Advanced Imaging and Data Analysis to Support Structure Similarity of Polymeric Formulations

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 2, Session 1: (Cutting Edge Science)

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Learning Objectives

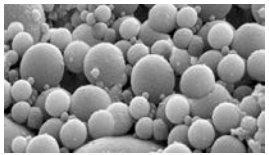
- Identify complex polymeric formulations
- Describe the role of structural analysis to support development of complex generic products: GDUFA research highlight

Overview

- Examples of complex polymeric formulations
- Imaging technologies and data analysis
  - "New" imaging technologies for pharmaceutical use
  - Advanced imaging data analysis
- Summary

Complex Polymeric Formulations

- Non-biodegradable
  - Intrauterine systems (IUS)
  - Intravaginal rings (IVR)
  - Solid implants
- Biodegradable
  - Microspheres
  - In situ forming implants
  - Solid implants



	IUS	IVR	Implant	Microspheres
Generic ?	N	Y	N	N

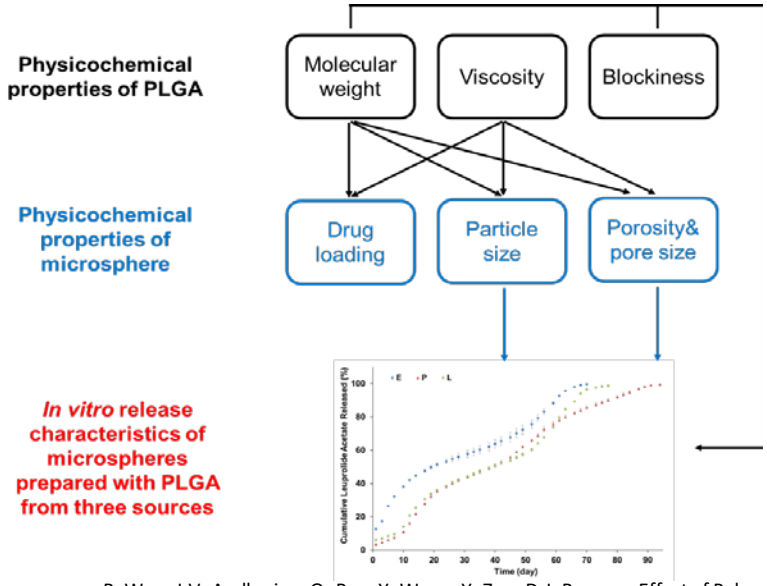
Why is generic development of complex polymeric formulations challenging?

Formulation Composition

Example: Poly (lactide-co-glycolide) (PLGA) microspheres

Remaining scientific gap:

- What are key polymer properties to ensure similar PLGA polymers produce formulations with comparable performance?



Observations:

- PLGA polymers from three different sources with similar inherent viscosity, monomer (lactide/glycolide) ratio, and end group as per the manufacturers' certificate of analysis (COA)

- ✓ Differences in physicochemical properties (such as particle size, porosity and average pore diameter)
- ✓ *Difference in vitro* drug release characteristics (burst effect and release rate).

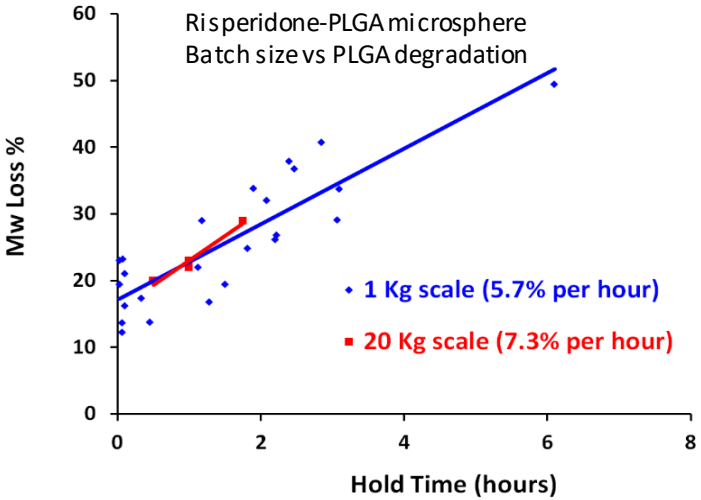
B. Wan, J.V. Andhariya, Q. Bao, Y. Wang, Y. Zou, D.J. Burgess, Effect of Polymer Source on *In Vitro* Drug Release from PLGA Microspheres, *International Journal of Pharmaceutics* 607 (2021) 120907: https://doi.org/10.1016/j.ijpharm.2021.120907

