J|A|C|S
COMMUNICATIONS

Construction of Hydrolytically-Degradable Thin Films via Layer-by-Layer Deposition of Degradable Polyelectrolytes

Eduardo Vázquez, David M. Dewitt, Paula T. Hammond,* and David M. Lynn*,†

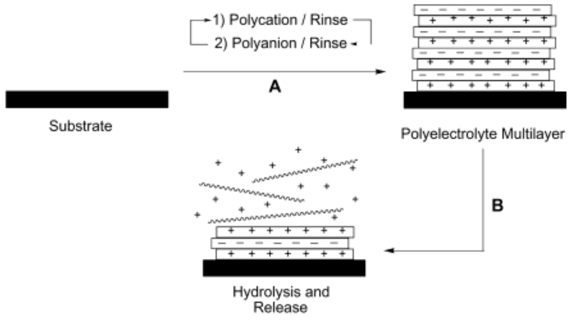
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, and Department of Chemical Engineering, University of Wisconsin - Madison, Madison, Wisconsin 53706

Received April 3, 2002

The development of new methods for the fabrication of thin films that provide precise control over drug release profiles could lead to significant advances in the fields of drug delivery and biotechnology. The layer-by-layer (LBL) deposition of polyelectrolytes has emerged as a versatile and inexpensive method for the construction of polymeric thin films, often with nanometer-scale control over the spatial distribution of ionized species within a film.[1,2] Despite the incorporation of new functionality into such films, there remain few examples of functional multilayer assemblies designed to *release* incorporated material.[3−5] Further, to the best of our knowledge, no system has been reported which allows controlled release of film components under physiological conditions.[6] Herein, we describe the construction of hydrolytically degradable thin films via LBL deposition of degradable polycations with nondegradable polyanions. Our studies suggest that these structures erode gradually under physiological conditions and that they are suitable for the incorporation and subsequent release of functional polyanions such as DNA.

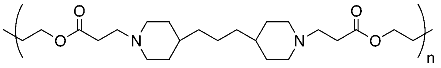
Sukhishvili, et al. have demonstrated that hydrogen-bonded multilayer films incorporating weak poly(acids) dissolve upon changes in environmental pH and that these systems could be used to release model fluorescent dyes.[3] Additionally, Schüler, et al. recently demonstrated the NaCl-induced “deconstruction”,[4] or disruption, of layered polyelectrolyte assemblies incorporating calf thymus DNA.[5] These systems represent important advances toward the development of functional delivery systems using the LBL technique.[6] However, multilayer deconstruction generally requires high salt concentrations (ca. 0.6−5.0 M) that are currently not suitable for release under physiological conditions, and these approaches do not allow control over the sequence by which incorporated layers are released or exposed.

Scheme 1. (**A**) Construction of Degradable, Layered Thin Films via Layer-by-Layer Deposition of Hydrolytically Degradable Polycations and Nondegradable Polyanions; (B) Degradation of Polycations Layers via Hydrolysis with Release of Anionic Components



We hypothesized that the deposition of hydrolytically degradable polyelectrolytes could be used to construct thin films that would degrade and release incorporated components under physiological conditions. Scheme 1 illustrates our general approach using a degradable polycation and a nondegradable polyanion. In this system, the polycation is expected to play a dual role, serving as a structural component of the film as well as a transient element designed to trigger release; similarly, the polyanion serves as a structural component and as an entity to be released or delivered.

The success of this strategy clearly requires either that a polycation with a suitably slow degradation rate be selected or that fabrication be carried out under conditions that slow or minimize degradation during the LBL process. We selected poly(β-amino ester) **1** for use in initial experiments, on the basis of the relatively slow degradation rate of this polymer at acidic pH ($t_{1/2} > 10$ h at pH = 5.1, 37 °C).[7] As polymer **1** has also been shown to form electrostatic complexes with polyanions such as DNA in solution, we hypothesized that it would readily adsorb to negatively charged surfaces and model polyanions such as poly(styrene sulfonate) (SPS) and poly(acrylic acid) (PAA) commonly used for LBL assembly.



