PLGA Microsphere Stability Characterization Using Image-based Key Performance Attributes and Release Prediction

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PURPOSE

Using Arestin as an example, this project investigated the microstructure change of PLGA microspheres in a year of storage. The goals are to:

1) Visualize the morphological evolution of microporosity, active pharmaceutical ingredients (APIs) and polymer matrix;
2) Quantify key performance attributes;
3) Assess the impact of microstructure change on release profiles via image-based release predictions.

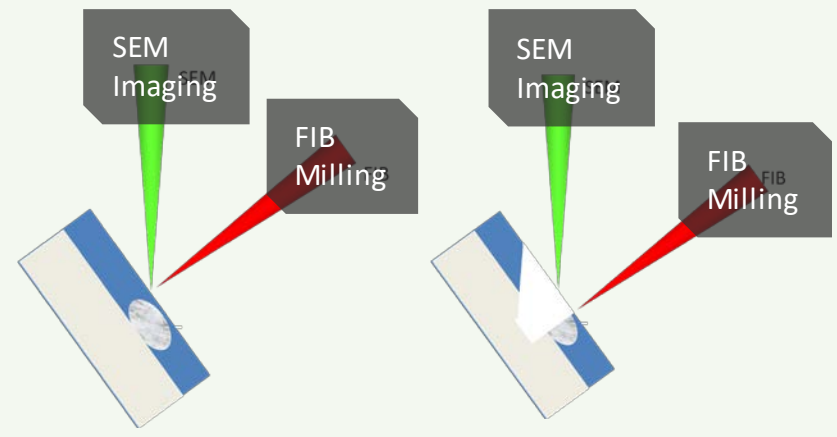
OBJECTIVES

- Demonstrate the use of high-resolution imaging and image-based modeling as a tool for characterizing product stability.
- Provide direct visualization of the microstructure changes over time.
- Investigate porosity impact on API release from PLGA matrix.

METHODS

- Focused Ion Beam – Scanning Electron Microscopy (FIB-SEM), a thin sectioning imaging technique, was used to collect the image of individual PLGA microspheres from both the one-year-aged and the two-year-aged Arestin sample.
- The collected images were quantitatively analyzed with an artificial intelligence (AI)-based image analytics.
- Image-based release prediction model based on the porosity and API network reconstructed from the imaging data predicted the API release rates.

