PEG/Poly(acrylic acid) Semi-IPN Hydrogels for
Post-Synthesis Electrostatic Antibiotic Loading and Controlled Release

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Purpose: Because of the increasing significance of infection, particularly biomaterials-associated infection, antimicrobial delivery from various hydrogels has been receiving more attention. Typically, the loading is controlled by the synthesis conditions, and the release is controlled by the network tortuosity. We are exploring a different method for antimicrobial loading and controlled release. Specifically, we are studying how electrostatic interactions can enable the *post-synthesis* electrostatic loading of antibiotics into PEG-based hydrogels and how these electrostatic interactions influence the subsequent antibiotic release. We introduce electrostatic charge by blending poly(acrylic acid) (PAA) into PEG diacrylate followed by photopolymerization to entrap the PAA in a controllably crosslinked PEG gel network (Fig. 1). We study the loading, release and antimicrobial effectiveness of 2 FDA-approved antibiotics (amikacin, colistin). Both are small enough to traverse the gel mesh and both have a net positive charge that interacts strongly with deprotonated PAA acid groups (Fig. 1B).

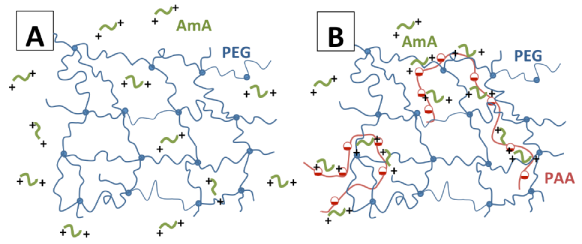

Fig. 1 – Schematic illustration of small-molecule cationic antimicrobial agents (AmA) loading preferentially into PEG/PAA semi-IPN gels (B) than into pure PEG gels (A).

Methods: PEG gels were created by photopolymerizing poly(ethylene glycol) diacrylate (PEGDA, Mw 575 Da) and PEG/PAA semi-IPN gels were created by photopolymerizing PEGDA in the presence of polyacrylic acid (Mw 450 kDa; 1:7 PAA:PEG). In both cases the PEGDA macromer and PAA homopolymer were dissolved in water-ethanol (50:50 v:v) mixtures to achieve a final polymer concentration of 7 vol%. After polymerization, the gels were washed in water for 1 week. Antibiotic loading was achieved by soaking gels in solutions of amikacin or coliston dissolved in 0.01 M phosphate buffer (pH 7.4). The antibiotics were subsequently released into PBS (pH 7.4) under low salt (0.01 M) or physiological salt (0.15 M) conditions. The time-resolved antibiotic release was followed by UV absorbance spectroscopy. The effectiveness of the gels to inhibit bacterial growth was studied using *S. aureus* (ATCC 12600) and *E. coli* (NEB 5-alpha competent) cultured on Mueller-Hinton agar for Kirby-Bauer tests.

Results: Since both amikacin and coliston are colorless, we demonstrated electrostatic loading using methylene blue, a small-molecule cationic dye. Fig. 2 illustrates a typical result. Soaking a pure PEG gel in a methylene blue solution loads the gel to a concentration roughly equal to that in the surrounding solution. In contrast, the PAA semi-IPN introduces a substantially higher thermodynamic driving force for the dye absorption. Consequently, the PEG/PAA gel has a significantly deeper blue color than the pure PEG gel. Similar effects are seen with amikacin and coliston. PEG/PAA gels load over 40x more amikacin or coliston than pure PEG gels.

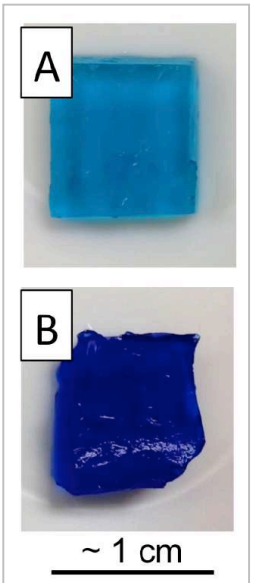

Fig. 2 - (A) PEG and (B) PEG/PAA gels after soaking overnight in a methylene blue solution.

We performed Kirby-Bauer tests on antibiotic-loaded gels after soaking them for 30 days immersion in eluting buffers. None of the PEG gels exhibited an inhibition halo. What little antimicrobial was absorbed rapidly diffused out of these gels. In contrast, the amikacin-loaded (Fig. 3) and colistin-loaded PEG/PAA gels have significant inhibition halos. The electrostatic interactions provide both a high drug reservoir and greater resistance to antibiotic diffusion through the gels (i.e. lower diffusivity).

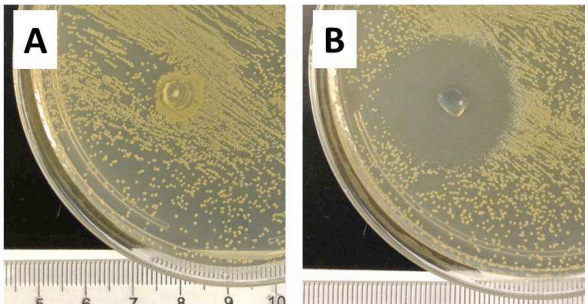

Fig. 3 - *S. aureus* inhibition zones by amikacin-loaded (A) PEG and (B) PEG/PAA gels after 30 days immersion in eluting buffer.

Conclusions: Electrostatic interactions introduce by simply polyacid blending into a neutral gel enable post-synthesis antibiotic loading and influences the subsequent antibiotic release.