

## Control of Macromolecular Drugs Delivery Using Polysaccharide Microgels

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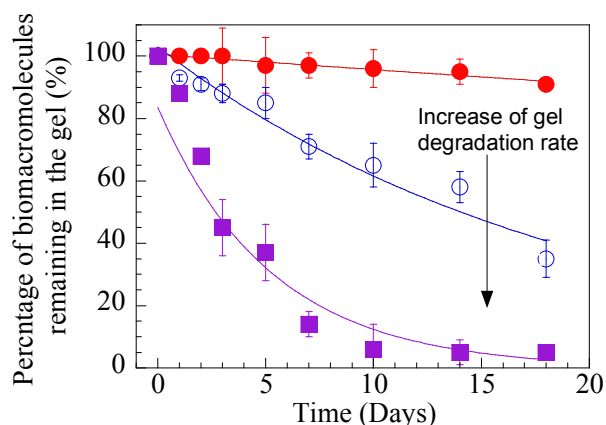
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**Statement of Purpose:** Implants have been extensively used to replace bone severely damaged from disease, accidents and trauma. Several osteogenic growth factors and plasmid DNAs encoding for these growth factors are often used to improve implant fixation as effectively as autogenous bone grafting by stimulating differentiation of host bone-forming stem and progenitor cells. These stimulatory effects may be further improved with local and sustained delivery of growth factors using biodegradable microparticles. These growth factor-encapsulating microparticles are commonly placed in a gap between implants and original bone, but the presence of these particles may sterically hinder the development of new bone matrices in the gap. We hypothesized that the degradation rate of microparticles plays an important role in regulating the engineered bone density in the gap due to the changes of interstitial volume between microparticles. This hypothesis was examined with microparticles releasing growth factors via degradation and those releasing growth factors via diffusion. The polysaccharide microgels were used as model growth factor delivery devices and bone morphogenic protein (BMP)-2 and transforming growth factor-beta (TGF- $\beta$ ) were used as model osteogenic growth factors. The degradation rate of microgels was controlled by modifying molecular weights and chemical structure of polysaccharides. The results of this study will be broadly useful to improving fixation of a broad array of implants.

**Methods:** BMP-, TGF- $\beta$  and plasmid DNA-encapsulating microparticles of calcium cross-linked alginate hydrogels (FMC, molecular weight  $\sim$  250,000 g/mol) were prepared by dropping the mixture of the growth factors and alginate solutions into CaCl<sub>2</sub> solution using a capillary extruder with varied diameters. The growth factor concentration in the microgel was kept constant at 100  $\mu$ g/ml. The degradable microgels were prepared by modifying the molecular weights and chemical structure of alginate molecules. Specifically, the molecular weight (MW) of alginates was reduced to 50,000 g/mol by irradiating them under  $\gamma$ -rays. One percent of uronic acid residues in both high MW alginates and low MW alginates were next oxidized to induce hydrolytically labile acetal linkages in the polymer chains. The microgels releasing growth factors via diffusion were prepared by reducing the concentration of unmodified alginate molecules in the gel. The degradation rates of microgels were monitored with mass changes of microgels. Growth factor release rates were measured using ELISA kits. The bioactivity of the released growth factors from the microgels was evaluated with osteogenic differentiation level of preosteoblasts (BMP-2) and inhibition of mink lung epithelial cell proliferation (TGF- $\beta$ ).

### Results:

Microgels consisting of unmodified high MW alginates and those consisting of the mixture of oxidized high MW alginates and oxidized low MW alginates were prepared. As expected, the incorporation of oxidized units into alginate molecules and reduction of MW accelerated the degradation rates of microgels and subsequent growth factor release rates. The reduction of concentration of unmodified alginate molecules in the gel also lead to the increase of growth factor release rates without significant degradation of microgels. The growth factors released from these microgels maintained bioactivity.



**Figure 1.** Drug release rates accelerated with degradation rates of microgels.

**Discussion:** This study showed that the rate of growth factor release can be controlled using both degradable and non-degradable microgels. In vivo, the use of degradable microgels for promoting the development of bone tissue adjacent to the implant and subsequent fixation of implants may be preferable to the use of non-degradable microgels, which are expected to sterically limit bone ingrowth, leading to poor fixation of implants.

### References:

1. Kong, H. J et al Design of Biodegradable Hydrogel for the Local and Sustained Delivery of Angiogenic Plasmid DNA *Pharmaceutical Research* (In press, 2008).
2. Kong, H.J. et al Controlling rigidity and degradation of alginate hydrogels via molecular weight distribution. *Biomacromolecules* 5:1720 (2004).