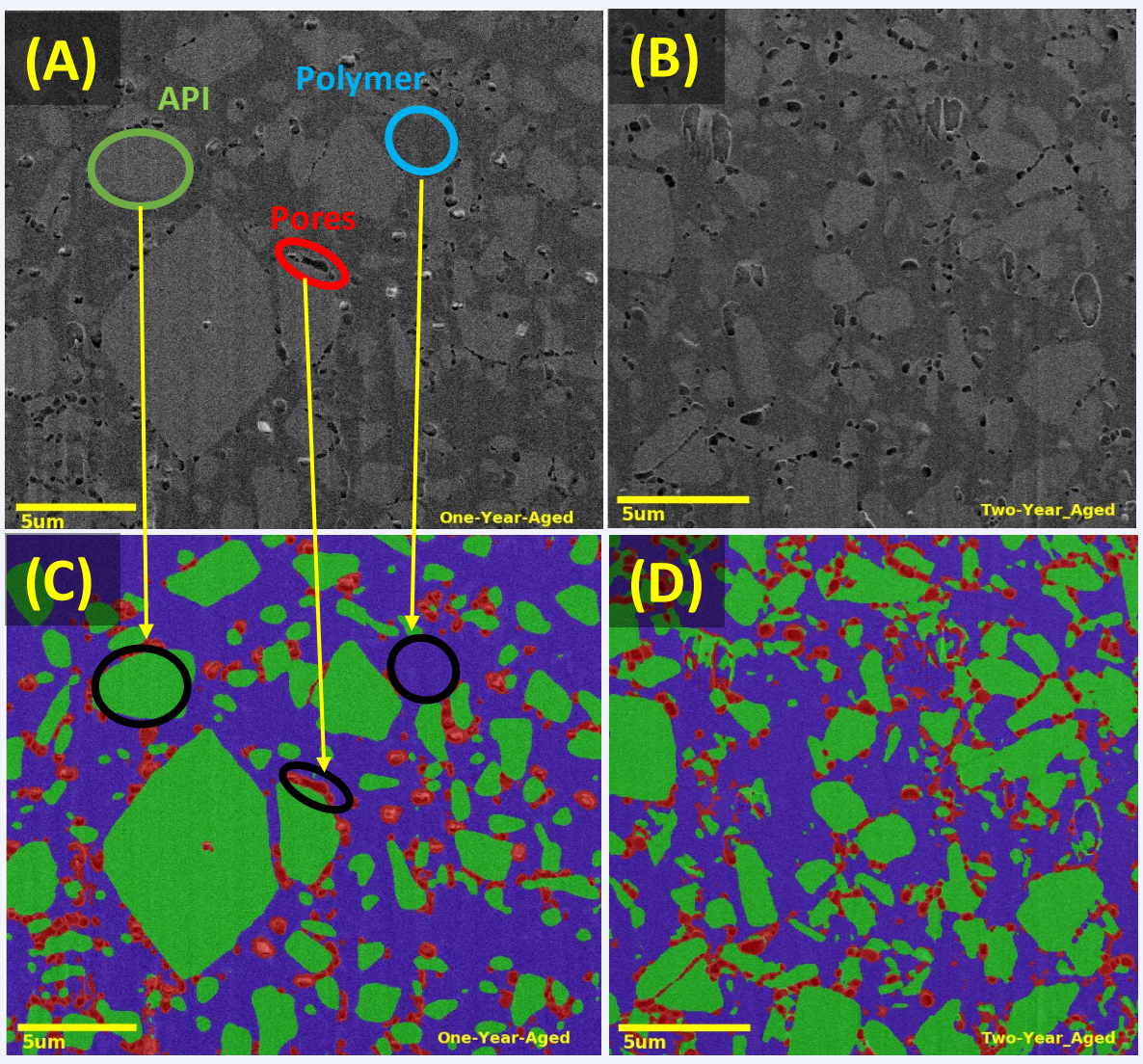
Figure 1. Cartoon demonstrating the FIB-SEM technique



RESULTS

Image Overview

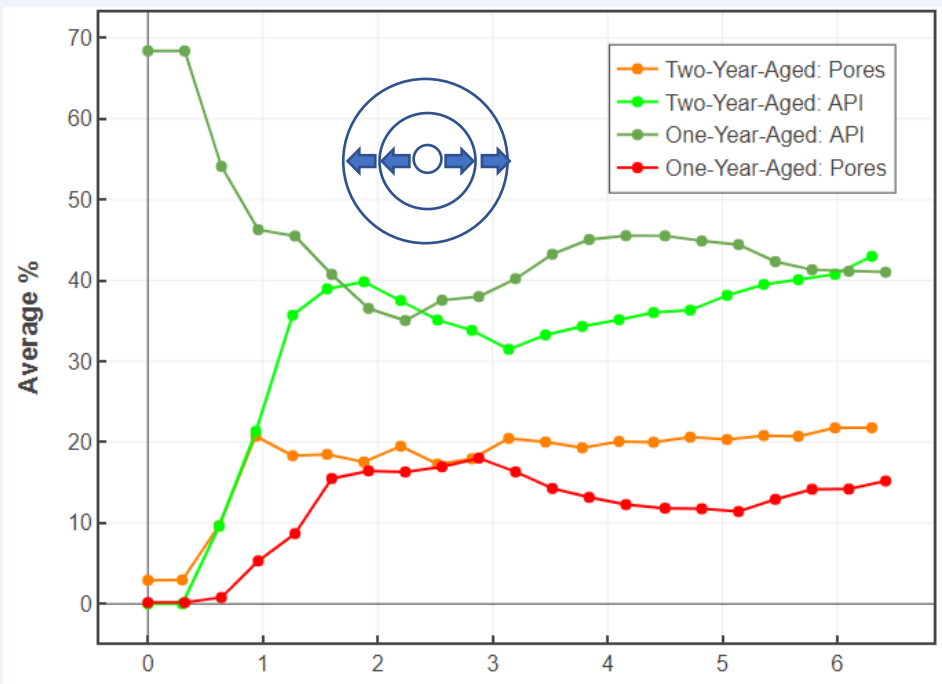
Figure 2. Display of FIB-SEM sample images and related segmentation



