The Role of Varying PLGA Molecular Weight Blends Drug Release and Phase Inversion

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Statement of Purpose: Systemic administration of chemotherapy has had only limited success as a standalone therapy for treating non-resectable tumors, due in part to the intrinsic tumor penetration barriers and as well as their highly toxic side effects. Several strategies have been employed to overcome these barriers; some of the more promising technologies utilize phase sensitive *in situ* forming drug eluting polymer implants (ISFIs) for controlled local delivery of therapeutic agents. The most favorable advantage over traditional preformed implants is that they are initially a liquid solution that can be easily and non-surgically injected directly into a lesion. Once exposed to an aqueous environment, they transition into a solid drug depot by a process known as phase inversion [1]. The rate of drug release and phase inversion of these implants has been shown to be related to the polymer molecular weight (Mw) [2]. In addition to polymer Mw, use of excipient agents have also been an effective method for altering the drug release profile of ISFIs, however the effects are often lost over time due to diffusion of the excipient out of the matrix [3]. The goal of this study is to evaluate the effects of blending different Mw ISFI formulations on the phase inversion, swelling, and controlled release of a low Mw hydrophilic mock drug (fluorescein) without the use of excipients.

Methods: 1:1 molar blends of three molecular weight poly (DL-lactide-co-glycolide) (PLGA) polymers were used for comparison in the study: (15 kDa, 0.16 dL/g; 29 kDA, 0.28 dL/g; 64 kDa, 0.46 dL/g). Implants were formulated using a 60:39:1 mass percent ratio of solvent to polymer to mock drug. 50 µl implants were formed in 10 ml of 37°C PBS and kept well mixed on an incubated shaker. The release profile was determined through a standard dissolution study, followed by degradation of the implant to determine the total mass of fluorescein released. Ultrasound images were analyzed by an applying a threshold to the images, and a total area image was generated by filling the interior region [4]. Statistical significance was determined using ANOVA ($P<0.05$, $N=4$).

Results/Discussion:

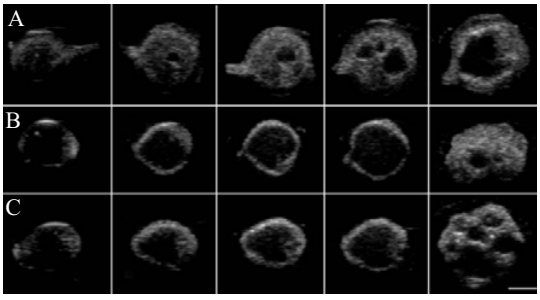

Fig 1 Gray-scale US images of 15kDa (**A**), 64 kDa (**B**), and 15 kDa:64 kDa 1:1 (**C**) implants 1 h, 48 h, 72 h, 120 h, and 216 h after implant formation. (Scale bar represents 2.5 mm).

In all cases the implants first formed a thin solid shell, which could be visualized with ultrasound due to the change of acoustic impedance relative to the surrounding PBS bath solution (**Fig 1**). As the polymer solution solidified, the interior region began to develop ultrasound backscatter due to polymer precipitation creating acoustic impedance within the center of the implant. After the implants phase inverted into solid drug depots, a pore formed in the center of the implant which we hypothesize to be caused by an entropically driven phase separation of the polymer and the water that has diffused into the implants (**Fig 1**). The rate of phase inversion of the implants was dependent on the Mw of the polymer used, with the 15

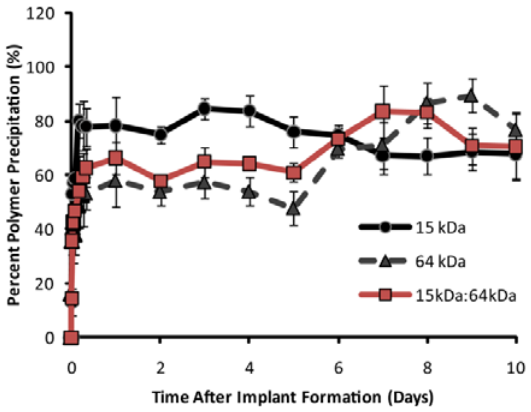

Fig 2 Quantitative formation data for three different ISFI polymer formulations implants over 10 days

kDa polymers phase inverting significantly faster than 64 kDa or 15 kDa:64 kDa blend after 48 h, with the implants phase inverting 74±3%, 54±4%, 58±2% respectively (**Fig 2**). Additionally, our results showed that the polymer blends provided an effective avenue for altering the drug release profile of ISFIs without the use of an excipient. The effects of blending on drug release were dependent on the polymers used. Blends of 15 kDa and 29 kDa PLGA showed intermediate release relative to the pure polymers during the diffusion period of release (24 h - 168 h) from the 15 kDa:29 kDa polymer blend was 33.1±7.7%, compared to 44.1±9.0% and 24.8±5.5% respectively for the pure polymer implants. While release of fluorescein from blends of 15 kDa and 64 kDa PLGA were not significantly different from the pure 64 kDa implant during the diffusive period of release, but showed intermediate release relative to the pure polymers during the degradation period of release (170 h - 400 h). Additionally, swelling data based on the size of the implant cross-section relative to the original cross-sectional area shows that PLGA blends have a lower degree of swelling than the pure form.

Conclusions: Our study demonstrates the potential for modulating the drug release of ISFIs utilizing polymer blend formulations. Additionally, US imaging and quantitative image analysis can potentially be used to characterize the formation process of a variety of *in situ* forming platforms nondestructively. This work was supported by R01CA1118399 to AAE and TRN103514.

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