Slow, Sustained Release of Corticosteroids from a Polymeric Liquid for Use in Osteoarthritis

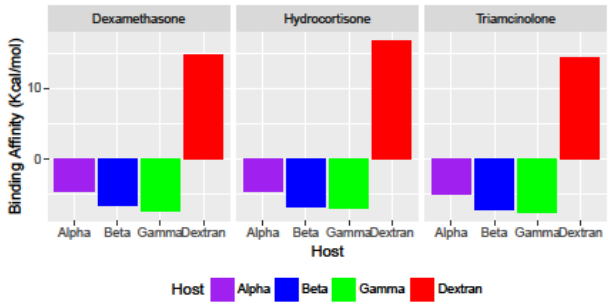
Edgardo Rivera-Delgado[1], Ashley Djuhadi[1] and Horst A. von Recum[1]
[1]Department of Biomedical Engineering, Case Western Reserve University Cleveland, Ohio

Statement of Purpose: Treating knee osteoarthritis with local injections of small molecule drugs remains difficult due to the rapid escape of drug from the articular joint. In this project, we aim to increase the residence time of drugs in the knee by using our polymer formulation capable of slowing drug release by using a high density of affinity hosts. Our lab has previously made insoluble polymers from the affinity host cyclodextrin, and shown them capable of slow sustained delivery of many drugs from to antibiotics to anticancer drugs. However, that implant structure, namely insoluble polymer disks, is not a feasible surgical intervention in the treatment of osteoarthritis. Engineering cyclodextrin polymers into a viscous liquid is more clinically useful, since viscoelastic supplementation treatment is currently used for many of the patients suffering from knee osteoarhritis. The problem with engineering polymeric delivery systems that are not solids is that as water content increases, the diffusivity increases, allowing drug to more rapidly escape the polymer. We observed that a viscous liquid polymer can be obtained by altering the amount of crosslinker and that this material maintains its affinity-based release properties, in accordance with affinity binding predictions. In the absence of affinity this behavior disappears, and release is near instantaneous.

Methods: To prepare the viscous liquid polymers Gamma-Cyclodextrin, pre-polymerized with epichlorohydrin was further polymerized with hexamethylene diisocyante to just below its gelation point tested via the vial tilt method. After polymerization the reactions were quenched, product purified by dialysis, and reconstituted in water to 1mg/ml and 100mg/ml in order to study the effect of concentration to the release kinetics. A drug release experiment from the polymeric liquid was carried by adding the polymer solutions to a dialysis bag and bathing them in 18 ml of phosphate buffered saline supplemented with 0.25% v/v of sodium dodecyl sulfate. Polymers were then loaded with one of the three drugs (dexamethasone, hydrocortisone, and triamcinolone). Release aliquots were taken periodically and endpoint absorbance measured by spectrophotometer. Plots corresponding to the cumulative release were generated for the individual data points. To control for release from a polymer without specific affinity we generated a viscous liquid polymer from linear dextran, a polysaccharide with the same chemical composition but without the host/guest affinity ring structure. The control polymers were used at the same concentrations as mentioned above. Binding affinities were calculated with Autodock Vina to the monomeric units of each one of the polymers.

Results: Polymers containing cyclodextrin presented a slower release than their non-affinity (dextran) counterparts. Release from affinity polymers was extended up to 12 days. In contrast, release from non-affinity polymers was depleted within the first few hours of release. We found that the rate as seen by the slopes in the graph in Figure 1 vary according to the predicted affinities of the individual cyclodextrins to all three drugs. Drug release was faster for 1mg/ml polymer solutions than for 100mg/ml solutions for all polymers except for the dextran polymers, where the release was the same regardless of polymer amount.

A



B

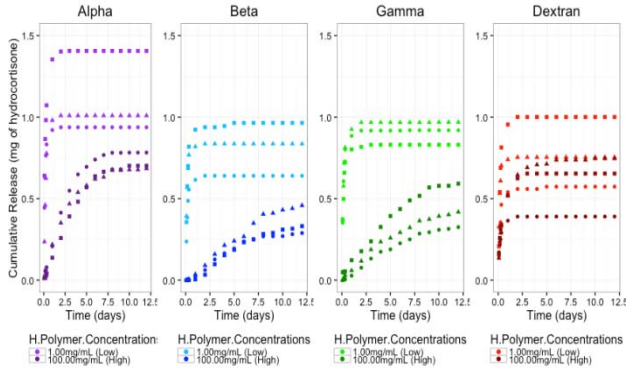


Figure 1. *A. Affinity predictions for three different relevant anti-inflammatory drugs used clinically to treat osteoarthritis B. Drug escapes rapidly in the absence of affinity but remains inside of the polymer for a longer period of time when affinity is present. Release from 100 mg/ml polymer solutions show much slower release than from 1mg/ml polymer solutions.*

Conclusions: Adding an affinity host, even in a liquid polymeric system results in the substantial delay of the total hydrocortisone release. The release of hydrocortisone across polymer types seems to be in accordance with the predicted docking affinities for their monomeric subunits. Specifically, Gamma-CD and Beta-CD polymers showed the slowest release (over several days) followed by a faster release from Alpha-CD polymers. With affinity-based polymers this process was also dependent upon the concentration of polymers in the release solution. Our future work aims to answer how biocompatible these new polymers are to relevant cells in the knee structure and how bioactive is the release of these after polymer processing.

Acknowledgements: This work was supported by NIH T32 AR007505 30