Microstructural Analysis of In Situ Formed Depots for Universal In Vitro Assessment

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BACKGROUND AND LEARNING OBJECTIVES

In situ forming depots are a popular long-acting injectable platform due to their biocompatibility, stability, and ability to provide the desired drug concentration over a prolonged time. In situ forming depots are notoriously challenging to characterize without PK studies due to the lack of reliably consistent in vitro testing methods. XRCT is demonstrated here as an in vitro tool to characterize the depot structure to inform on depot performance. This structural characterization approach can offer a potential pathway to a universal in vitro performance assessment.

- **Learning Objective 1:** Demonstrate the use of cold stage XRM imaging to collect microstructural imaging data on in situ forming depots in their frozen wet state.
- **Learning Objective 2:** Provide direct visualization of the microstructural differences between different in situ forming depots, specifically wet vs dry state samples.
- **Learning Objective 3:** Investigate how specific variations in the depot microstructures correspond to in vitro and in vivo performance variability.

METHODS

- Imaging data was collected on six different in situ forming depots: four in house and two on market formulations (PLGA, NMP, and risperidone or leuprolide acetate).
- X-ray computed tomography (XRCT) was performed at both room temperature and at -20°C, to promote phase contrast in the gel. The 3D imaging data was used for structural analysis and reconstruction of visible features.
- Key performance attributes calculated include total porosity, pore size distributions, API size distributions, and density spatial uniformity. In silico release predictions are computed from the imaging data and compared to in vivo and in vitro test results.

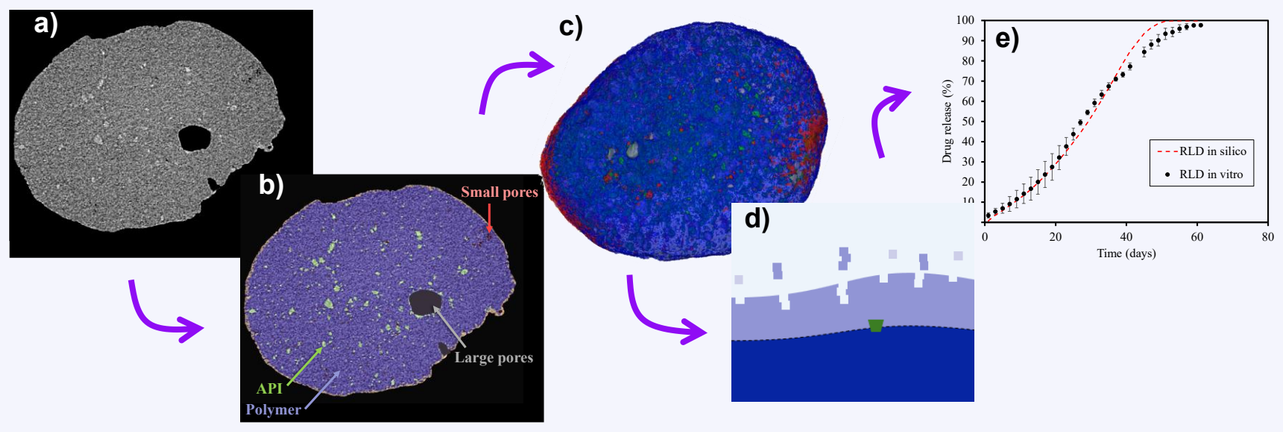

Figure 1. *(a) Raw XRM imaging data, (b) segmented image (with phases indicated), and (c) digitally reconstructed 3D volume of the depot. (d) Schematic of surface erosion release simulated on depot images, where dark blue represents unexposed polymer, light blue represents diffusing polymer, and green represents a dissolving drug particle at the erosion front) (e) In silico release prediction.*

