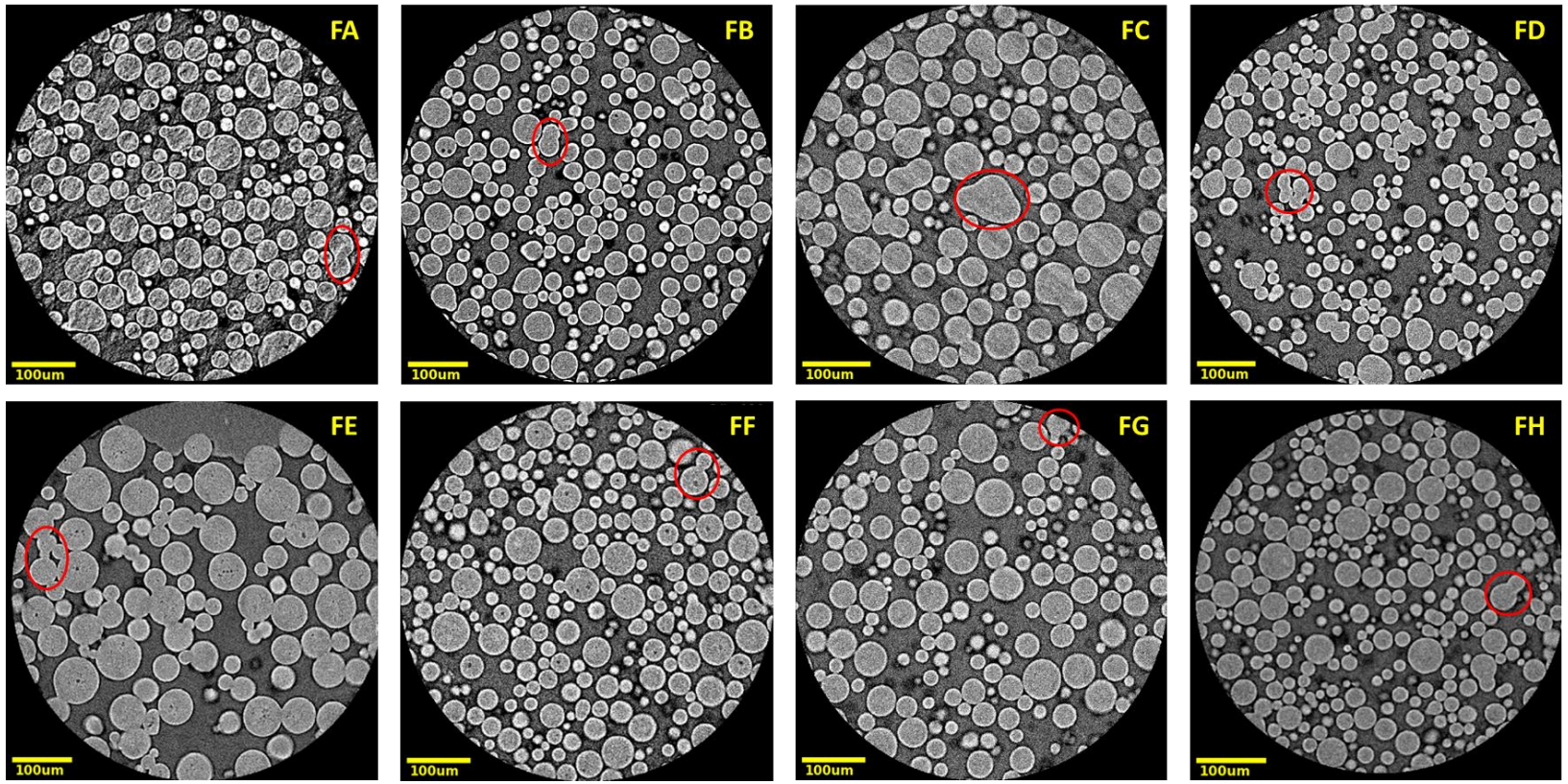


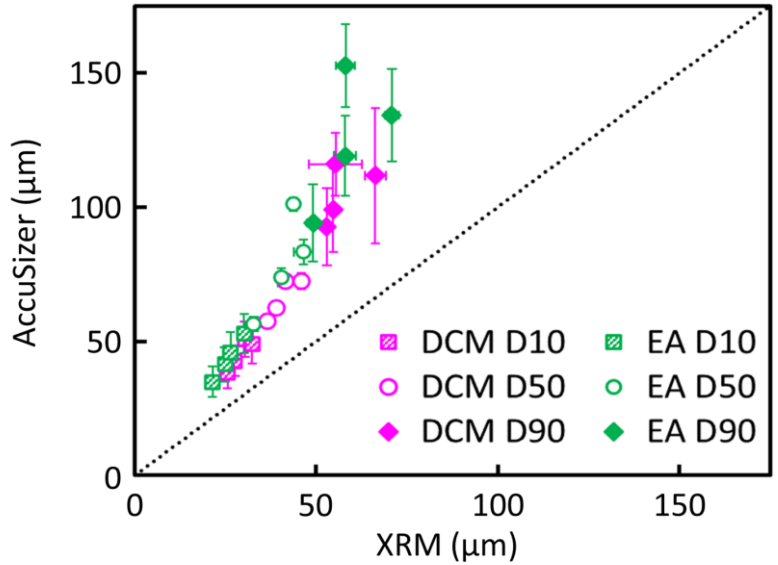
XRM provides digital transformation of 1000s of microspheres

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