Manufacturing Factors

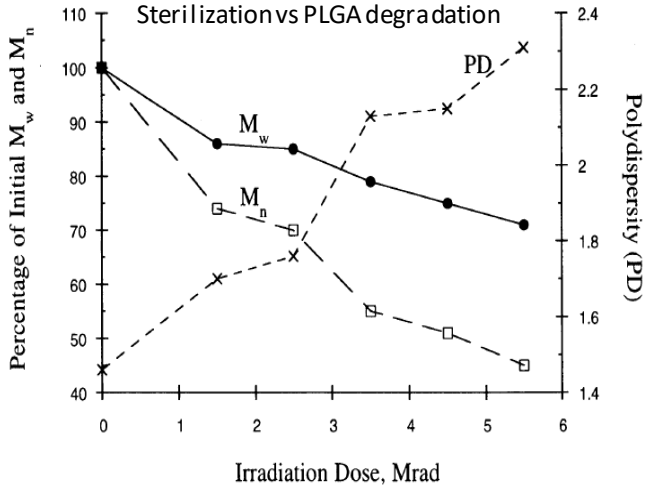
Example: Poly (lactide-co-glycolide) (PLGA) microspheres

Remaining scientific gap:

- What is the raw PLGA polymer used in the reference product?
- What are key manufacturing parameters and how do they impact product performance?
- How to scale up without altering formulation characteristics?



Alkermes, US 6,264,987 B1, 2001



Angela Hausberger, Pharm Res 1995, 12(6): 851

Bioequivalence Approaches

Example: Mirena (Levonorgestrel intrauterine system/device)

Remaining scientific gap:

- What is the drug release mechanism?
- Can accelerated in vitro drug release corelate to real-time in vitro drug release, thus be sufficient to ensure bioequivalence?

Dosage Form; Route: Intrauterine Device; intrauterine

Strength: 52 mg

Recommended Studies: Two studies: in vitro and in vivo/ex vivo

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

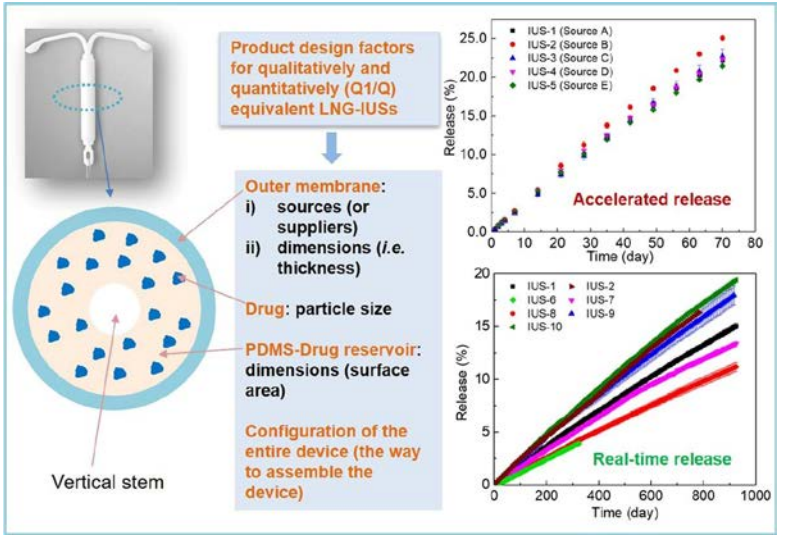
- Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
- Equivalent physicochemical and mechanical characteristics including 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) Degree of crosslinking of poly(dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane; 3) Mechanical properties of the drug reservoir and the drug rate controlling membrane; 4) Appearance, memory, mechanical properties of the T-body; and 5) Breaking force of the removal thread comparable to the Reference Standard (RS).
- Same dimensions with respect to each component as the RS.

A. Comparative in vitro drug release

Acceptable comparative in vitro drug release of levonorgestrel from the test and RS products throughout the intended period of product use (5 years). Any accelerated dissolution method that correlates to the real-time drug release behavior may be submitted for the Agency's consideration through either a controlled correspondence or as part of a pre-ANDA meeting request.