XRM IMAGING AND STRUCTURAL ANALYSIS

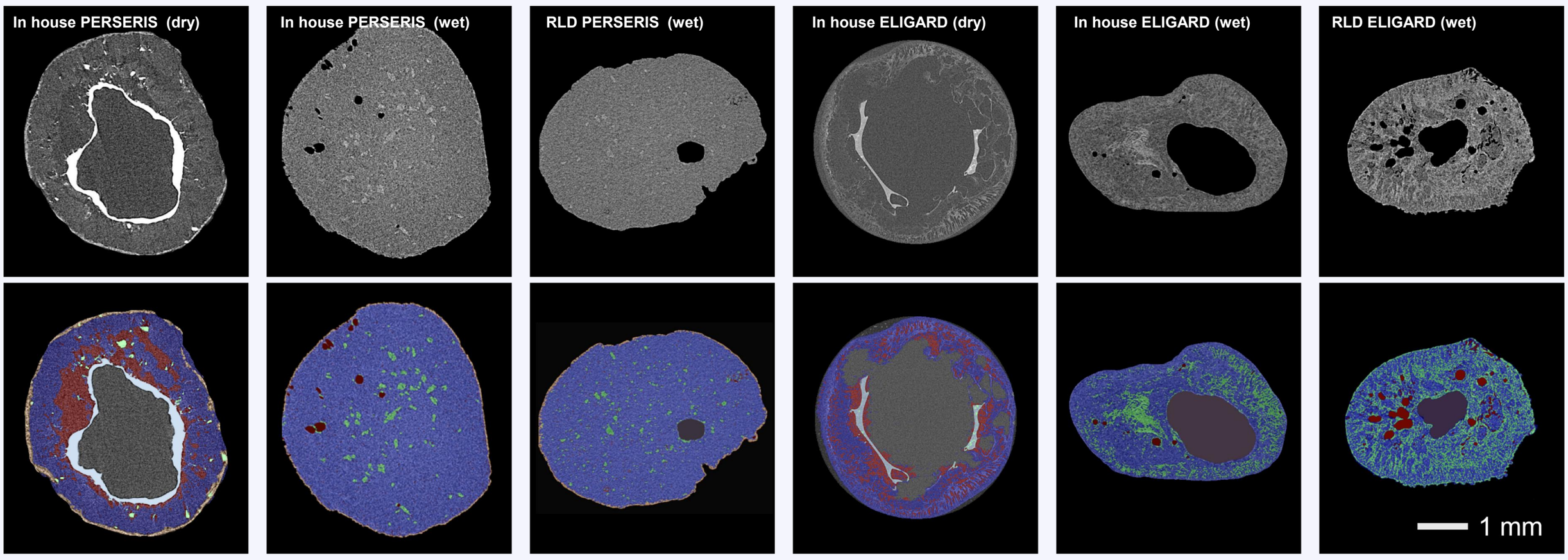

Figure 2. *Representative XRM images in greyscale (top) and segmentation of the different material phases overlaid on the images (bottom). Segmentation colors are as follows: Blue – polymer, green – API rich domains, grey – large pores, red – small pores.*

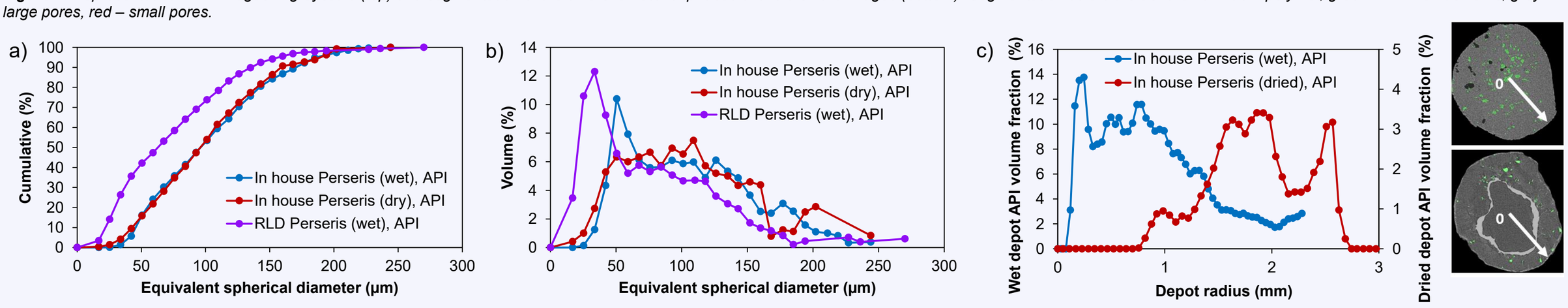

Figure 3. *API particle size distributions are represented as **(a)** cumulative and **(b)** volume percent distributions. Both in house depots reveal highly comparable API particle sizes that are slightly larger on average compared to the API in the RLD. **(c)** Radial spatial distribution of API particles in the wet and dry in house Perseris samples, where API particles are preferentially localized towards the center of the wet depot with a sharp decrease towards the depot walls. Spatial distributions reveal the lyophilization process drives API particles from the center to the outside of the depot.*

