In Vivo Kinetic Degradation Analysis and Biocompatibility of Aliphatic Polyester Polyurethanes

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Statement of Purpose: The versatile nature of polyurethanes has made them a popular choice when designing biomaterials. Both understanding the biologic response to degrading polyurethanes and the degradation mechanism of the polyurethane itself are at the forefront of current research interests, but these two goals are often not assessed at the same time. Although excellent *in vivo* studies have been presented, few groups investigate how degradation changes the architecture/composition of the sample which can lead to a different cellular response at later stages of the healing process. Specifically, monitoring changes in molecular weight and crystallinity are critical to understanding both the material and cellular response to implantation. This study presents a comprehensive look at both the biocompatibility and biodegradation *in vivo* of a novel family of polyurethanes, addressing both the cellular and material changes over time. The polyurethanes discussed are of a hybrid organic-inorganic nature and combine the degradability of a polylactide-based soft block with the crystallinity of a polyhedral oligosilsesquioxane (POSS) hard block. Previous publications on these materials have commented on the tunable nature of their mechanical and thermal properties as well as their potential for controlled drug delivery applications.[1]

Methods: The polyurethanes were synthesized in a manner previously discussed with variation focusing on changes to the soft block.[1] *In vitro* degradation was performed on cast film samples in PBS at pH=7.4 and 37 °C. *In vivo* degradation involved sterilizing cast film samples using ethylene oxide exposure and then implanting subcutaneously into the backs of Sprague-Dawley rats. Both degradation studies were carried out for 24 weeks with time points taken at 1, 2, 3, 4, 8, 12, 16, 20, and 24 weeks. Explanted samples were stained with Hematoxylin and Eosin (H&E) and Masson's trichrome for histological analysis. Gel permeation chromatography with in-line multi-angle laser light scattering was used on all degraded samples to monitor changes in molecular weight. Kinetic analysis of results from the first four weeks of degradation was performed using the pseudo-first order equation of $\ln(M_t) = \ln(M_0)-kt$ where M_t is the number-average molecular weight at time t, M_0 is the initial molecular weight of the polymer, and k is the degradation rate constant. This equation is suitable for bulk degrading polymers autocatalyzed by carboxylic acid endgroups created through hydrolysis of the ester bonds.[2] Material property changes during degradation were analyzed using differential scanning calorimetry and wide-angle x-ray diffraction.

Results: The molecular weight of each sample was found to decrease quickly over an eight week period and then became constant through week 24. Kinetic analysis of the initial molecular weight change showed faster degradation for the more hydrophilic polyurethanes with correlated results from *in vitro* and *in vivo* studies (Figure 1). Crystallinity, melting temperature, and heat of fusion of the polyurethanes were found to increase during degradation. The histological analysis of each polymer demonstrated rapid resolution of the acute and chronic

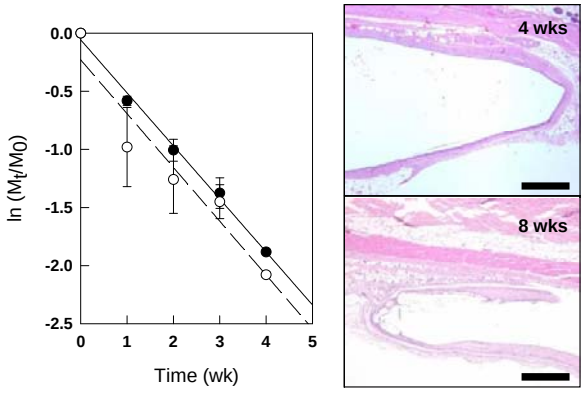

Figure 1. Left: Kinetic plot of molecular weight versus time during 4 weeks degradation *in vivo* (closed circles) and *in vitro* (open circles). Right: Histology pictographs of the same polyurethane after 4 and 8 weeks of degradation *in vivo* and stained with H&E.

inflammatory responses and the development of expected, normal foreign body reaction, consisting of adherent macrophages and foreign body giant cells on the surface of the polymers, and fibrous capsule formation around the polymer (Figure 1). No acute and/or chronic inflammation was seen after 3 weeks. The wound healing response was identical for the POSS polyurethanes when compared to a polyurethane with polycaprolactone as a crystalline hard block.

Conclusions: After 8 weeks of the amorphous polyester soft block degrading through hydrolysis, only the nondegrading crystalline hard block remained, as evidenced by GPC, DSC, and WAXS studies. Kinetic analysis confirmed that the degradation rate was dependant on the soft block composition and such associated factors as hydrophilicity and initial glass transition temperature. Histological analysis indicated that the polymers in the film form and in the biodegraded form, i.e. particles, were biocompatible and did not elicit inflammatory responses expected for toxic or non-biocompatible materials. Importantly, POSS inclusion did not alter cellular response to implantation.

References: [1]Knight P.T. et al. Biomacromolecules 2008; 9:2458-2467. [2] Anderson JM. Biomedical Applications of Synthetic Biodegradable Polymers. New York: CRC Press; 1995. p 223-233.