1

We first investigated the deposition of films constructed from polymer **1** using SPS as a model polyanion. Multilayers were deposited on planar silicon substrates using the alternate dipping method;[1,2] substrates were precoated with 10 bilayers of linear poly(ethylene imine)(LPEI)/SPS or poly(dimethyldiallylammonium chloride) (PDAC)/PAA (ca. 100−200 Å thick) terminated with polyanion layers to ensure a suitable charged base surface for the adsorption of **1**.[8] Repetitive dipping of substrates into dilute aqueous solutions of polymer (pH = 5.1, 150 mM NaCl, [**1**] = 5 mM with respect to polymer repeat unit) resulted in the deposition of multilayered films ranging from 10 to 100 nm thick, as determined by ellipsometric analysis of dried films (Figure 1). Assembly conditions were carefully chosen to avoid the range of conditions for which degradation occurs rapidly.

As shown in Figure 1, film growth was proportional to the number of **1**/SPS bilayers deposited (for up to 10 bilayers) with an average bilayer thickness of 7.0−10.0 nm. Analysis of films deposited on gold-coated substrates using reflective FTIR revealed a carbonyl stretch at 1734 cm^{-1}, confirming the incorporation of **1** into the multilayered structure. Films constructed using PAA, a weak polyacid, were considerably thicker under equivalent fabrication conditions. For example, films composed of 10 bilayers of

---

* To whom correspondence should be addressed. E-mail: hammond@mit.edu; dlynn@engr.wisc.edu
† University of Wisconsin - Madison.

10.1021/ja026405w CCC: $22.00 © 2002 American Chemical Society

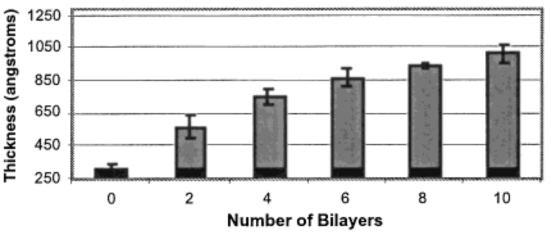


Figure 1. Plot of ellipsometric film thickness vs number of bilayers deposited for a **1**/SPS multilayer film. Black bars represent the thickness of a LPEI/SPS film used as a sublayer during film deposition.

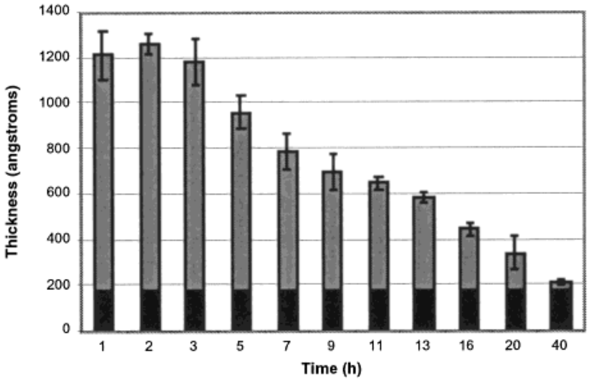


Figure 2. Plot of ellipsometric film thickness vs time for a **1**/SPS multilayer film incubated in PBS buffer at 37 °C (pH = 7.4, [NaCl] = 150 mM). Black bars represent the thickness of a nondegradable LPEI/SPS film used as a sublayer during film deposition.

1/PAA formed at pH 5.1 were up to 600 nm thick. These results are consistent with previous studies showing a relationship between film thickness and pH for weak polyacid systems.[9] Films incorporating **1** were smooth, having RMS roughness values ranging from 1.7 nm for films of **1**/SPS to 6.0 nm for thicker films incorporating PAA as a polyanion (RMS determined by profilometry).

