Tuning Properties of Poly(β-amino ester) Degradable Hydrogel Systems for Growth Plate Regeneration

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Statement of Purpose: The growth plate, or physis, is the site of new longitudinal and latitudinal growth at the ends of bones in children and adolescents. Because of its importance to normal bone growth, a severe injury has the potential to cause growth arrest, which could eventually create angular deformity or complete growth arrest.. Approximately 18.5% of childhood fractures involve this region of bone [1]. Currently, several approaches have been attempted to help repair damaged growth plates, however the results show only a 40% success rate. Here, the goal is to develop a hydrogel construct that displays the mechanical properties inherent to the natural growth plate, as well as a degradation profile that would allow new tissue to form and repair the damaged physis. In order to promote tissue ingrowth and mimic the properties of the natural growth plate, a porous system would be ideal. This system would have a slow degrading outer matrix hydrogel to provide the mechanical properties and would have encapsulated faster degrading hydrogel particles that would allow controlled pore opening and potentially release a bioactive component.

Methods: Macromers were synthesized in an overnight condensation reaction between a diacrylate and amine as outlined in the literature [2]. For this project diethylene glycol diacrylate (A) and poly(ethylene glycol) 400 diacrylate (H) were used with isobutylamine (#6) to create both A6 and H6 degradable hydrogel systems. Free radical polymerization was carried out through the use of chemical initiators ammonium persulfate (APS) and N',N',N,N-tetramethylethylenediamine (TEMED). For both systems, degradation was characterized by gravimetric analysis of samples immersed in 37°C PBS. Mechanical testing was carried out on the A6 system throughout the first few weeks of degradation using a BOSE ELF 3300 Mechanical Testing System. Cytotoxicity data was obtained by exposure of the final degradation products to D1 pluripotent mesenchymal cells followed by MTT assay.

Results: For all systems created, degradation, toxicity, and mechanical analyses were completed. The relative toxicities of all macromer systems have been studied in comparison to that of PLGA (50:50 carboxylate end group, iv=0.55-0.75 dL/g) using MTT analysis. The MTT toxicity curves and 50% toxic concentration values (TC_{50}) of the degradable hydrogel systems, the amine precursor, and PLGA are shown in Figure 1. Based on this analysis, the H6 system has lower toxicity than that of PLGA, and the A6 is higher. However, we believe this toxicity will be mitigated by the much slower degradation of the system, which will allow byproducts to be cleared always before these concentrations are reached. Degradation plots, like that shown in Figure 2, have been obtained for both systems studied. From this data, A6 appears to be a viable option for the outer matrix material, while H6 would serve as a porogen. Initial studies also indicated that intermediate degradation profiles can be obtained by mixing the two macromers together prior to polymerization. This would allow a wide range of potential porogens and outer matrices to be developed. Measurement of compressive modulus during degradation of the A6 system showed that in the first 5 weeks of degradation, the modulus remained relatively constant within 0.5 to 1.0 MPa, thus making it appropriate for this particular orthopedic application.

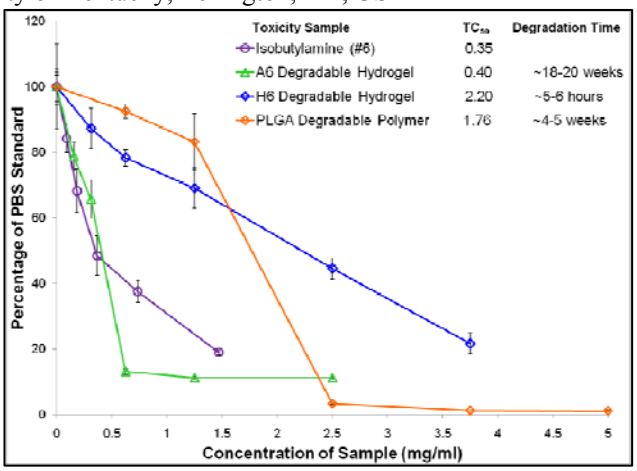

Figure 1: MTT cytotoxicity assay results for the degradable hydrogels A6 and H6, isobutylamine, and PLGA.N = 4 ± 1 SD

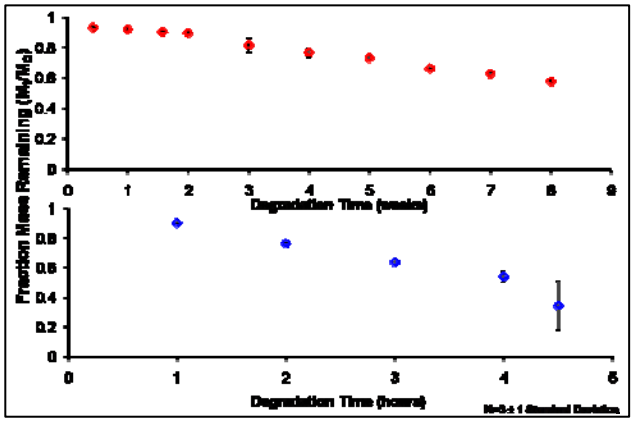

Figure 2: Gravimetric degradation analysis of the A6 (top) and H6 (bottom) degradable hydrogel system. N = 3 ± 1 SD

Conclusions: Several hydrogel systems were successfully synthesized, and their degradation and compressive properties were analyzed. MTT cytotoxicity analysis was also completed. The results showed that these particular systems have properties that match or are easily tunable to meet the target properties for growth plate regeneration.

References:

(1) Worlock P, Stower M. J Pediatr Orthop. (1986:6:656-660).
(2) Anderson, DG, et al. Adv Mater. (2006:18:2614-2618).

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