Drug Release and Mechanical Effects of Poly(β-Amino Ester) and Hydroxyapatite on *In Situ* Forming PLGA Systems

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Statement of Purpose: *In situ* forming implants (ISIs) are formed by adding drug to a dissolved polymer, which solidifies via solvent exchange into a solid scaffold upon injection into an aqueous environment[1]. However, ISIs designed for rapid precipitation suffer from high initial burst release of small molecule drugs because drug is removed with the solvent before solidification can occur[2]. By incorporating drug-loaded poly(β-amino ester) (PBAE) microparticles into the poly(lactic-co-glycolic acid) (PLGA) matrix, burst may be attenuated and release can be prologned. Hydroxyapatite (HA) additives may improve mechanical properties and bind to dianionic drugs, such as bisphosphonates, to reduce initial burst. The addition of these particle types can create a system suitable for intraosseous injection due to the mechanical reinforcement and delivery of both osteogenic and anti-resorptive treatments from a single injection.

Methods: PLGA was dissolved into N-methyl-2-pyrrolidone (NMP) at 20 w/w%. Drug-loaded microparticles were prepared by imbibing PBAE slabs with either simvastatin or clodronate, and grinding with 50 v/v % HA microparticles into microparticles. Drug was introduced to the PLGA solution either mixed freely, mixed freely with 30 total w/w % microparticulate HA (mHA), or in drug-loaded PBAE particles with 30% HA. Dropwise injections were used to create spherical scaffolds for release studies. The 20 and 30 w/w% PLGA containing 5 w/w % PBAE microparticles and increasing amounts of mHA or nano-HA (nHA) were injected into cylindrical agarose molds. These scaffolds were immersed in buffer for 3 days to ensure complete solidification, then compressed at increasing strain rates to 50% total strain. Compressive modulus was calculated from the initial linear portion of the stress-strain curve, and yield stress was defined as the stress at the end of the linear region. Polyurethane scaffolds (Sawbones) with architecture and mechanical properties similar to trabecular bone were cut into cubes and injected with ISIs containing different combinations of micro- and nano-HA, and then tested for modulus and yield stress.

Results: The ISI system containing simvastatin-loaded PBAE microparticles exhibited significantly reduced burst (81% vs 39%) and extended release (95% release by 28 days vs 10 days). Clodronate burst was reduced by the addition of HA (49% vs 32%) but was unaffected by loading into PBAE microparticles (Figure 1). Compressive modulus and yield stress of cylindrical scaffolds increased up to 30 w/w % HA. Modulus and yield stress were significantly increased by replacing mHA with nHA at equivalent weight percentages. A combination of 15% nano- and 15% mHA offered mechanical properties comparable to pure nHA (Figure 2). Sawbones injected with ISIs had significantly increased moduli at the highest HA content (30% nHA and 15%/15% n/mHA). Yield stress of injected sawbones was significantly increased after injection of 30% PLGA (1 MPa vs. 2.8 MPa) without added HA, and was further increased with additional HA content.

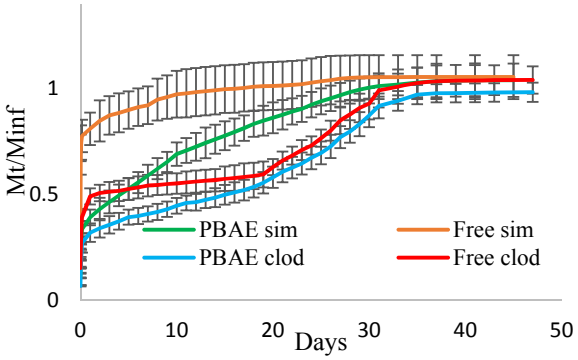

Figure 1. Release profiles of freely mixed vs. PBAE loaded simvastatin and clodronate

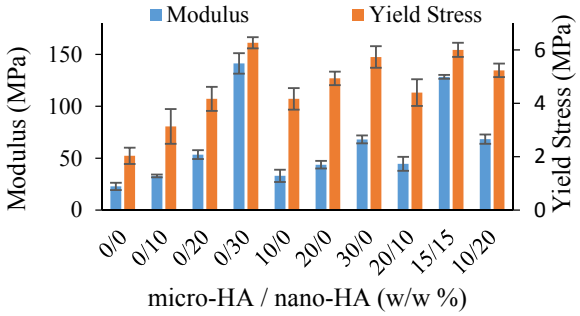

Figure 2. Mechanical properties of cylindrical scaffolds prepared with different micro- and nano-HA content

Conclusions: Additives were demonstrated to improve both release and mechanical properties of traditional ISIs. PBAE microparticles and hydroxyapatite reduced the initial burst of simvastatin and clodronate, respectively, which may be suitable for intraosseous injection where a treatment period of weeks is preferable but rapid precipitation is required. Mechanical properties could be controlled by varying HA content and particle size, and the system was capable of space-filling throughout a trabecular bone-like sample and improving its mechanical properties, which may be useful for acutely salvaging diseased or damaged bone while the drug release component takes effect.

References:

1. Parent M. J Contr Rel. 2013;172:292-304
2. Graham PD. J Contr Rel, 1999;233-245