B. In vivo/ex vivo clinical study

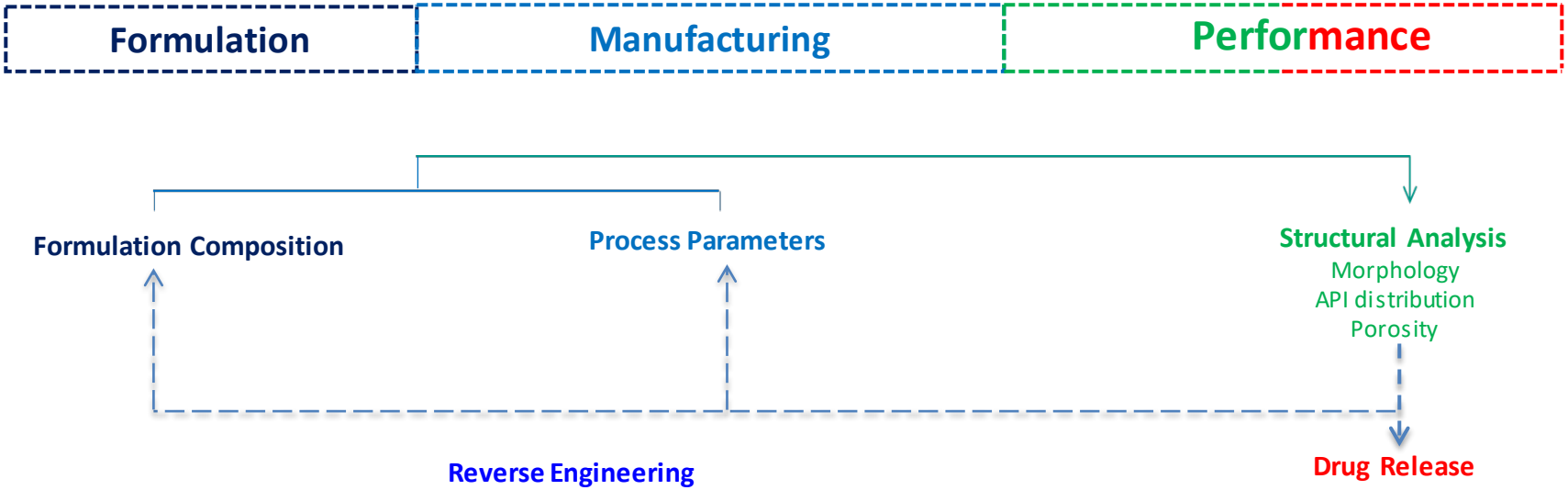
Type of study: In vivo/ex vivo study of residual levonorgestrel and serum levonorgestrel
Design: One year, single-dose, randomized, parallel in vivo study
Strength: 52 mg
Subjects: Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive. The enrolled population should include a sufficient number of nulliparous women.



Q. Bao, Y. Wang, Y. Zou, S. Choi, D.J. Burgess, Effect of Polymer Source on *In Vitro* Drug Release from PLGA Microspheres, *International Journal of Pharmaceutics* 578 (2021) 119135: https://doi.org/10.1016/j.ijpharm.2020.119135

🤔 What is the role of structural analysis?

