Controlled sequential release of multi-agents from layer-by-layer films for surface delivery applications

Jouha Min, Richard D. Braatz, Paula T. Hammond*
Massachusetts Institute of Technology, Cambridge, MA 02139

Statement of Purpose: Recently, the concept of generating "smart" delivery systems that can provide controlled sequential release of multiple bioactive components over the right timescales and with the precise doses has gained great attention for its promise in the treatment of infectious disease, cancer, cardiovascular and neurological conditions and many other applications[1]. For orthopedic implants, sequential release of an antibiotic and a growth factor from the surface can effectively treat implant-related infection and promote bone generation around the implant to ensure a strong and stable connection, ultimately eliminating unnecessary two-stage surgeries [2].

Among a variety of delivery platforms that have been utilized for controlled sequential release, we chose to use ultrathin polyelectrolyte layer-by-layer (LbL) films, due to its versatility, ease of application, and water-based assembly. Recent efforts have been directed at developing truly stratified LbL films, but unfortunately, many such approaches have been unsuccessful because of interlayer diffusion.

We proposed that the use of intermediary barrier layers with nanostructured materials such as graphene oxide and clay is an effective strategy that can resolve the interlayer diffusion issue and thus enable true sequential release of multiple agents over more suitable timeframes.

Methods: The tetralayer architecture of [Polycation/ Polyanion/ AGENT/ Polyanion]$_n$ was constructed by the LbL assembly technique – a method involving the alternate adsorption of oppositely charged polymers or bioactive materials from dilute solutions one layer at a time.

For therapeutic agents, we used small molecular gentamicin (GS) as antibiotic and rhBMP-2 (BMP2) as growth factor or lysozyme (Lys) as model protein. To generate controllably erodible LbL films, we used a degradable polyβ-amino ester that undergoes hydrolytic cleavage.

Results: We first examined the effectiveness of intermediary barrier and/or capping layer on sustaining the release of a single agent, gentamicin. As shown in Fig.1, the characteristic time (*i.e.*, $\tau_{0.693}$) of gentamicin release from a film with the laponite clay barrier layers (denoted as 'sample') is an order of magnitude greater than that from a gentamicin film (denoted as 'control'): from 1 to 20 days.

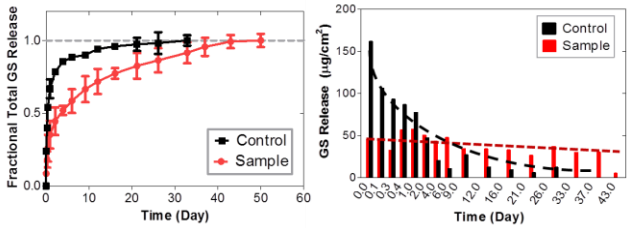

Figure 1. Comparison of normalized cumulative release of gentamicin (left) and amount released between time points (right) from GS film '*control*' and from GS film with barrier layers '*sample*'.

Subsequently, we fabricated various types of films incorporating two agents, namely gentamicin and lysozyme and conducted *in vitro* release test in PBS maintained at 37˚C (i.e., at physiological condition).

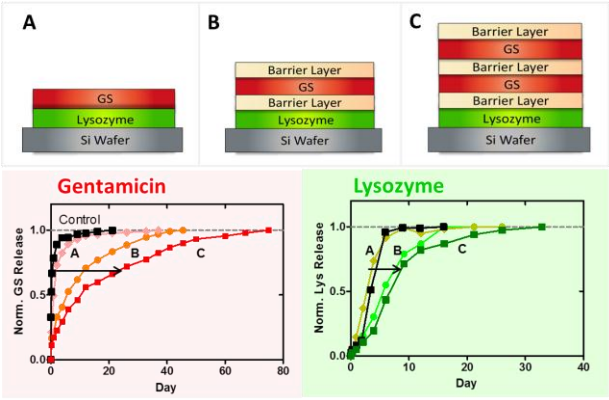

Figure 2. Comparison of normalized release of gentamicin (GS) and lysozyme (Lys) from various types of films: (1) *control* (individual film of GS or Lys), (2) *system A* (composite film of Lys and GS with no barrier layer), (3) *system B* (composite film with 2 barrier layers) and (4) *system C* (composite film with 3 barrier layers)

As shown in Fig.2, we could modulate the release kinetics of gentamicin and lysozyme by introducing intermediary and/or capping barrier layers.

Conclusions: Collectively, our results demonstrate that the incorporation of intermediary barrier layer is effective at blocking the interlayer diffusion during assembly and transport of biomolecules during release, resulting in controlled sequential release of gentamicin and lysozyme (or rhBMP-2). We could achieve sustained release of small molecular gentamicin from micron-scale thin films over periods of several days to several weeks at physiological conditions.

References:

[1] P.T. Hammond, Nanomedicine (London, England), 7 (2012) 619.
[2] J.C. Wenke, S.A. Guelcher, Expert Opinion on Drug Delivery, (2011) 1-15.