Development of a Novel Release Phantom for Improved In Vitro-In Vivo Correlation of Drug Release From In Situ Forming Polymer Implants

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Statement of Purpose: Phase inverting *in situ* forming implants (ISFI) typically consist of a biodegradable polymer dissolved in a biocompatible organic solvent (such as 1-methyl-2-pyrrilidinone, NMP), which precipitates into a solid depot upon injection into the body. ISFIs can provide a means for effective sustained delivery of chemotherapeutic drugs to a targeted tissue such as a cancerous tumor. However, the lack of correlation between *in vitro* and *in vivo* drug release profiles has hindered systems from being used in clinical applications. In the past only polymer concentration, solvent type, drug type and bath side components have been shown to alter the release behavior of implants *in vivo*. Recently research from our group has shown that the stiffness of the implant injection site could also have a direct effect on the drug release profile [1]. When placed *in vivo*, polymer swelling can be constrained by the surrounding tissue and may result in increased drug release (Fig.1). Thus, the typical bench top drug release studies carried out in solution (typically PBS or normal saline) may not be representative of the *in situ* scenario.

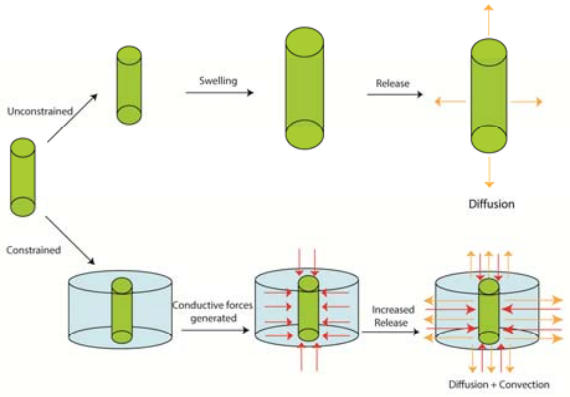

Figure 1. Forces generated in constrained polymer environments

In this study, we investigated the use of a new polymer hydrogel phantom, which can limit implant swelling and mimic the *in vivo* scenario better than a traditional dissolution setup. The phantom is used to elucidate the role of injection site properties on drug dissolution kinetics.

Methods: Fluorescein sodium salt was used as mock drug to evaluate the drug release profiles. Implant formulations consisted of 50:50 19 kDa poly(lactic-co-glycolic acid) (PLGA) polymer dissolved in NMP with a 1% mass ratio of fluorescein. The drug release profile was observed under three conditions: (1) implants formed in PBS bath, (2) constrained implants formed in tissue-mimicking hydrogels and (3) implants formed subcutaneously on the back of Sprague Dawley rats. Implants were constrained by encapsulation in polyacrylamide hydrogel phantoms, which had physiologically relevant elastic modulus (40 kPa). Polyacrylamide hydrogels were crosslinked with bis(acryloyl) cystamine (bis-CA) and polymerized with N,N,N',N'-tetramethylethane-1,2-diamine (TEMED) and ammonium persulfate (APS) inside a phantom mold. Following implant formation inside tissue molds, phantoms were then placed inside a 37°C PBS bath, and incubated for predetermined time points. To carry out the release study, implants were then degraded in sodium hydroxide to determine the mass of the residual fluorescein within the implant (Fig.2) via UV/vis spectroscopy.

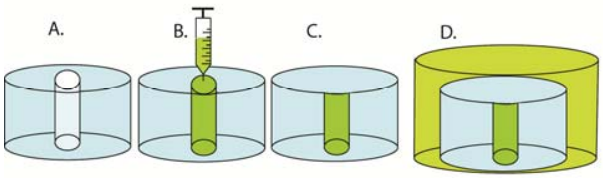

Figure 2: (A) Preparation of polyacrylamide phantom (B) Injection of liquid polymer(C) polyacrylamide capping (D) incubation in PBS at 37°C

Results: Preliminary results indicate that when implants are constrained, deviation between *in vivo* and *in vitro* release decreased over time. Compared to release in PBS, when implants are constrained the initial release is elevated, followed by a period of near zero order release not seen with spherical unconstrained implants.

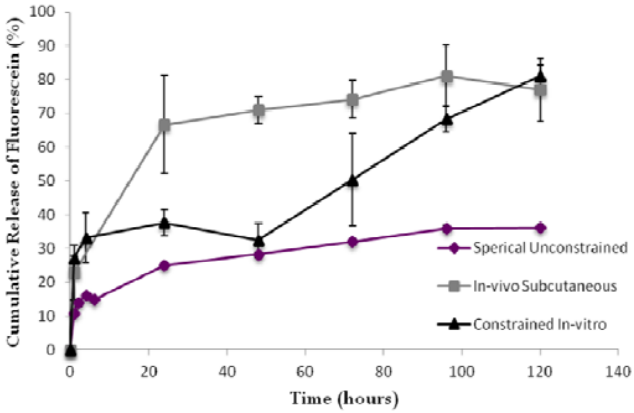

Figure 3. Cumulative release of fluorescein

Conclusions: These results indicate that the reactive forces surrounding the implants play a role in the drug release profiles of ISFIs. Accordingly, the *in vitro* release of drug from these implants may need to be carried out in specifically designed phantoms not in solution, to predict *in vivo* behavior more accurately. Better phantoms would include characteristics such as perfusion and similar drug/phantom interactions to that of drug/tissue. These differences could account for the deviations in release profiles during the early time points. Future studies will optimize the phantom formulation to better approximate the *in vivo* scenario.

References:

Solorio, L., J Control Release. 2010; 143:183-190

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