The Role of Structural Analysis



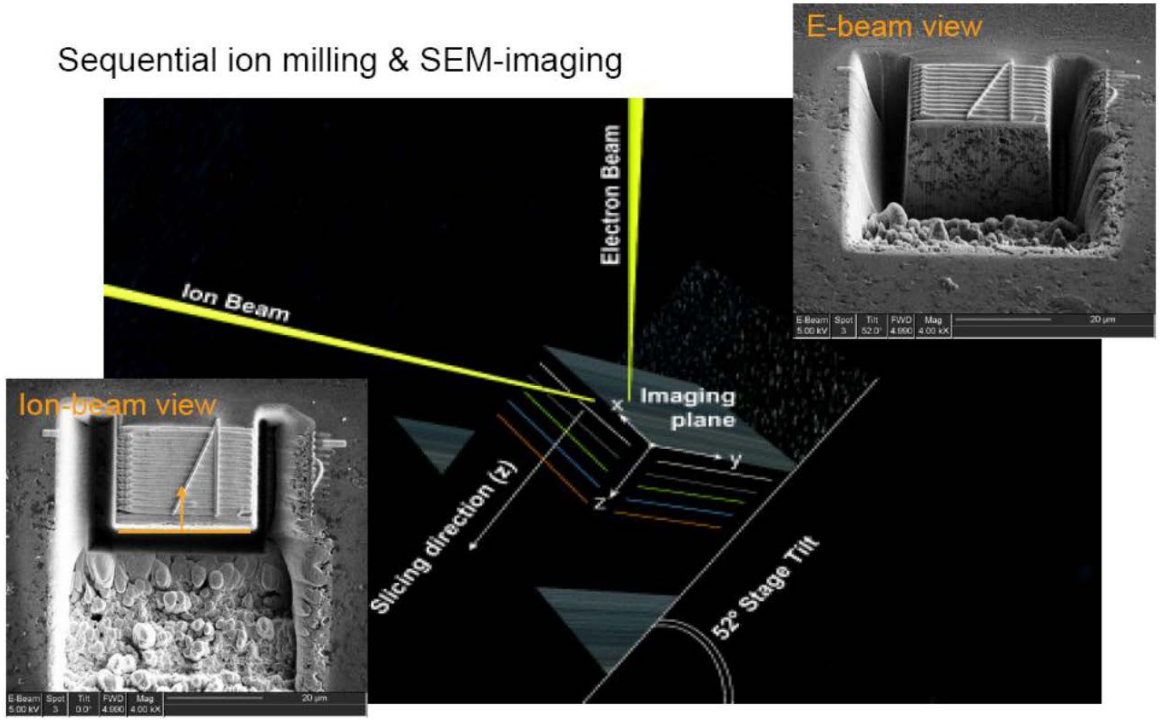
- Formulation composition and process parameters can affect structural characteristics of a formulation (i.e., morphology, API distribution, porosity), which in turn impacts drug release.
- Structural analysis can facilitate reverse engineering to trace manufacturing history and better understand drug release mechanism.

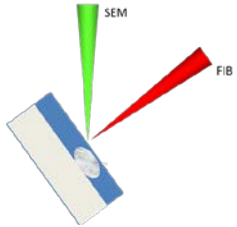
Imaging Tools

- Light Microscopy
- Electron Microscopy
  - Transmission Electron Microscopy (TEM)
  - Scanning Electron Microscopy (SEM)
    - Focused Ion Beam Scanning Electron Microscopy (FIB-SEM)
- Micro-Computed Tomography (MicroCT)
- X-Ray Microscopy (XRM)
- Near Infrared and Raman Spectroscopy
- Chemical Imaging
- …..

Advantages of FIB-SEM

Schematic diagram of FIB-SEM imaging station





- 3D images with superior z-axis resolution (down to 3nm)
- Image data coupled with modeling and computation tools

- ✓ Depth profile through the polymeric matrix
  - o API distribution
  - o Polymer domain
  - o Porosity

