Development of tunable polyHIPE microspheres for controlled drug release

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Statement of Purpose: Large bone defects often require surgical intervention to fully heal, typically in the form of bone grafts. Growth factors, such as bone morphogenetic protein-2 (BMP-2), are commonly used to improve bone regeneration and fusion. These products commonly result in rapid release of BMP-2 within the first 24 hours, which is often mitigated by using a large excess of growth factor. This excess BMP-2 drastically increases treatment cost and raises concern due to the side effects of BMP-2 including ectopic bone formation and severe inflammation. Alternatively, porous microspheres have been made using a double emulsion technique that can provide local and sustained release. Typical methods require solvents that can denature growth factors and increase manufacturing costs. In contrast, polymerized high internal phase emulsion (polyHIPE) microspheres have tunable pore structures and utilize solvent-free methods. Pore and particle size could be tuned to facilitate a more effective BMP-2 release profile complementary to the healing process. These microspheres can be combined with new and existing bone grafts to allow for site specific delivery of growth factors at lower doses with an extended release profile. Drug eluting polyHIPE microspheres have the potential to improve healing, decrease side effects, and reduce treatment costs.

Methods: Ethylene glycol dimethacrylate (EGDMA, Sigma-Aldrich) purified to remove inhibitor and fabricated into HIPEs in the presence of polyglycerol polyricinoleate (PGPR, Palsgaard) surfactant. A (water-in-oil)-in-water ([W/O]/W) double emulsion was created by pumping an external aqueous solution (3% PVA) through small diameter tubing, while the HIPE was slowly injected into the aqueous stream forming droplets.[1] The monodisperse droplets were polymerized via UV light, filtered, and dried *in vacuo* overnight. Microsphere size ranged from 200-700 µm and exhibited interconnected pores throughout. Fluorescein isothiocyanate-labeled dextran (FITC-dextran, 20k MW, Sigma-Aldrich) was chosen as a BMP-2 analogue and dissolved into the internal aqueous phase to measure particle loading efficiency and release kinetics. Microspheres were also added into polyHIPE monoliths and tested with an Instron 3300 to determine their effect on scaffold compressive properties.

Results: PolyHIPE microspheres were created with tunable diameters and pore sizes that have the potential to controllably deliver growth factors at bone defects. The fabrication process is done at near-physiologic temperatures and without toxic solvents, significantly reducing the need for particle purification. Fabrication parameters were varied generate monodisperse microspheres with diameters from 200-800 µm, and decreasing PGPR concentration during HIPE fabrication increased microsphere pore sizes from 10-27 µm. External flow velocity was found to be the most influential variable on particle diameter, whereas HIPE injection rate and tubing diameter had minor effects. Scanning electron microscopy (SEM) indicated the particles possessed interconnected porous structures throughout. Furthermore, particle diameter and pore size were changed independent of each other. Therefore, nine different particles were made with different combinations of diameter and pore size. The effect of these variables on FITC-dextran loading efficiency and release rate is currently being studied. Additionally, the presence of microspheres in polyHIPE monoliths had minimal effect on scaffold compressive modulus and strength. This supports their use as a component in systems designed to regenerate bone in load bearing applications.

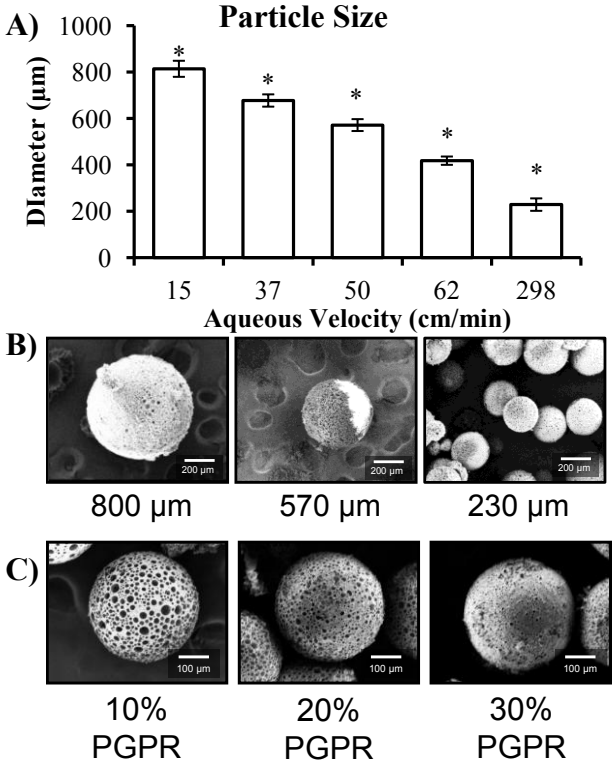

Figure 1: Effect of aqueous velocity on particle size (A); SEM of particle diameters (B) and pore sizes (C).

Conclusions: Highly tunable polyHIPE microspheres were created as a potential growth factor eluting system to enhance bone regeneration. Both particle size and pore structure can be tuned independently, facilitating control over release profile. Additionally, the solvent-free fabrication allows for higher loading efficiencies and prevents solvent-induced denaturation of encapsulated growth factors. This system can also be combined with tissue engineered bone grafts to deliver BMP-2 directly to the defect, greatly improving treatment effectiveness and reducing both cost and side effects.

References:

[1] Gokmen MT. *Macromolecules*. 2009;42(23):9289-9294.