Controlled Multi-Agent Delivery of Small Molecule Therapeutics for Applications in Medicine

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Statement of Purpose: The field of drug delivery is plagued by the lack of local delivery methods for multiple therapeutics over relevant release timescales and at efficacious local concentrations. Such capabilities are needed to efficiently treat cellular dysfunction while avoiding the potential systemic toxicity of the associated therapeutic agents. A clear illustration of this problem is the systemic use of broad-spectrum antibiotics to treat bacterial infections, which has lead to a rise in antibiotic resistant bacteria worldwide.

In this work, we have examined the use of layer-by-layer (LbL) assembled thin films to deliver a weakly charged glycopeptide antibiotic, vancomycin hydrochloride (vanco), together with a hydrophobic non-steroidal anti-inflammatory drug (NSAID), diclofenac (diclo). This technology can easily be applied to scaffolds, bandages, nanoparticles, and various other surfaces for local drug delivery applications.

Methods:

Film deposition: Film construction utilized combinations of a bilayer architecture anti-inflammatory containing film, and a tetralayer architecture antibiotic containing film. Glycosaminoglycan, chondroitin sulfate (CS), was utilized as a polyanion in vanco film architecture. Both sprayed and dipped LbL assembly was utilized.

Release characterization: Films were released in pH 7.4 phosphate buffered saline at 37ºC. High performance liquid chromatography with a fluorescence detector was used to quantify drug release over time.

Small molecule activity: Vanco activity from film release samples was assessed using a macrodilution assay against *Staphylococcus aureus 25923*. Diclo activity was monitored by measuring the inhibition of cyclooxygenase in A549 human lung carcinoma cells upon exposure to release samples.

Results: In the gentle aqueous LbL assembly technique, the sequential adsorption of complementary charged polymer groups onto a charged substrate, leads to the electrostatically driven buildup of a polymer thin film. Vanco was directly incorporated into the film via its net positive charge. Diclo was encapsulated in an anionic poly(caroxy-methyl-β-cyclodextrin) (polyCD) and subsequently layered. Hydrolytically degradable poly(β-amino esters) (PBAEs) were also incorporated in the films to attempt a surface-erosion based release of the drug, demonstrating control over drug release profiles (Lynn DM. J Am Chem Soc. 2000;122:10761-10768.)

Applications for the particular class of therapeutics explored here are broad, ranging from use in orthopedic implants, wound dressings, and intraocular lenses amongst others. Film deposition on medically relevant substrates, including porous bandage materials and intraocular lenses is currently being explored.

Several film architectures were examined, along with studies to elucidate interactions between components of the films. These results were use to create films with favorable release profiles for both vanco and diclo, on the order of several days. It was found that in all cases thin film architectures containing polyCD stabilize vanco release from the film, by exchanging with CS. This effectively extends the 1 day release of a vanco containing film to 4 days of therapeutic vanco release from the multi-agent film. Additionally there is a large increase in diclo incorporation in films layered upon this vanco film architecture, as diclo is encapsulated within the polyCD, which exchanges with CS. The value of total diclo released increases to approximately 60 μg/cm^2 over 12 days, as compared to the previously reported 5 μg/cm^2 in a diclo containing film (Smith RC. Angew. Chem. Int. Ed. 2009;48:8974-8977.)

The release profiles from a particular multi-drug film architecture can be seen in Figure 1. Film released vanco and diclo retained activity against both *S. aureus* and their cellular targets, respectively.

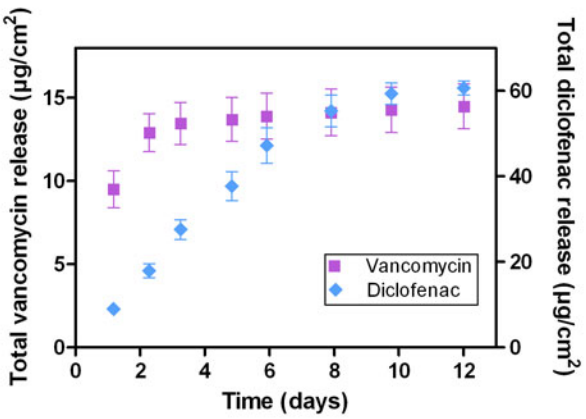

Figure 1. Therapeutic release from a polymer film containing both vancomycin and diclofenac.

There is also strong evidence for an interaction between polyCD and vanco, which is primarily electrostatic in nature. This interaction is seen only to occur in films and not in solution.

Conclusions: In this work, we have demonstrated the effective co-incorporation and release of a weakly charged antibiotic, vancomycin hydrochloride, and a hydrophobic NSAID, diclofenac, from degradable polymer thin films. We have obtained a wide range of release profiles, by exploring and taking advantage of the favorable interactions noted between film components. This is the first demonstration of the release of two small molecule drugs from a thin film LbL construct. Additionally, the molecules are entirely different and complementary in both chemistry and therapeutic nature, further demonstrating the versatility of LbL assembly.