Injectable Absorbable Liquid Gel-Forming Systems for Localized Delivery of Therapeutic Agents

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Statement of Purpose: Localized drug delivery holds multiple advantages over systemic delivery. Drugs can be utilized more efficiently, toxicity issues can be minimized, and uptake issues can be circumvented. To this end, an injectable drug delivery system has been developed to administer bioactive agents. The system is absorbable and biocompatible rendering polymer toxicity issues and explantation irrelevant. Most significant is the fully modular nature of the therapeutic release profile from the system. Drug release can be controlled from short (3-5 day) administration to long-term (>45 day) treatment. Through the use of additives and manipulation of the base polymers, release can also be shifted from burst kinetics to zero-order release. Multiple drugs have been incorporated with this system lending to the possibility of a myriad of clinical applications. This communication presents the entirety of variables examined which can be manipulated to represent the modular nature of the system.

Methods: In these studies, the release of drugs from poly-ether-ester urethane (PEEU) based systems have been analyzed and controlled. These polymers, termed the OC series, were synthesized at Poly-Med using a method outlined in previous publications.[1,2] The preparation of each system follows three steps. First, a pre-synthesized OC polymer and acetylated PEG400 polymer (G4A) diluent are mixed using heat. Next, selected additives (examples include microparticles, linear and tri-axial polymers) are introduced into the mixture to induce the desired release profile. Finally, the desired drug is introduced into the liquid gel and mixed physically to homogeneity. These samples were examined through a batch *in vitro* release study simulating physiological conditions. At predetermined time points, eluents were analyzed for drug concentration via HPLC. The results of this analysis were compared with those of a standard curve quantifying drug release, and thus curves of cumulative amount released versus time were developed.

Results: Over 300 studies have been performed to allow for the framework of a drug delivery model. Figure 1 shows four curves indicative of the modularity of our system. The left most curve (OC4/G4A) exhibits a burst profile where the majority of the payload is delivered in 3-5 days. The bottom curve (OC9/G4A/SW2) shows a near zero-order release profile that has been attained. The other curves shown are examples of drug delivery systems developed to release "in between" these two systems. Figure 2 shows one of the ways in which a system can be further manipulated. By introducing A6, a polar micro particulate additive, into our mixture the polar drug in this example can be retained for a longer period of time. Also, by increasing the percentage of A6 used this effect can be seen to be strengthened. Similar effects have been seen with other related additives. Other avenues of control include blending of base OC polymers, varying of diluent percentage and type, and end-group modification of polymers.

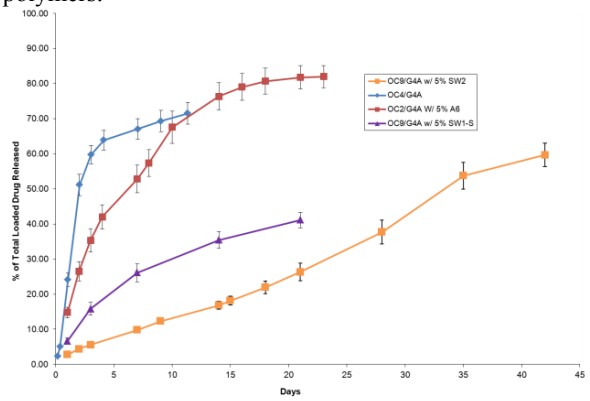

Figure 1. Release of a water-soluble drug from various OC systems

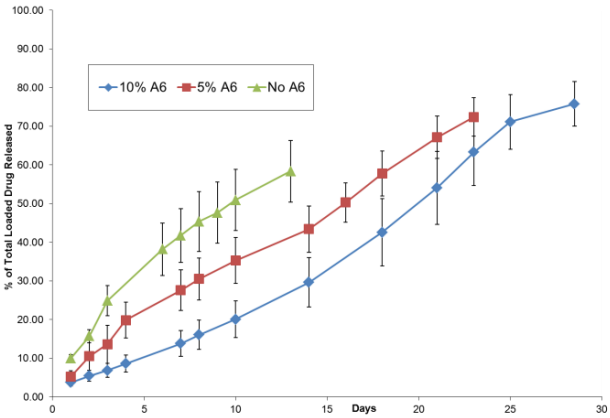

Figure 2. Effect of introduction of A6 additive on release curves of a water soluble drug

Conclusions: This polymeric system has demonstrated full modularity and the major controlling variables have been identified through extensive *in vitro* testing. This control can be achieved through a variety of ways including introduction of polymeric additives and end group modification. Future work with this system will include *in vivo* testing and correlation to *in vitro* models. The end goal entails a fully customizable platform technology that inputs drug characteristics and desired release specifications and outputs the required polymeric system, which could serve as a delivery vehicle for bioactive agents such as antibiotics, peptides, hormones, and antineoplastics among others.

References:

1. Shalaby, S.W. et al., U.S. Pat app. 12/454,774 (2009).
2. Shalaby, S.W. et al., U.S. Pat app. 61/211,800 (2009).