Effect of Drug Physicochemical Properties on Release Profiles from an Absorbable *In situ*-forming Implant

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Statement of Purpose: The effects of key physico-chemical properties of drugs on the release profiles of different drugs from fast-absorbing absorbable polyether-ester-based gel-forming liquid formulations have been the subject of several studies in this laboratory.[1-5] Recent development of new polyether-ester-urethanes and their use in *in situ*-forming bioactive implants revealed that they have prolonged absorption profiles compared with the faster absorbing polyether-ester gel-forming formulations.[6,7] This development evoked the need to assess the effects of the physicochemical properties of drugs on their release profiles from polyether-ester gel-forming formulations. The present study examines these properties by examining the release profiles of different drugs from a poly-ether-ester urethane (PEEU).

Methods: The polymer OC4 was synthesized following a procedure outlined in a previous publication[5]. The following drugs were evaluated as part of this study: amikacin sulfate, cefuroxime sodium, clindamycin hydrochloride, dicloxacillin sodium monohydrate, doxycycline hyclate, metronidazole, and tobramycin sulfate.
The polymer blend of OC4 and acetylated PEG400 polymer (G4A) was created in a 2:1 ratio. Each drug was then combined (5% by weight) with the polymeric blend in a mortar and pestle to ensure thorough mixing. After mixing, the drug-loaded polymer was then evenly distributed into three glass vials. Once the gel evenly coated the bottom of the vial, ten milliliters of phosphate buffer (pH 7.2) was added to each vial. The samples were then incubated at 37 °C to simulate physiological conditions. At each time period, the buffer was removed from each sample, filtered and analyzed by HPLC. The results of this analysis were compared with those of a standard curve to allow quantification of drug release from the samples.

Results: As shown in Figure 1, each of the drugs tested had a unique release profile. Interestingly, the drugs in sulfate form (amikacin and tobramycin) released the lowest percentage of total payload. These were both on the lower end of the solubility spectrum, which can be seen in Table I. In contrast, cefuroxime, which is highly soluble in water, released the greatest percentage of drug. Molecular weight also appears to have an effect on release profiles. Metronidazole is a relatively small compound that, despite its low water solubility, still exhibited a strong release. In addition, drugs with similar solubilities (clindamycin, dicloxacillin, doxycycline, and tobramycin) have varying release profiles that appear to correspond with their molecular weight. Specifically, those with lower molecular weight released more than those with higher molecular weights.

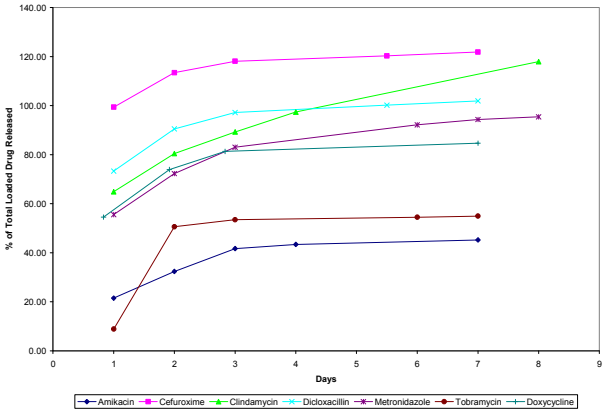

Figure 1: The Overall Averaged Release Curves of Each Drug

Table I: Drug Information

Drug	Solubility in water (mg/ml)	Mw	Total Release % / Day Duration of Release
Amikacin	>10	781.75	45.2/7
Cefuroxime	>200	661.6	121.9/7
Clindamycin	>50	461.45	117.93/8
Dicloxacillin	>50	510.3	101.9/7
Doxycycline	>50	1025.87	84.7/7
Metronidazole	>10	171.15	95.42/8
Tobramycin	>50	1425.45	54.91/7

Conclusions: These results indicate that it may be possible to predict the release of drugs from poly-ether-ester urethane (PEEU) polymers based on the compound form, solubility, and molecular weight of the drug. This type of model would allow direct tailoring of a drug loaded product for a defined application. Future work will focus on quantifying the effect of each variable on the release profile of the system.

References:

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