(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.

Quantitative Analysis

Figure 3. 3D API and Porosity Spatial Uniformity



The spherical microsphere was first equally partitioned by radius along radial axis, then the volume fractions of pores and drugs of each region starting from the center of the sphere was calculated. API and pores are fairly uniform for both samples.

Figure 4. 3D API and Pores Size Distribution

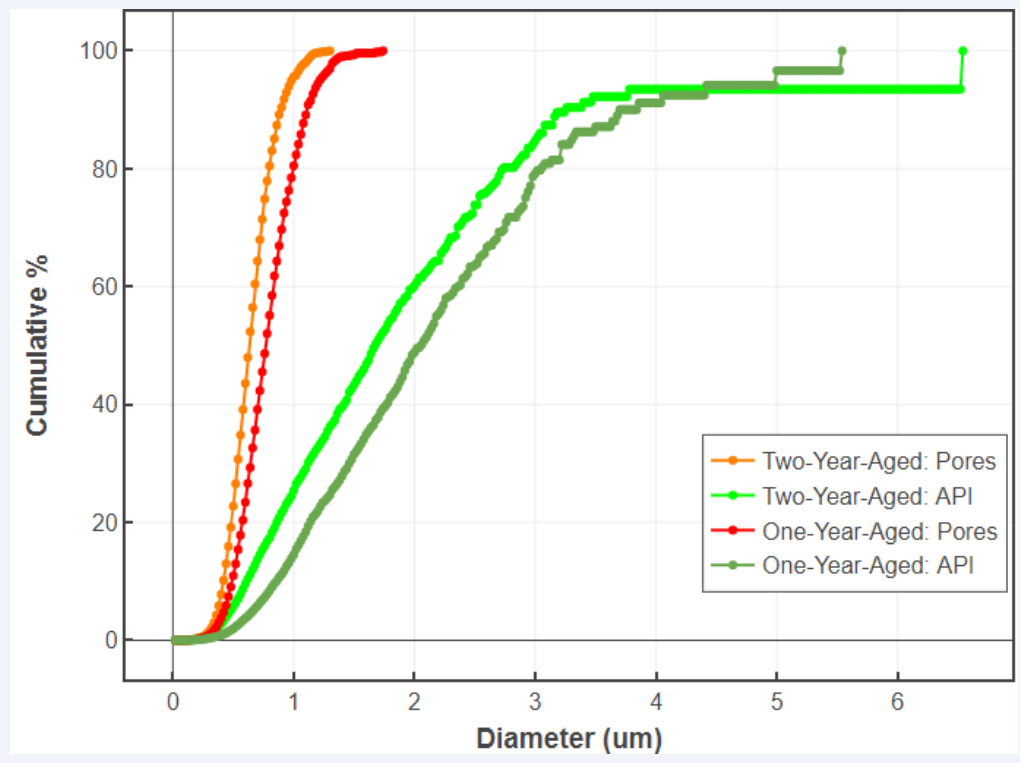


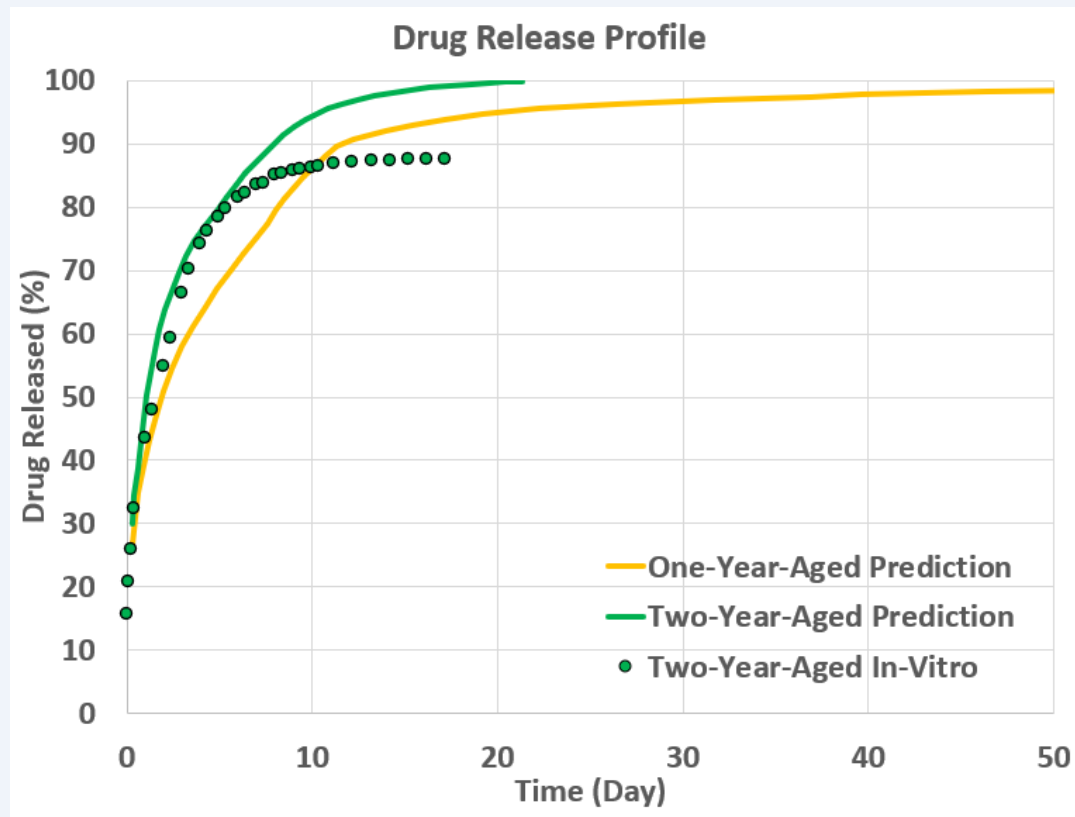
Table 1. Particle Volume Fraction and Permeability

Sample	Volume Fraction		Permeability (Darcy)
	API	Pores	
One-Year-Aged	42.4%	15.8%	0.16×10^{-18} m^2
Two-Year-Aged	38.2%	22.9%	1×10^{-18} m^2

An increase in porosity was observed from the two-year-aged sample. API size and pore size are comparable, while pore size slightly decreased as sample aged. Higher permeability, computed using image-based computational fluid dynamics method, was observed from the two-year-aged sample.

Release Characterization

Figure 5. FIB-SEM image-based release prediction using T0 samples



The simulated release profile matched well with the in vitro (no dash, italic) release curve during the first week for two-year-aged samples. Release profile prediction suggest an acceleration in release rate as samples age, most likely associated with the porosity increase.

CONCLUSION

- High resolution imaging provides direct visual and quantitative support of a suspected porosity increase over time of a PLGA microsphere product.
- The correlation between porosity change and release rate increase due to aging is investigated through image-based release predictions.

ACKNOWLEDGEMENTS

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