Accelerated Formulation Characterization and Development with AI Image Analysis and Image-Based Release Modeling for PLGA Implant

Shawn Zhang[1], Karthik Nagapudi[2] , Debby Chang[2], Joshua Lomeo[1], Lisa Ma[1]

[1]DigiM Solution LLC, [2]Genentech

Contact: shawn.zhang@digimsolution.com

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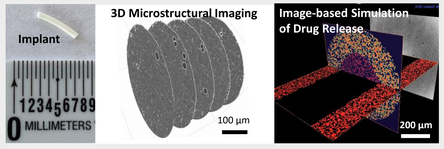
PURPOSE

Overcoming Development Challenges for Long-acting Dosage Forms

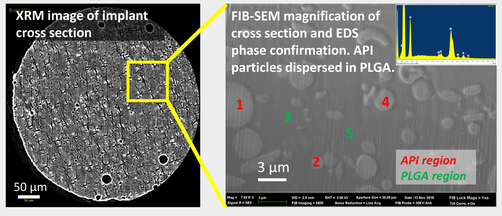
- **Ensuring drug content uniformity and reducing manufacturing variations.**
- **Understanding microstructure correlation with release performance.**
- **Reducing lengthy *in vitro* studies that lead to extended development times.**

OBJECTIVES



In this work, the aim was to accelerate development decisions and performance evaluation by applying high-resolution 3D imaging, artificial intelligence (AI) microstructure quantification, and prediction of release profiles from microstructure images.

METHODS



High-resolution imaging including X-ray microscopy (XRM), focused ion beam scanning electron microscopy (FIB-SEM), and energy dispersive X-ray spectroscopy (EDS) were applied to study implant microstructures in 3D. Using supervised machine learning, an AI processing software quantifies microstructural properties. With numerical simulation, release profiles were predicted directly from a digitized implant microstructure.

Imaging
- XRM (0.5 µm res.)
- FIB-SEM (3 nm res.)
- EDS

→ **Phase and Geometric Quantification with A.I.**
- 3D Reconstruction
- Transport Properties
- Particle Size Distribution

→ **Image based Simulation**
Release Profiles

RESULTS

RELEASE PREDICTION FROM XRM MICROSTRUCTURE IMAGE DATA

Initial Blind Prediction

- API particle size, porosity, and permeability are calculated for several implants with different drug loading.
- The implant microstructures are digitally reconstructed in 3D, and release curves are computed from quantified release properties.
- An initial simulation provides the correct rank order performance of implants by their drug loading.

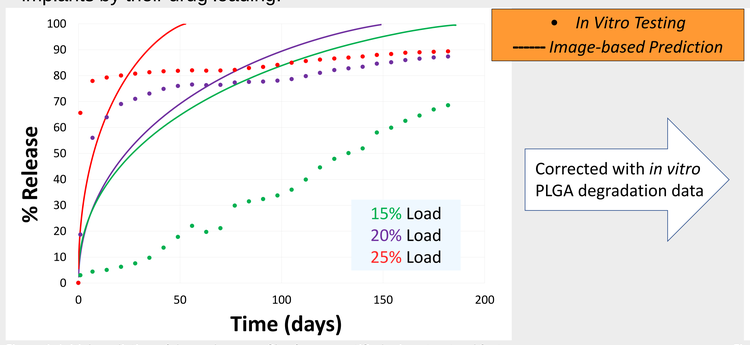


Figure 1. Initial prediction of drug release profiles from quantified microstructural features.

Corrected with *in vitro* PLGA degradation data

Polymer Degradation Corrected Prediction

The effect of PLGA degradation on the microstructural release network and API release was included by adding a correction factor from *in vitro* PLGA degradation data. The new profiles matched strongly with *in vitro* data and provided a months long prediction beyond available *in vitro* test data.

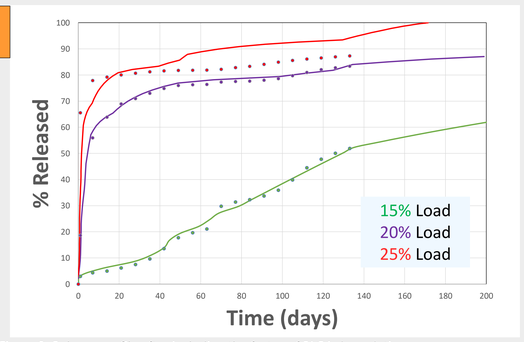


Figure 2. Release profile after including the factor of PLGA degradation.

QUANTITATIVE DRUG PROPERTIES

Drug content uniformity and transport properties

Porosity, permeability, and diffusivity were computed from microstructure image data. FIB-SEM provided internal visualization of microporosity, API, and excipient domains. AI analysis was used to quantify particle size distribution, domain volumes, and drug uniformity.

Table 1. Porosity and permeability measurements for implants with different drug loads.

Drug Load	Porosity (%)	Permeability
15%	7.2	22.4
20%	7.5	57.5
25%	8.6	128.9

Table 2. The internal API particle size, quantified from FIB-SEM images, found particle size was consistent with particles as received before manufacturing. This indicated that manufacturing does not significantly affect the API particles.

Size (µm)	As Received	In Rod
D_{10}	1.1	1.4
D_{50}	2.9	3.1
D_{90}	7.0	5.3

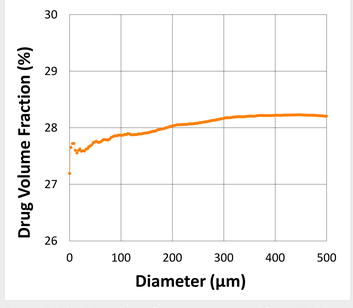


Figure 3. The API volume fraction, measured from XRM images, found that the drug is uniformly distributed across the implant rod diameter.

PROCESS QC OF DIMENSIONAL VARIATIONS

Physical parameters analyzed for process consistency and acceptable dimensional deviations

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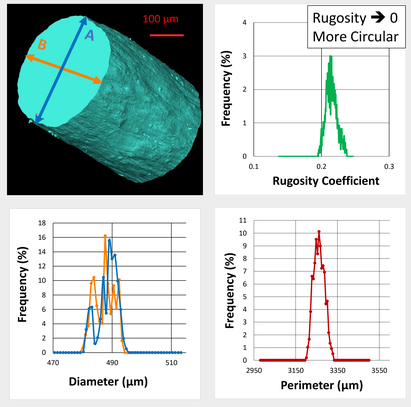

Figure 4. Quantitative measurements of the implant rod dimensions.

SUMMARIZED RESULTS

After digitally reconstructing the implant from high-resolution 3D images, quantitative AI analysis and image-based release prediction revealed that:

- The implant manufacturing process has little to no impact on the source API particle size.
- The implant has uniform dimensions and low rugosity suitable for consistent administration.
- The drug volume was found to be uniformly distributed across the rod.
- Transport properties including porosity and permeability were computed from image data.
- After correcting for polymer degradation, release profiles predicted from microstructure image data accurately match, and predict beyond, the results of real time *in vitro* tests.

CONCLUSIONS

- Image-based analytics can provide a direct correlation and understanding of the microstructure impact on release performance.
- A correlative imaging approach is needed to capture both the microstructure and bulk performance properties.
- XRM and AI analysis can be applied in product quality control.
- By predicting release profiles in a matter of days, image-based release simulation can accelerate formulation development cycles and selection of lead formulations.

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