In Situ Forming Drug Delivery Scaffold for Treating Avascular Necrosis of the Femoral Head

Paul D. Fisher[1], J. Zach Hilt[2], Todd A. Milbrandt[1,3,4], and David A. Puleo[1].
[1] Center for Biomedical Engineering, University of Kentucky, Lexington, KY, USA
[2] Department of Chemical and Materials Engineering, Lexington, KY, USA
[3] Department of Orthopaedic Surgery, University of Kentucky, Lexington, KY, USA
[4] Shriners Hospital for Children, Lexington, KY, USA

Statement of Purpose: Avascular necrosis of the femoral head (AVNFH) is the death of bone tissue due to an interruption in blood supply and affects over 10,000 new patients annually in the United States (Lavernia, 1999). Current treatment methods are ineffective after dead tissue begins to collapse, and there exists a need for a treatment that can provide both osteogenic stimulation and mechanical support. A locally injectable, *in situ* forming scaffold was developed to accommodate biodegradable microparticles for prolonged drug release as well as filler particles for mechanical reinforcement. The scaffold was designed to be space-filling in order to bypass spatial limitations of fixed-form implants.

Methods: Poly(lactic-co-glycolic acid) (PLGA) was dissolved in N-methyl-2-pyrrolidone (NMP) to produce an injectable solution that precipitates in aqueous environments. Poly(beta amino ester) (PBAE) microparticles were fabricated to deliver drugs from the system. PBAE hydrogel was synthesized and ground into microparticles using 2:1 or 3:1 ratios of PBAE:hydroxyapatite (HA) to prevent aggregation. Drug was loaded by swelling particles with drug solution and evaporating out the solvent. Simvastatin, an osteogenic drug, and clodronate, an anti-resorptive drug were loaded into separate sets of particles. These drug-loaded microparticles, as well as additional HA at various weight ratios, were mixed into the PLGA solution prior to injection. Drug release was simulated by injecting the mixture into excess buffer and replacing buffer at intervals. Drug concentrations at each time point were detected using UV-vis spectroscopy. For microstructure and mechanical analysis, a cylindrical agar mold was used to control scaffold geometry. For mechanical analysis, cylindrical samples with increasing HA content were tested in compression at a strain rate of 20% / minute, and stress vs. strain data were used to calculate compressive modulus. Moduli were compared using unpaired, 1 tailed t-tests. MicroCT was used to quantify porosity as well as to qualitatively assess scaffold homogeneity.

Results and Discussion: While drugs showed burst release when freely mixed or encapsulated within gelatin microspheres (not shown), PBAE particles allowed for more prolonged release. Clodronate exhibited moderate burst and complete release within 8 days, while simvastatin exhibited 30% burst with continuous release through 30 days (Figure 1). Increasing the hydroxyapatite content from 2:1 to 3:1 HA:PBAE during particle formation eliminated simvastatin burst (not shown). Initial mechanical testing showed increasing compressive modulus with increasing HA content (Figure 2), with significant increases in modulus going from 10% to 30% HA ($p=.032$) as well as 30% to 50% HA ($p=.045$).

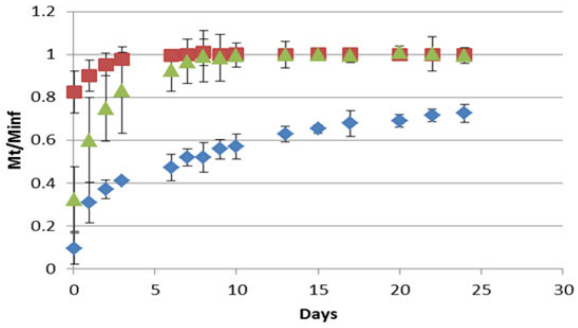

Figure 1. Release profiles showing rapid NMP solvent exchange (red) followed by intermediate clodronate release (green) and prolonged simvastatin release (blue).

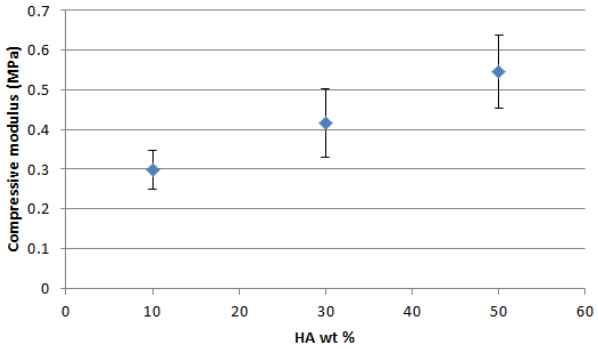

Figure 2. Increasing HA content improved compressive modulus ($p<.05$)

MicroCT scans revealed macropores with diameters on the scale of millimeters present in most scaffolds, with the remaining volume composed of microporous networks with lower overall porosity than typical trabecular bone (not shown).

Conclusions: The difference in release kinetics between drugs is likely due to their different aqueous solubilities as well as PBAE chemical properties, indicating that scaffolds are capable of providing multiple drug release with tunable kinetics. By increasing HA content, scaffold compressive modulus can be increased to provide additional mechanical support for diseased bone, which may prevent structural collapse that leads to permanent damage in AVNFH. Scaffold porosity is important to allow new bone ingrowth, and scaffolds will degrade over a period of months to accommodate tissue regeneration.

References: Lavernia CJ. J Biomed Mat Res B. 1999; 7:250-61

Acknowledgments: This work was supported by NSF-IGERT.