Study of Doxycycline Release Profiles from Different *In situ*-forming Polymeric Implants

J. M. Olbrich, S. D. Nagatomi, J. T. Corbett, K. A. Nichter, K. J. L. Burg†, S. W. Shalaby
Poly-Med, Inc., Anderson, SC
†Department of Bioengineering & Institute for Biological Interfaces of Engineering, Clemson University, Clemson, SC

Statement of Purpose: Since the development of a family of fast-absorbing polyether-esters as injectable *in situ* hydrogel-forming formulations about a decade ago, and the use of typical formulations as matrices for the controlled delivery of antibiotics, there has been a consistent interest in exploring a new family of polymers having prolonged absorption profiles and broader scope of clinical applications.[1-3] This directed our attention to exploring the potential of a new family of absorbable, segmented polyurethanes as *in situ*-forming implants and the use of typical members of this family of polymeric systems as matrices for the controlled release of various drugs. More specifically, these absorbable polyurethanes are represented by a group of amorphous polyether-ester-urethanes and crystalline polyether-ester-urethanes.[4,5] This communication deals with evaluating the effect of typical formulations of both groups on the controlled release of doxycycline, which has been extensively studied in hydrogel-forming formulations.[6]

Methods: In these studies, the release of doxycycline hyclate from amorphous poly-ether-ester urethanes was reviewed. These polymers, termed OC, were synthesized at Poly-Med using a method outlined in previous publications.[4,5] The non-crystalline series of these polymers are denoted by OC2 through 9. Each of these polymers were processed into a gel by first synthesizing a polymer blend of the OC polymer and acetylated PEG400 polymer(G4A) in a 2:1 ratio. Doxycycline was then combined, at 5% (by weight), with the polymeric blend with a mortar and pestle to ensure thorough mixing. Once homogeneity was visually achieved, the mixture was then evenly distributed into three 20 mL glass vials. These samples were allowed to flow out to create comparable surface areas. Once the gels evenly coated the bottoms of the vials, 10 mL of phosphate buffer (pH 7.2) was introduced into each glass vial. These samples were then placed into a 37°C incubator to simulate physiological conditions. At each time period, the buffer was removed from each sample, filtered and analyzed by HPLC. The HPLC method for analysis of doxycycline was developed at Poly-Med using reverse-phase liquid chromatography and analyzed at 350 nm. The results of this analysis were compared with those of a standard curve to allow the quantification of drug release from the samples.

Results: Doxycycline release profiles from the OC3 through OC8 systems were similar (Figure 1). In contrast, OC9 exhibited lower overall release at all time periods tested, with a noticeably lower initial release during the first two days. The OC2 system exhibited a low initial burst of release on the first day, but had a cumulative release that was comparable to that of other systems. The OC2 and OC9 polymers have higher molecular weights and polydispersity indices than the other polymers (Table I). In addition, OC2 was polymerized with the highest diisocyanate concentration compared to the other formulations.

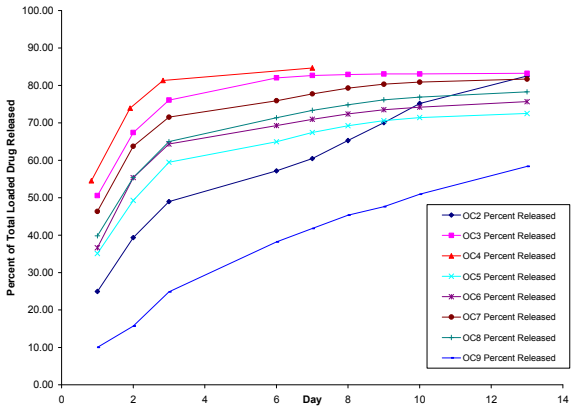

Figure 1: Cumulative Release of Doxycycline from Various OC Polymers

Table I: Properties of Amorphous OC Polymers

Polymer	PP to Diiso (molar)	Mw (Da)	PDI
OC2	1 to 1.2	31,259	1.86
OC3	1 to 0.8	14,175	1.55
OC4	1 to 0.8	13,571	1.61
OC5	1 to 0.8	15,641	1.59
OC6	1 to 0.8	13,981	1.44
OC7	1 to 0.8	15,858	1.61
OC8	1 to 0.8	14,297	1.51
OC9	1 to 0.8	18,566	1.81

Conclusions: Lower initial release with a comparable cumulative release suggests that the OC2 system may be an excellent candidate for a controlled-release drug delivery system. Furthermore, the release profile of the OC9 system indicates that, after 2 weeks, approximately 50% of the drug that was initially loaded may still be available for release. These results suggest that the OC9 system may be an even better candidate for the long-term delivery of drugs. Future work will concentrate on optimizing variables that will allow the creation of tailored, polymeric, drug-delivery vehicles.

References:

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