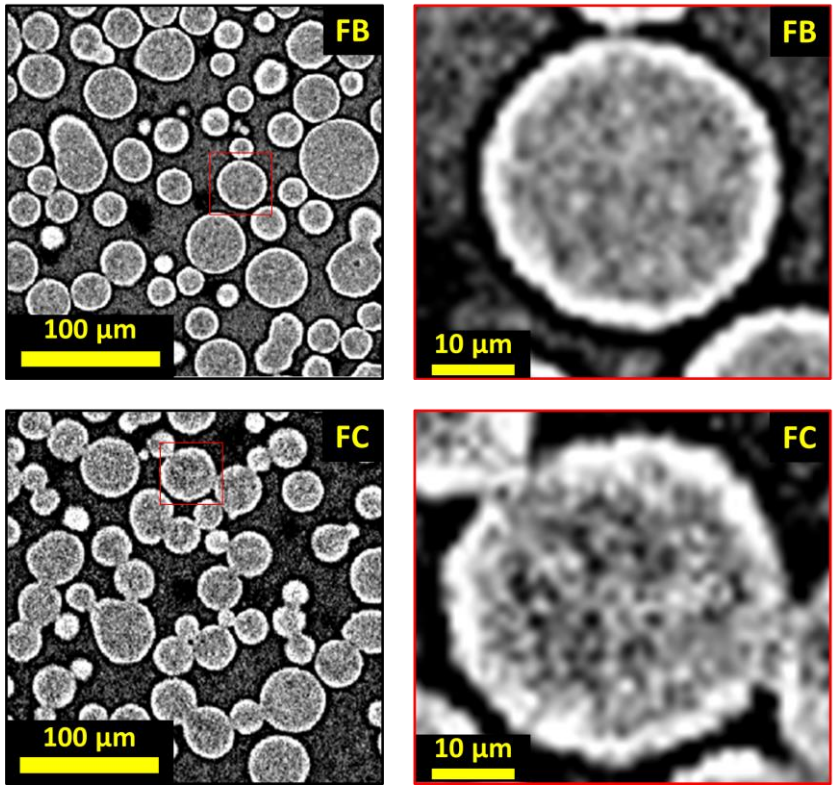
Initial XRM images show comparable microsphere morphologies and an alternative approach for PSD determination



