In Vitro and *In Vivo* Comparison of Sequential Drug Release

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Statement of Purpose

A bioerodible, multilayered device capable of delivering four different drugs in a sequential manner was previously developed. Drug delivery systems are routinely characterized for their *in vitro* release performance. For more complex delivery systems, such as one that sequentially releases multiple drugs, it is important to confirm that *in vivo* release properties correlate with the expected "programming" achieved *in vitro*. The present research evaluated and compared biomaterial erosion and sequential drug release from a multilayered delivery system *in vitro* and *in vivo*.

Methods

CAPP films were prepared by dissolving CAP and Pluronic in the ratio of 90:10 in acetone. This polymer solution along with 1 or 5 wt% of drug was cast in Teflon dishes, and the films were obtained by solvent evaporation at 4°C. Metronidazole (M), ketoprofen (K), doxycycline (D), and simvastatin (S) were loaded in the CAPP films. The multilayered device was fabricated by attaching alternating layers of blank and drug-loaded CAPP films in the required sequence to achieve sequential release of more than one drug in a particular order. These multilayered devices were also incorporated with poly(sebacic acid) layer in between the blank layers to achieve slower erosion and drug release. The poly(sebacic acid) was also used as a barrier coating to obtain unidirectional polymer erosion and drug release. After *in vitro* characterization, devices were implanted in a rat calvarial onlay model and retrieved at specific time points. *In vivo* mass loss, thickness loss, and drug release were measured and compared with the corresponding *in vitro* profiles.

Results and Discussion

The cumulative release profiles of metronidazole, ketoprofen, doxycycline and simvastatin from multilayered CAPP devices showed sequential release of four drugs both *in vitro* and *in vivo* (Figure 1). This behavior was observed for faster eroding devices (shown), slower eroding devices (data not shown), and devices with different drug doses (data not shown). The comparison of *in vitro* and *in vivo* drug release showed that drug release occurred at a relatively faster rate *in vivo* during the initial stages and slowed down during the final stages. This difference was confirmed by comparing *in vitro* mass loss and *in vivo* thickness loss. Figure 2 demonstrates the initially increased rate of erosion that later slowed *in vivo* in the slower eroding devices. This late reduction in erosion and release rates *in vivo* result from the combined effects of the cup-shaped device design and growth of fibrous tissue.

Whereas many comparative studies of *in vitro* and *in vivo* drug release from biodegradable polymers are for a single drug, the present research demonstrated that sequential release of four drugs can be maintained following implantation.

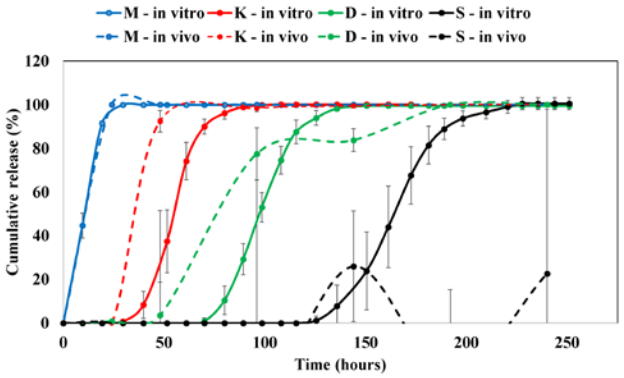

Figure 1. *In vitro* and *in vivo* cumulative sequential release of four drugs. Data are mean ± standard deviation (n=3).

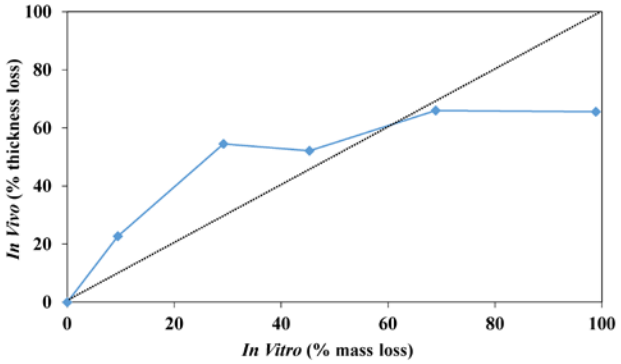

Figure 2. Comparison of *in vitro* mass loss and *in vivo* thickness loss of slower eroding devices.

Conclusion

Although this multilayered system was capable of releasing four drugs in a sequential manner both *in vitro* and *in vivo*, understanding differences in material erosion and drug release between *in vitro* and *in vivo* conditions are important for tailoring profiles for different applications.

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