Characterization of formulation parameters affecting low molecular weight drug release from in situ forming drug delivery systems

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Statement of Purpose: The use of in situ forming drug delivery implants (ISI) to deliver adjuvant chemotherapy to ablated tumors has shown significant promise[1]. In contrast to traditional solid implants, these injectable systems can be placed into a tumor volume in a minimally invasive manner. However while the properties of the ISI systems have been thoroughly investigated for delivery of large molecular weight (MW) protein therapeutics, little is known about their ability to deliver small MW drugs such as most commonly used chemotherapy drugs. To aid in the design of an optimized ISI system for intratumoral delivery of chemotherapy, several different formulation parameters were examined in a phase inverting ISI system comprised of poly(D,L-lactide-co-glycolide) (PLGA) dissolved in a polar organic solvent. Specifically, the effects of polymer MW and concentration of the excipient surfactant, Pluronic, were examined.

Methods: Formulations were comprised of PLGA (Lakeshore Biomaterials, Birmingham, AL), Pluronic P85 (P85, MW: 4600 Da), donated by BASF Corp. (Shreveport, LA), and 1-methyl-2-pyrrolidinone (NMP) from Sigma (St. Louis, MO). Fluorescein was incorporated into our implants as a small MW (376 Da) hydrophilic mock drug molecule. To study the effect of PLGA MW on drug release, 50:50 PLGA 2A, 3A, 4A, and 4.5A with mean MW of 18, 33, 50, and 60 kDa, respectively, were varied. To study the effects of the excipient P85 on limiting burst drug release, relative mass percentage of P85 was varied from 0-5% in tested formulations. For each formulation, a dissolution experiment (n = 4) was begun by injecting 100 µL of polymer solution into 50 mL of PBS (pH 7.1, 37 °C). Implants were placed in an incubator shaker at 37 °C and 80 rpm and samples were taken at 20 sec., 10 min., 30 min, 2 h, 4 h, 8 h, 24 h, 48 h, 96 h, and 168 h. Drug release was quantified using a fluorescence plate reader (Tecan Ltd., Infinite 200 series) with an Ex/Em wavelength of 485/535 nm. Drug release was normalized based on the actual drug loading determined from ultimate degradation studies. Statistically significant differences between mass percent of drug released at 1 h, 1 day, and 1 week for each formulation were determined using a one way ANOVA with Tukey's significant criterion test.

Results/Discussion: The drug release data indicates a dependence of drug release on polymer MW as well as Pluronic loading density. At lower polymer MW, the initial burst release is decreased and the drug release is slower. However this disparity begins to disappear by one week (Fig 1A). In addition, formulations with up to 2.5% P85 decrease the initial burst release particularly after 1 hour, but after day 4 expedite the drug release to a point equivalent to those formulations without P85 (Fig 1B).

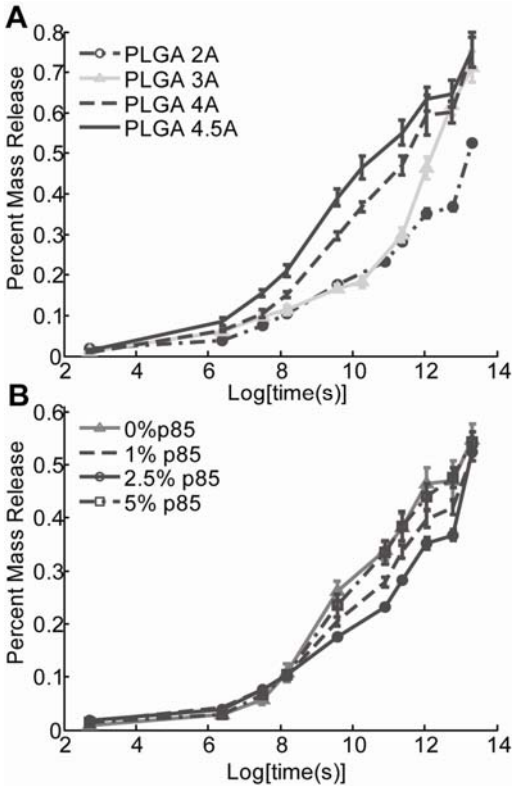

Figure 1. Percent of initial drug mass released as a function of time in log scale is shown for varying MW (A) and varying P85 (B) formulations.

Percent mass (0-1) of drug released for the lowest MW PLGA 2A formulation at the 1 hour, 1 day and 1 week intervals was 0.10, .28, and 0.52 and was significantly ($p<0.05$) less than that for the highest MW PLGA 4.5A formulation, 0.21, 0.55, and 0.76 for the same time points. For the same intervals in the formulations with varying P85, only the formulation with 2.5% P85 had a significantly lower percent mass drug release than the other trials for the 1 day time point. No differences between groups at the 1 hour and one day interval were found.

Conclusions: Our study shows that the molecular weight of the PLGA back bone used in our ISI systems may have a much greater effect on limiting burst drug release than excipient Pluronic for small molecular weight drugs. Current studies being undertaken to further understanding of the ISI systems include examining the critical water concentration required to initiate precipitation of these formulations and analyzing their morphology using scanning electron microscopy. This work was supported by R01CA1118399 to AAE and T32GM07250.

References:

1. Krupka, T., Invest Radiol. 2006;41:890-897.