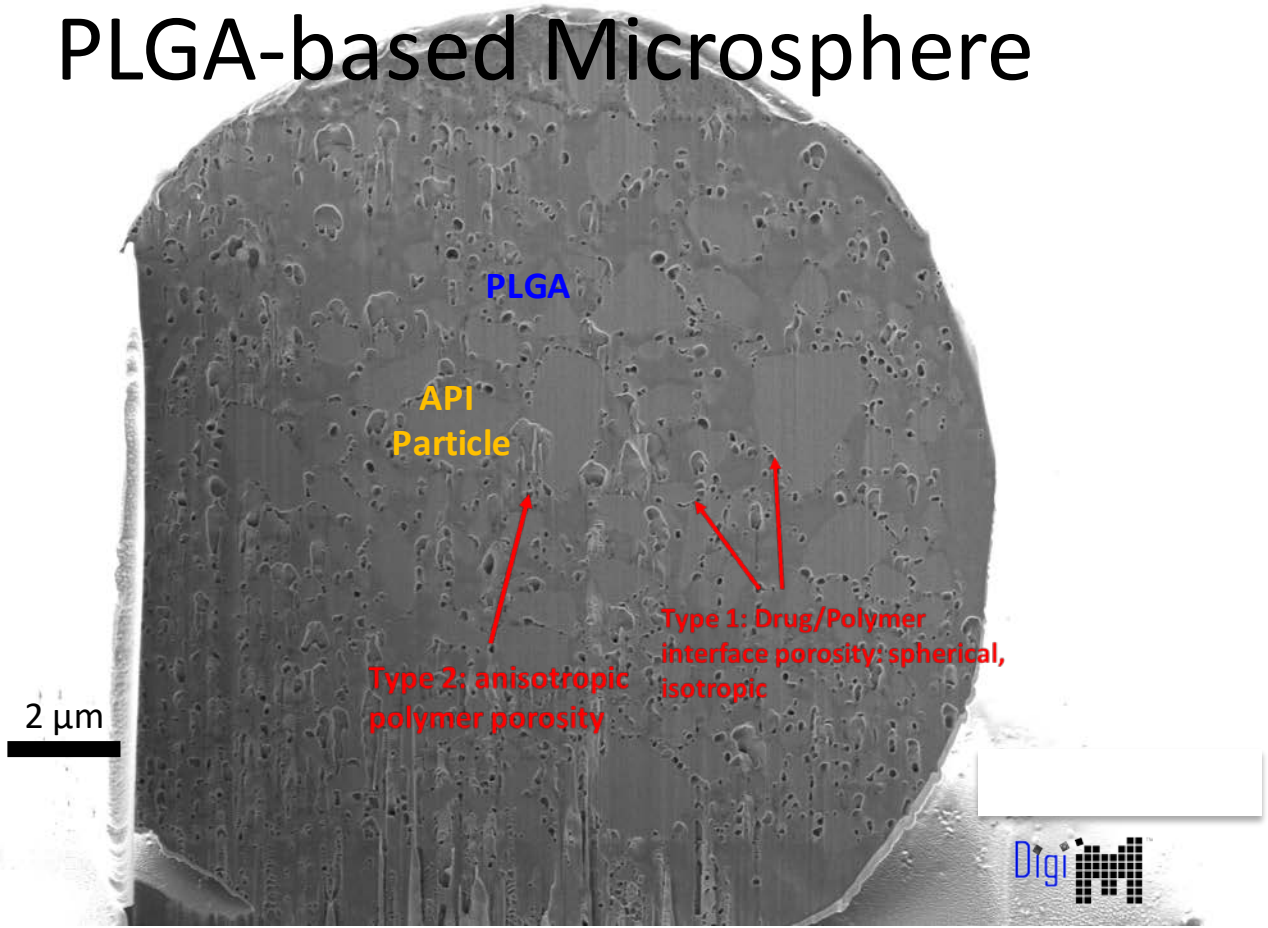
GDUFA Funded Research

- **Microstructure characterization with micro-imaging and image-based analytics: a new tool to characterize complex polymer-based long-acting drug products** (Contract #75F40119C10157)

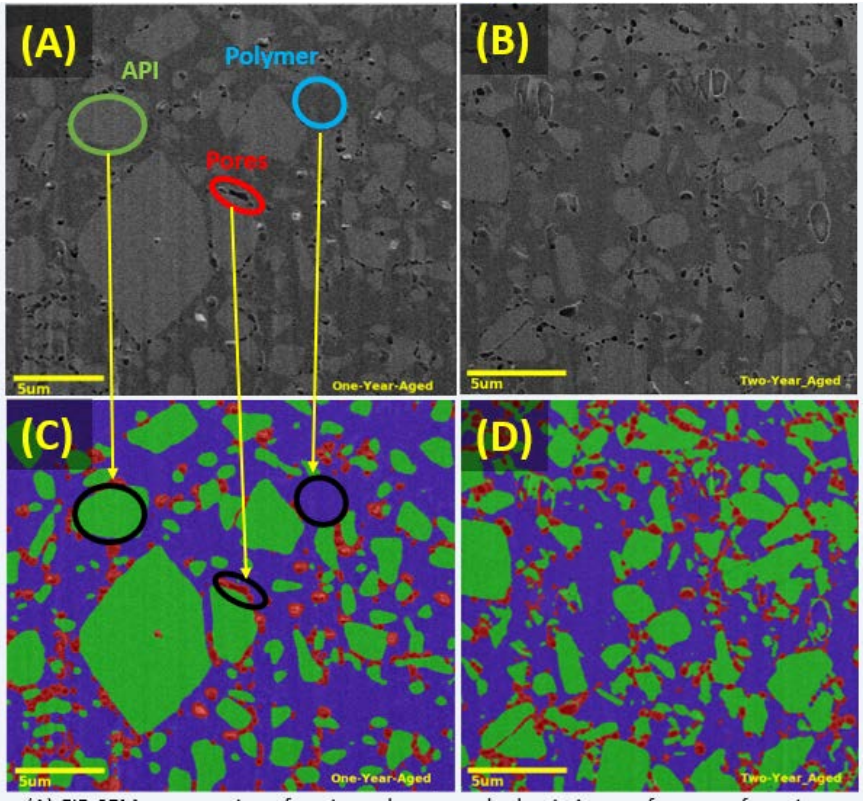
Main focuses:

- Improve understanding of the micro-scale physical and structural arrangement for two different types of long-acting complex drug products (i.e., IUS and poly (lactide-co-glycolide) (PLGA) microspheres).
- Determine the impact of manufacturing process on the physicochemical properties and in vitro release characteristics of PLGA microspheres.
- Develop an image-based model to predict the in vitro release characteristics of long-acting complex products.
- Establish correlations between the quantitative parameters of image-based microstructure and the in vitro release characteristics of the long-acting complex products.

Example FIB-SEM Cross Section of a PLGA-based Microsphere



FIB-SEM Sample Images of PLGA Microspheres



(A) FIB-SEM cross section of a microsphere sample that is 1 year after manufacturing.

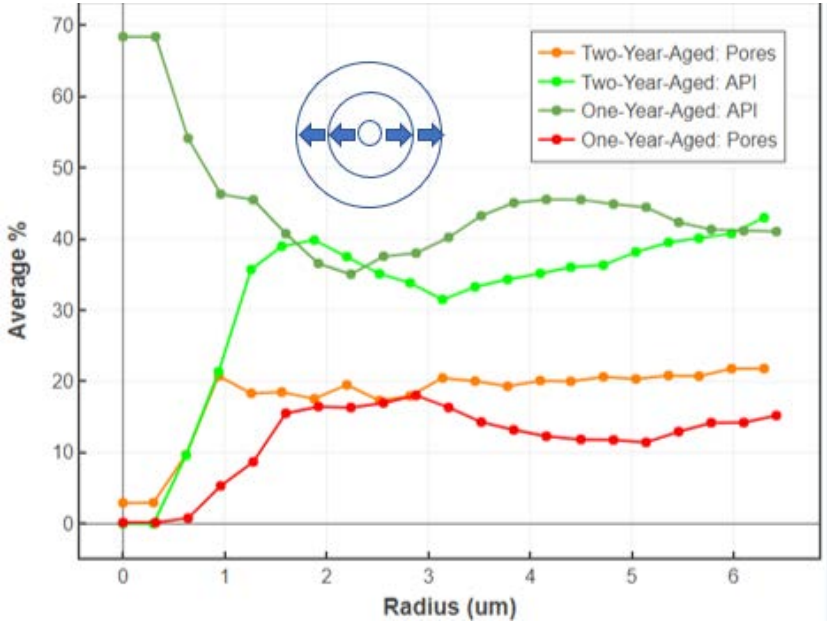
(B) FIB-SEM cross section of a microsphere sample that is 2 years after manufacturing.

(C) AI-based image segmentation of the FIB-SEM cross section of a microsphere sample that is 1 year after manufacturing. Green: API; Red: Pores; Blue: Polymer.

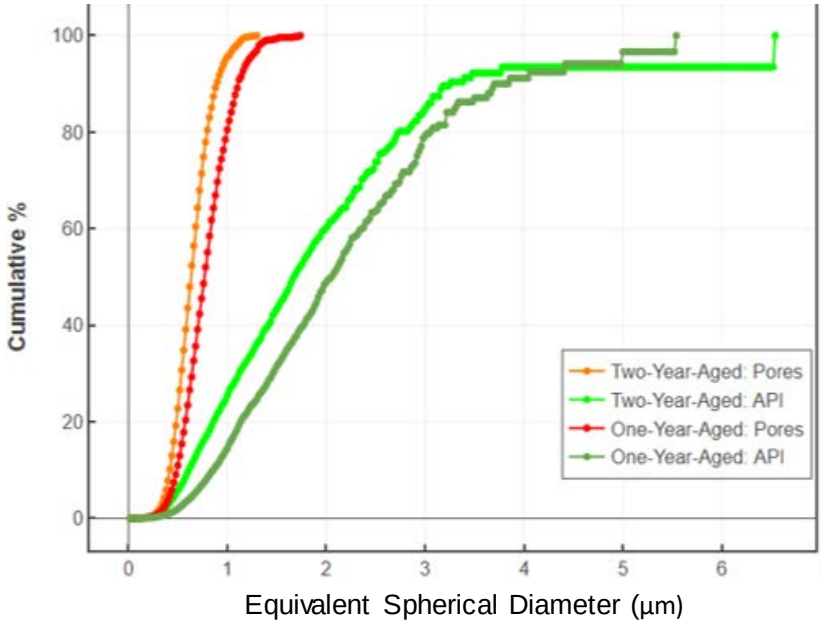
(D) AI-based image segmentation of the FIB-SEM cross section of a microsphere sample that is 2 years after manufacturing. Green: API; Red: Pores; Blue: Polymer.