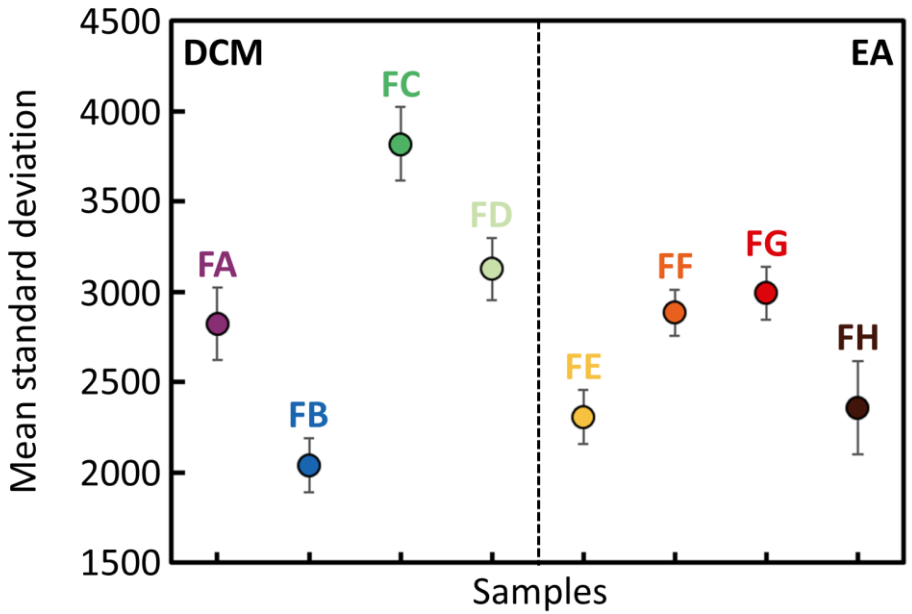


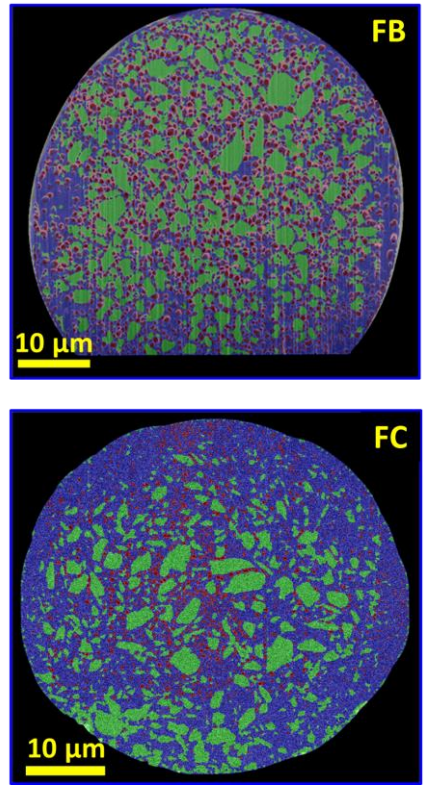
XRM allows for particle size distribution measurements that are less subject to agglomeration than in traditional light-based methods.

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



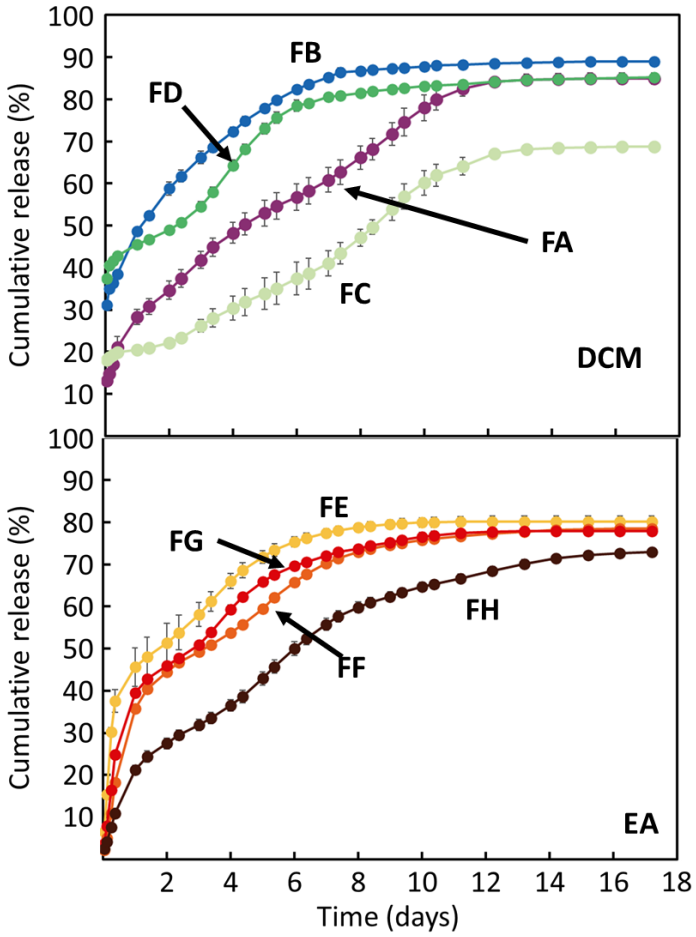
Variations in the microsphere pixel intensities per microsphere indicate variations in their structure

