Dual mechanism for toughening and sustained aminoglycoside elution from a polyphosphate hydrogel

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Introduction: Bacteria preferentially colonize biomaterial and medical device surfaces, often leading to the formation of an exopolysaccharide matrix or biofilm, capable of increasing resistivity to antibiotics by up to 1000 fold.[1] As a result, infections in chronic wounds or on medical device surfaces may require hospital readmission, long courses of high-dose antibiotics, revision surgeries, culminating in patient discomfort, increased morbidity rates, and elevated health care costs.[2] Hydrogels have been explored as potential drug carriers with good biocompatibility. A major drawback has been the weak, brittle nature of hydrogels. Here we report on a polyphosphate hydrogel with a dual mechanism for both toughening and prolonging aminoglycoside drug release.

Materials and Methods: Polyphosphate hydrogels were formed by free radical polymerization of: methacrylated poly(phosphoethyl-methacrylate-co-acrylic acid) polymer (6.5 wt %), acrylamide and bis-acrylamide (1 wt %) with APS and TEMED as initiators. Hydrogels were then loaded with either 50 mM Ca2+, 5 mM tobramycin or a combination of both. All loading solutions contained 150 mM NaCl and were pH adjusted to 7.7. Volume changes during loading were measured by photography and image J software. Hydrogels were immersed in 130 mM NaCl, plus 1.5 mM Mg2+ and 2.5 mM Ca2+ at pH 7.3, the solution was changed daily and tobramycin content measured colorimetrically to determine the release behavior. The initial modulus was measured using an Instron 3342 material test system and derived from the linear slope from the first 10% of compressive strain, errors are +/- 1 S.D., n=3.

Results and Discussion: Both divalent metal cations and positively charged drugs will electrostatically crosslink phosphates in the hydrogel structure.[3] Hydrogels shrank by ~50% after the addition of Ca2+ or tobramycin antibiotic, resulting from dense metal-phosphate or drug-phosphate crosslink formation.[3] Ca2+ has a toughening effect resulting in a compressive modulus of 0.8 +/- 0.07 MPa, Fig. 1B. In contrast tobramycin loading has a limited toughening effect, 0.04 +/- 0.01 MPa compressive modulus, but results in prolonged release of tobramycin above the measured MBC for P.Aeruginosa (2 µg/ml) for greater than 50 days, Fig 1A. The prolonged release has been shown effective at total eradication of P.Aeruginosa biofilms (9 log10 reduction) in a biomimetic flow cell. Preliminary studies combining both Ca2+ crosslinks and tobramycin crosslinks in a single hydrogel have resulted in a hydrogel that is both tough, compressive modulus of 0.2 +/- 0.01 MPa, and maintains the prolonged release profile for tobramycin.

Conclusion: Polyphosphate hydrogels with the dual toughening and drug releasing mechanism could be capable of a structural role in arthroplasty procedures or as a protective bandage in wound care or surgery and still sustain local release of antibiotics.