Charged Hydrogels for the Controlled Elution of Vancomycin

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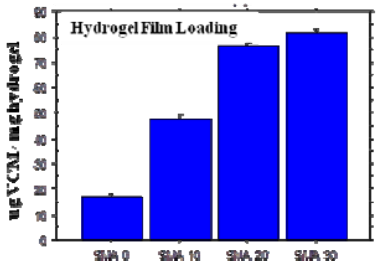
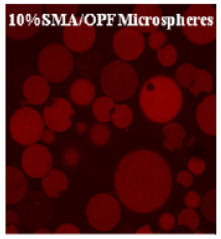
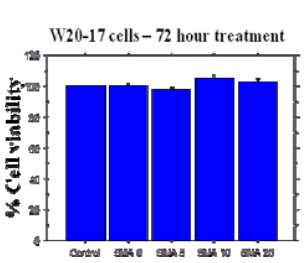
Statement of Purpose: Orthopedic surgery, bone grafting and tissue reconstruction procedures are closely paralleled to a high rate of infection at the wound site (1,2). This complication often requires a second surgical procedure – risking further complications and lengthening patients' recovery time. The effectiveness of antimicrobial agents to combat infection is hindered by systemic toxicity, bacterial resistance and patient adherence to dosing schedules(1). The use of localized, extended release formulations for antimicrobial compounds would provide clinicians the ability to prevent infection at the wound site while controlling dosage and decreasing adverse side effects (3). Localized delivery also limits unwanted bacterial exposure and decreases risk of development of bacterial resistance. Here, we present a biodegradable, polymer hydrogel formulation capable of controlled release of vancomycin (VCM) for clinical applications. Oligo(poly(ethylene glycol)fumarate) (OPF) hydrogels have been produced and characterized by our lab and show promise as an implantable delivery vehicle for prophylaxis of infection following surgery.

Methods: Oligo(poly(ethylene glycol)fumarate) (OPF) was synthesized according to methods previously reported (4). OPF was characterized by ^{1}H-NMR and GPC. OPF/Sodium methacrylate (SMA) copolymer hydrogel films and microspheres were prepared according to previously published methods (5). Characterization of OPF/SMA films and microspheres was performed by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Analysis of drug concentrations was performed by measurement of drug absorbance at 280 nm using a SpectraMax Plus UV-visible spectrophotometer (Molecular Devices). Rabbit ear chondrocytes (REC) and mouse bone marrow cells (W20-17) were cultured in Dulbecco's Modified Eagle Media Advanced Formulation containing 10% fetal bovine serum and 100 units ml^{-1} penicillin and 100 ug ml^{-1} streptomycin. Cell cultures were plated in 12-well dishes at 50,000 cells / well and maintained for 24 hours before treatment. Methicillin resistant S. aureus bacterial culture originated from a clinical join infection and was obtained from the lab of Dr. Robin Patel (Mayo Clinic, Rochester, MN).

Results: Our results demonstrate that OPF/SMA copolymer hydrogels lack toxicity in both REC and W20-17 cell cultures. Cellular viability of REC and W20-17 cells was measured by MTS assay after 72 hour incubation with hydrogel samples. DSC results show that increased SMA in the OPF hydrogel does not change its melting point or glass transition temperature. The OPF/SMA hydrogels are able to be efficiently loaded with VCM and this loading is charge dependent. Release of the drug over time is delayed by increased hydrogel SMA content (charge incorporation). Extended release of biologically relevant drug concentrations is possible up to 14 days and is dependent upon ion exchange *in vitro*. Post release, hydrogel eluted VCM was shown to be effective in a strain of methicillin-resistant S. aureus that was obtained from a clinical joint infection.







Toxicity of eluted VCM in MRSA
-Drug samples recovered after 48 hr release
-Bacteria allowed to proliferate for 24 hrs

	Log10 CFU/mL
0% SMA/OPF	
10% SMA/OPF	
20% SMA/OPF	
30% SMA/OPF	
Hydrogel w/o VCM	7.65
DPBS	5.37

Conclusions: In this study, we identify a means by which to consistently deliver vancomycin over a 14 day period using a biodegradable hydrogel system. This delivery system is shown to be non-toxic *in vitro*. The loading of the hydrogels with vancomycin is dependent on incorporation of SMA into the hydrogel, and burst release of the drug is dampened by increased SMA concentration. Bacterial culture experiments revealed that released vancomycin was effective in inhibiting bacterial culture growth. Future directions of this study involve continued optimization of the hydrogels to allow sustained release or delivery of multiple therapeutic agents. Further, an animal model of infection may be employed to test the effectiveness of the drug eluting hydrogel *in vivo*.

References:

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