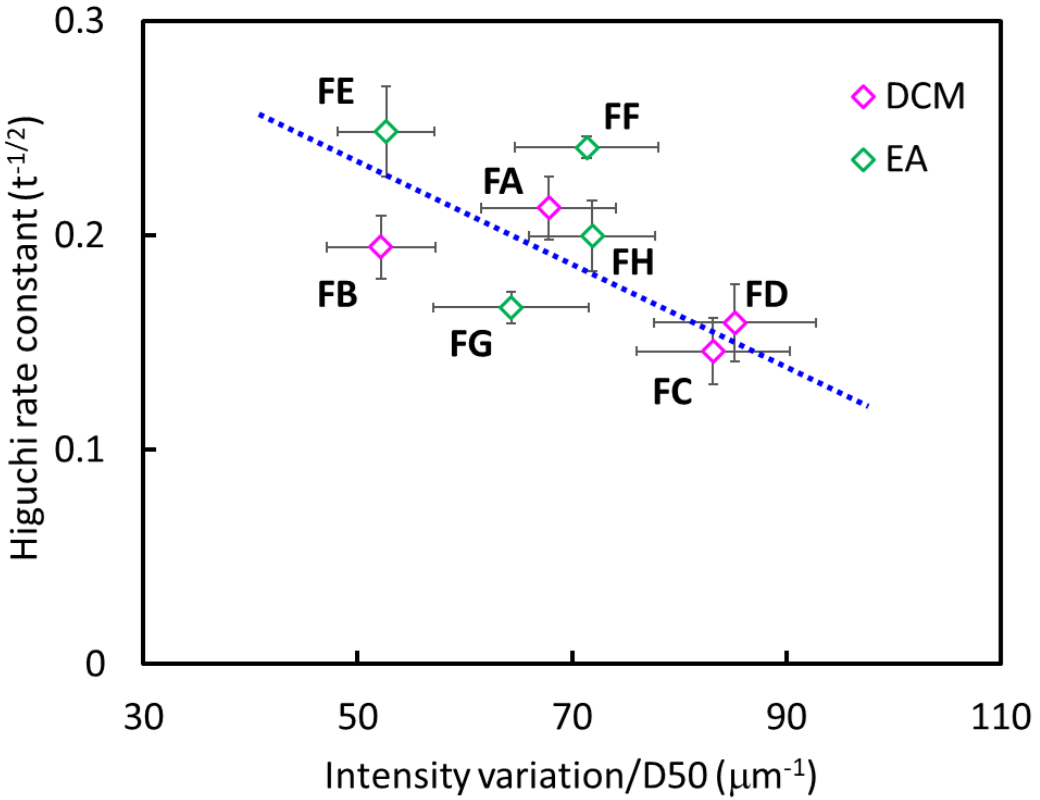




FIB-SEM characterized internal structure correlates to mean sphere intensity variations

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



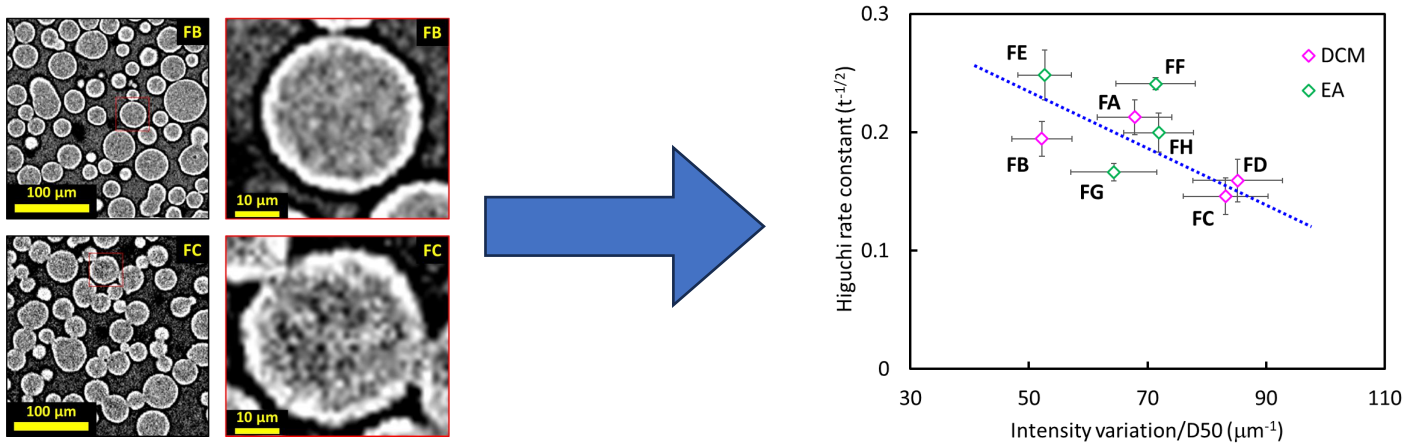


Conclusions

- 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 down stream *in vitro* release performance.



Acknowledgements

BAA Contract xxx

DigiM Team
Burgess Lab
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