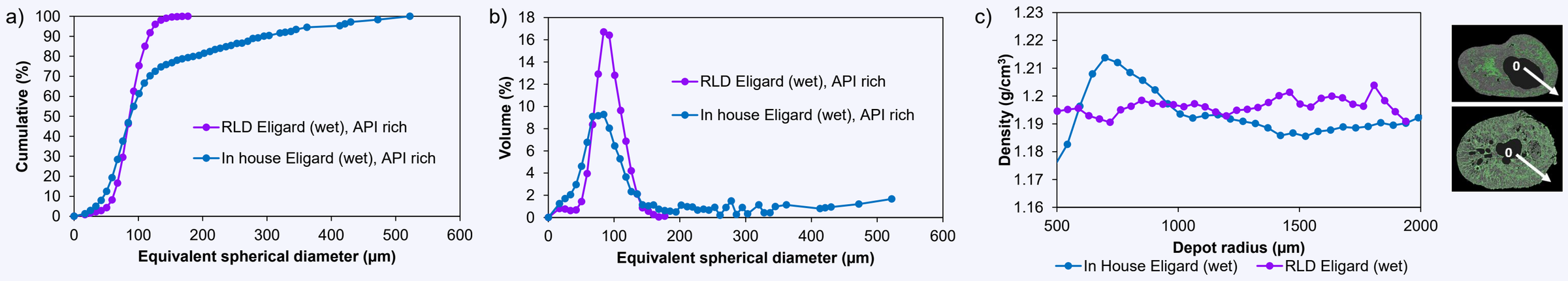

Figure 4. *The API in the Eligard samples is highly soluble and therefore does not appear as phase separated from the polymer domain in the wet samples. API rich domain size distributions are represented as **(a)** cumulative and **(b)** volume percent distributions in the wet Eligard samples. Some l*arger API rich sizes are identified in the in house formulation which may be due to the preferential localization of this phase. ***(c)*** *Radial density spatial distribution in the wet Eligard samples, where the RLD appears to have a more uniform density indicating more homogeneous distribution of the API.*

RLD PERSERIS IN SILICO RELEASE PREDICTIONS

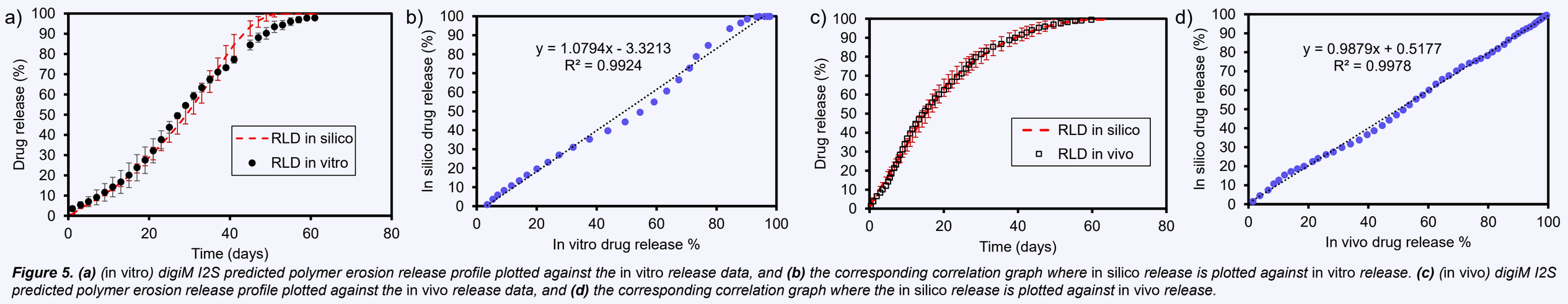

Figure 5. (a) *(*in vitro*) digiM I2S predicted polymer erosion release profile plotted against the* in vitro *release data, and **(b)** the corresponding correlation graph where* in silico *release is plotted against* in vitro *release. **(c)** (*in vivo*) digiM I2S predicted polymer erosion release profile plotted against the* in vivo *release data, and **(d)** the corresponding correlation graph where the* in silico *release is plotted against* in vivo *release.*

CONCLUSIONS

XRM imaging and structural analysis have been shown as a promising approach in characterizing in situ forming depot microstructures, enabling rapid evaluation in early stages of product development to predict downstream performance. Structure-based release modeling demonstrates a versatile and efficient tool as a universal alternative to conventional in vitro release testing. This structural analysis–based approach has demonstrated that A level IVIVC can be achieved without ever requiring real world in vitro release testing, potentially providing a new tool for innovator and generic drug development.

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