M. Shen, et al., PLGA microsphere stability characterization using image-based key performance attributes and release prediction, poster, 2021 Controlled Release Society Annual Meeting and Exhibition

Quantitative Analysis of FIB-SEM Images of PLGA Microspheres



3D API and Porosity Spatial Uniformity

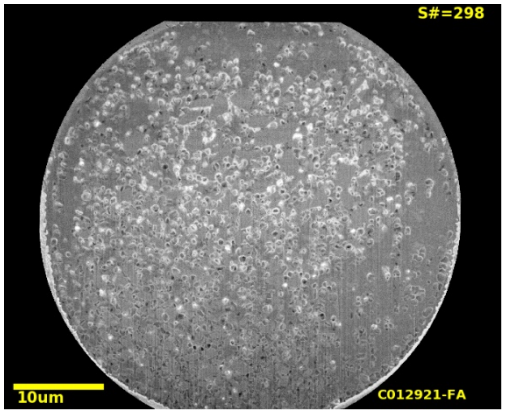


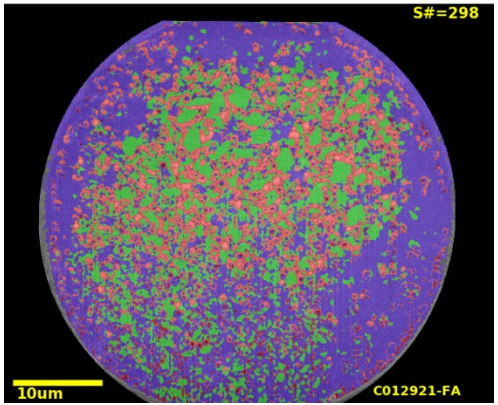
3D API and Pores Size Distribution

M. Shen, et al., PLGA microsphere stability characterization using image-based key performance attributes and release prediction, poster, 2021 Controlled Release Society Annual Meeting and Exhibition

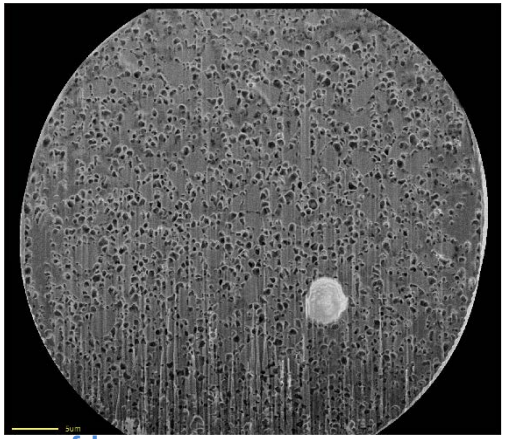
Microsphere Porosity and API Distribution

