Development of Vancomycin-Linked Poly(β-amino ester) Hydrogels

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Statement of Purpose: Drug release profiles of freely loaded small molecules into biomaterial constructs often exhibit an initial burst release, greatly impacting the long term ability of these materials to effectively sustain a desired zero order release profile[1]. Within the application of antibiotic releasing wound dressings, limiting the burst effect avoids the potential for multiple surgeries and aids in sustainment of a therapeutic output. In this research, an *in situ* formable and biodegradable poly(β-amino ester) hydrogel was developed for local drug delivery purposes to achieve sustained release of the antibiotic vancomycin. With the intention of limiting the initial burst effect of vancomycin and slowing the overall release to match more closely the degradation of the bulk matrix, the hydrogel was functionally modified to contain antibiotically active vancomycin. Further, the hydrophilic to hydrophobic content of the hydrogels can be varied during synthesis so as to allow large tunability in degradation rates, and thus vancomycin release rates.

Methods: Poly(β-amino ester) (PBAE) hydrogels were formed through free-radical polymerization. Initially, a macromer was formed via Michael-addition of isobutylamine (IBA) with a mixture of poly(ethylene glycol) 400 diacrylate (PEGDA) and diethylene glycol diacrylate (DEGDA), and then this macromer was mixed in with tetramethylethylenediamine (accelerator) and ammonium persulfate (initiator) to form a poly(β-amino ester) hydrogel to which free vancomycin could be added. For vancomycin incorporated hydrogels, IBA was replaced partially with a molar equivalent of free-amine containing vancomycin to participate in Michael-addition. Degradation of the hydrogels was performed using weight difference after sink-condition degradation in phosphate-buffered saline (PBS). Extended antibiotic release was also determined via sink-condition degradation in PBS, and was analyzed using HPLC. To determine the antibiotic activity on *Staphylococcus aureus*, a modified Kirby-Bauer assay was used where each day the same hydrogel was transferred to a freshly inoculated agar plate and zones of inhibition were measured until they were no longer present. Vancomycin incorporation was identified through mass spectroscopy (MALDI) of HPLC fractions collected of hydrogel degradation samples.

Results and Discussion: Depending upon hydrogel formulation, vancomycin release proceeded up to two weeks under PBS sink conditions. By incorporating vancomycin into the PBAE polymer backbone, vancomycin release was significantly delayed as compared to free-loaded vancomycin of the same degradation period (Figure 1). 90% release values were increased by four days using the covalently-linked vancomycin loading technique compared to free-loading. This release correlated with activity time-course on *S. aureus* using a modified Kirby-Bauer assay that lasted upwards of nine days. An m/z number correlating to vancomycin incorporation in mass spectroscopy was attained from an HPLC peak fraction collection. Through variation of DEGDA:PEGDA content, it was possible to vary the vancomycin-incorporated release rates from three to eight days (Figure 2).

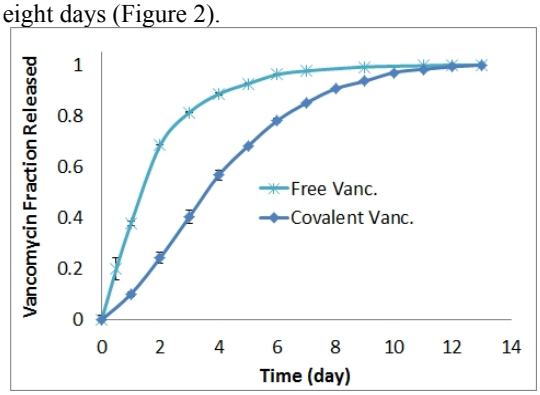

Figure 1. Comparison of vancomycin release from both free-loaded and covalently-loaded hydrogels.

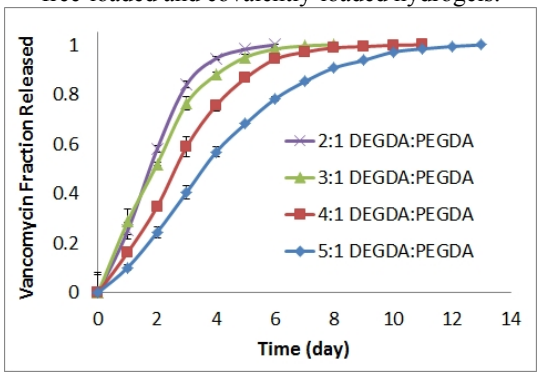

Figure 2. Variation of DEGDA:PEGDA ratio changes vancomycin release rate from vancomycin-incorporated hydrogels.

Conclusions: Vancomycin was incorporated into poly(β-amino ester) hydrogels which produced a modified release trend and provided an extended release of antibiotics compared to free-loading. With increasing hydrophilicity of the composition of the hydrogels, the release rate increases, and can be greatly expanded beyond the ratios provided in figure 2. This relationship is also present when analyzing the degradation periods of these hydrogels, as the more hydrophilic hydrogels also degrade more quickly. Further, the tunability of the hydrogel chemistry allows for wide variation in the drugs released, seeing how any drug with free amines may be used for covalent incorporation, and also for the modification of degradation times to allow adjustment of payload release.

References: 1. Huang, X. and C.S. Brazel, On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. Journal of Controlled Release, 2001. 73(2-3): p. 121-136.

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