Controlled release of novel anti-biofilm agents from a poly (2-hydroxyethyl methacrylate) Scaffold for the treatment of medical device associated bacterial biofilm infections

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Statement of Purpose: It is estimated that over 5 million artificial or prosthetic devices are implanted per annum in the U.S. alone. However, 70% of hospital-acquired infections are associated with implants or indwelling medical devices causing >$4.5 billion medical costs annually. Systemic antibiotic therapy to control medical device-associated infections typically fails to clear biofilm, promotes antibiotic resistance, and inevitably requires removal of devices. The goal of this proposed research is to develop a new non-antibiotic based concept in biomaterials design where the biomaterial promotes healing while preventing biofilm colonization and subsequent infection. In this study, we developed a model porous “template” constructs (PCTs) of poly(2-hydroxyethylmethacrylate) (pHEMA) hydrogels encapsulated with two complementary therapies: (a) an EPS polysaccharide dispersant and (b) a Ga-siderophore based antibacterial agent to enhance drug transport and uptake for the treatment of biofilm infection diseases. Enzyme-based therapies in combination with antimicrobial Ga-complexes produced synergic effects of reducing biofilm formation.

Methods: Two Gallium (Ga) complexes drugs were synthesized using a chelation reaction. HEMA monomer was mixed with tetraethylene glycol dimethacrylate (TEGDMA), ethylene glycol and UV photo initiator. Each drug was dissolved in diH2O and then added to above monomer mixture. Un-crosslinked poly(methyl methacrylate) (PMMA) microspheres of a desired diameter are ultrasonically packed into a mold. The mold is gently heated, which leads to sintering (fusion) of the spheres at their contact points. Next, the above mixed pHHEMA monomer is vacuum-drawn in liquid form into the mold, surrounding the sintered beads. Monomer is UV polymerized in-place into a solidified crosslinked network. Finally, the PMMA microspheres are solubilized from within the crosslinked network, leaving a porous, interconnected structure. The solidified pHEMA sca were punched into one-centimeter disks, and vacuum dried. The absorbances of the drug release from samples were measured by UV spectrophotometer at 576 nm wavelength periodically for 3 months. All drug loaded pHHEMA scaffolds showed significant reduction of adherent SA and PA cells versus control scaffolds in vitro. More importantly, our preliminary data indicated pHHEMA scaffolds releasing Ga-complex drugs show great promise as a novel non-antibiotic drug delivery system to prevent medical devices associated biofilm infections in vivo.

Conclusions: Incorporation of novel drugs into pHHEMA polymers achieved constant drug release rates throughout an extended period of time up to 3 months. Total amounts of drugs released from pHHEMA scaffolds in a controlled-sustained manner are sufficient to kill bacteria growth in the liquid phase, as well as to reduce bacteria adhesion on surfaces. Enzyme-based therapies in combination with antimicrobial Ga complexes produced Synergic effects of reducing biofilm formation. Gallium complexes and Dispersin™ were promising non-antibiotic therapeutic drugs both in vitro and in vivo that could be released from the pHHEMA scaffolds, thus enhancing the treatment effects to remove bacterial biofilm infections associated on medical devices.

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