Synthesis of Composite Bioactive Glass - Polymeric Microspheres for Controlled Drug Release

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Statement of Purpose: Osteomyelitis is an infection which attacks bony tissue. During the course of the infection, bone tissue is destroyed. Often, systemic antibiotic treatment cannot clear the infection and local drug delivery is necessary[1]. It has been demonstrated that beads of poly(methylmethacrylate) can be loaded with antibiotics to treat osteomyelitis locally. However, this material does not encourage regrowth of bone and must be surgically removed. There is a need for a material which is degradable, encourages the regeneration of bone, and releases antibiotics over a 3-4 week period. To meet this need, microspheres have been created that are composed of a bioactive glass-polymer composite. Bioactive glasses have been known to slowly dissolve and regenerate new bone. The polymers incorporated into the glass are common in drug release applications and may affect the degradation rate. Furthermore, these composite microspheres are prepared using low temperature, sol-gel chemistry, which allows them to be loaded with antibiotics. The purpose of this study is to demonstrate the influence that composition has on microsphere morphology and degradation in simulated body fluid (SBF).

Methods: A water-in-oil emulsion process is used to create the microspheres[2]. The oil phase consists of 1-octanol with 3wt% Span 80 emulsifier and 1.4 wt% hydroxypropylcellulose thickener. The aqueous phase contains calcium nitrate, an acid or base catalyst (HNO_3 or NH_4OH), and a water soluble polymer (polyvinylpyrrolidone (PVP) or gelatin). This study examines the relationship of catalyst and polymer on microsphere morphology. Tetra(ethylorthosilicate) and tri(ethylphosphate) are added to the emulsion and forms the $SiO_2 – CaO – P_2O_5$ glass network at the oil/water interface. The morphology of the microspheres are characterized using SEM/EDS. To determine the weight percent organic and inorganic material in the microspheres, thermogravimetric analysis is performed. The microspheres are immersed in SBF and analyzed by X-ray diffraction (XRD) for the presence of hydroxyapatite.

Results: Microspheres prepared by this method are polydisperse and have diameters ranging from approximately 1-50 µm. From SEM micrographs, both the catalyst (HNO_3 or NH_4OH) and polymer (PVP or gelatin) influenced the particle size (see figure 1). The particle size of microspheres prepared with PVP is larger than microspheres prepared with gelatin. Similarly, microspheres prepared with an acid (HNO_3) catalyst are larger than microspheres prepared with a base catalyst (NH_4OH). Energy dispersive spectroscopy (EDS) revealed that

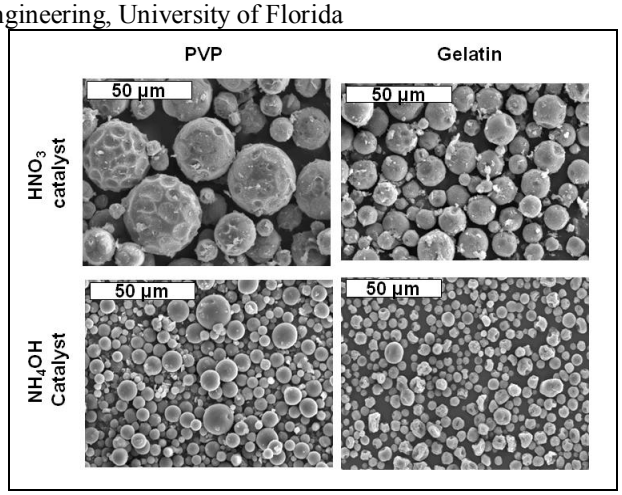

Figure 1. Scanning electron micrographs of composite bioactive glass microspheres.

microspheres prepared with a base catalyst contain significantly more calcium than microspheres prepared with an acid catalyst. Thermogravimetric analysis showed that the catalyst also dictates the relative organic/inorganic content. Microspheres prepared with an acid catalyst contain 50-60wt% inorganic material, while microspheres prepared with a base catalyst contain 20-30wt% inorganic material. After immersing the microspheres in SBF, the acid-catalyzed microspheres retained their shape, while the base-catalyzed microspheres broke apart into sub-micron particles. The XRD spectra on the immersed microspheres shows a peak at $2\theta = 32°$ which indicates that hydroxyapatite forms on all particles after immersion in SBF.

Conclusions: To our knowledge, this is the first study demonstrating the synthesis of organic/inorganic hybrid microspheres that show *in vitro* bioactivity. Furthermore, the composition of these microspheres influences their dissolution rate. Microspheres prepared with NH_4OH contained a larger amount of polymer and broke apart more easily in SBF. This indicates that this composition is more appropriate for a burst-release of drugs. However, microspheres prepared with HNO_3 did not break down after immersion in SBF, suggesting that this composition may provide a more sustained drug release profile. This study demonstrates that microspheres which are capable of bonding to bone can be prepared using a low temperature process. This low temperature process is suitable for directly encapsulating antibiotics into the microspheres.

References:

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