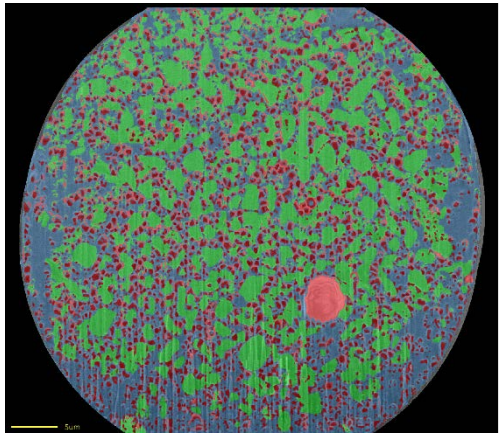
F1





F2





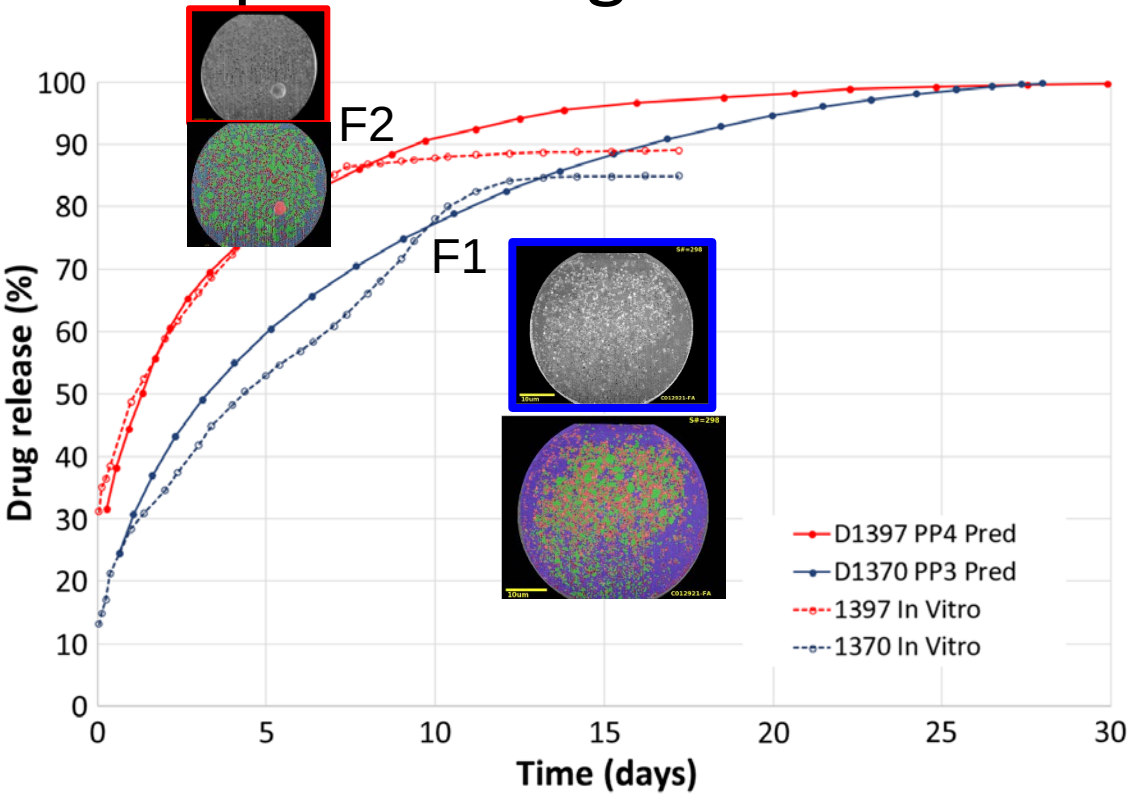
Parameters	F1	F2
Resolution (μm)	0.03	0.03
Porosity (%)	21.7	22.4
Drug Volume %	30.6	27.5
Polymer (%)	44.7	50.1

Pore | API | Polymer

Q: F1 vs F2

Will their drug release profiles be similar?

Microsphere Image-based Release Prediction



- F2 has higher burst release (30%) than F1 (10%), and faster release overall.
- Primary **structural CQAs** toward faster release,
  1. Smaller microsphere size, hence increased surface area
  2. API distribution heterogeneity – more on the surface
  3. Microporosity and its distribution

Release Simulation documented in US Patent No. 10,830,713 and validated in AAPS PharmSci Tech 2020(21)194.

Summary

- Structural analysis can provide insight on
  - Impact of manufacturing on formulation characteristics.
  - Impact of porosity and API distribution on drug release.
  - Mechanisms of release from the formulation.
- Artificial intelligence-based image data analysis is promising to facilitate development of models for predicting drug release, which can be further explored to enhance *in vitro* based BE approach.

Challenge Question #1

What can structural analysis support generic development of complex polymeric products?

A. Reverse engineering

B. Better understand impact of manufacturing on product performance

C. Support development of correlations between formulation characteristics and drug release

D. All of the above

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Questions?

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