Dried films were placed in PBS buffer (pH 7.4, [NaCl] = 150 mM) and incubated at 37 °C to investigate the erosion of films incorporating polymer **1** under physiological conditions. In most cases, the surfaces of films formed from **1**/SPS and **1**/PAA remained sufficiently smooth and consistent to allow film thickness to be monitored conveniently via ellipsometry throughout the erosion process. As shown in Figure 2, the ellipsometric film thickness of a 100-nm thick **1**/SPS film decreased gradually over a 40-h period. Film thickness decreased more rapidly upon incubation at higher pH (e.g., 9 h at pH = 8.3, [NaCl] = 150 mM) and more slowly under acidic conditions. Thus far, we have been unable to observe the products of ester hydrolysis within these films using FTIR. However, we believe that these pH/rate data are consistent with a hydrolytic mechanism of degradation and erosion, similar to that previously observed for polymer **1** in solution.[7,10]

Film erosion rates were also dependent on the structures of the incorporated polyanions. For example, while 100-nm thick **1**/SPS films eroded completely over a period of 40 h at pH 7.4 (Figure 2), 600-nm films formed from **1** and PAA degraded completely over a period of 9 h under identical conditions. This behavior is consistent with the pH/dissolution profile observed for other weak polyacid multilayer systems, in which the increased ionization of PAA at elevated pH contributes to repulsive electrostatic interactions.[3] Additionally, films containing thick layers of PAA often possess a lower overall effective cross-link density than more compact films constructed from strong polyelectrolytes such as SPS;[9,11] the less cross-linked morphology may support more rapid permeation of water and breakdown of the polymer layers.

The ellipsometric data in Figure 2 suggest that film erosion occurs gradually, rather than by the bulk deconstruction observed for weak polyacid or salt-deconstructed systems.[3−5] Preliminary AFM analysis of partially eroded films is also consistent with this gradual erosion process—surface roughness values for partially eroded films (RMS roughness = 6.9 nm) were less than the thickness of an average bilayer (~10 nm), and surfaces were consistent over 1 μm^2 portions of the film. We continue to investigate the factors governing erosion at various length scales and spatial resolutions, as the ability to control erosion in a “top-down” manner could introduce significant advantages from a release standpoint and allow precise control over the sequences by which one or more incorporated components are released. The differences in the erosion rates for films incorporating either SPS or PAA (as described above) also suggest a means of tuning release profiles for a broad range of systems.

We have also constructed films from 40- to 80-nm thick using polymer **1** and calf thymus DNA as a model functional polyanion. Our initial experiments show that these films erode slowly upon incubation under physiological conditions, suggesting that this approach could be useful for the release of genetic material in gene delivery applications. We continue to characterize the degradation of films incorporating **1** and other degradable polycations with a view to controlling erosion rates and developing tailored systems for the release of incorporated therapeutics.

Acknowledgment. We thank Dean Delongchamp for his assistance, advice, and helpful discussions, and Luis Abrishamian-Garcia and Marianne Terrot for help with AFM experiments. E.V. would like to thank the MIT Summer Research Program. This work made use of MRSEC Shared Facilities supported by the NSF under Award Number DMR-9400334.

Supporting Information Available: Experimental protocols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Decher, G. *Science* **1997**, *277*, 1232−1237.
(2) Hammond, P. T. *Curr. Opin. Colloid Interface Sci.* **1998**, *3*, 32−39.
(3) (a) Sukhishvili, S. A.; Granick, S. *Macromolecules* **2002**, *35*, 301−310. (b) Sukhishvili, S. A.; Granick, S. *J. Am. Chem. Soc.* **2000**, *122*, 9550−9551.
(4) For general examples of salt-induced “deconstruction” of polyelectrolyte multilayers, see: Dubas, S. T.; Schlenoff, J. B. *Macromolecules* **2001**, *34*, 3736−3740.
(5) Schüler, C.; Caruso, F. *Biomacromolecules* **2001**, *2*, 921−926.
(6) For related approaches to delivery devices based on diffusion of molecules *through* hollow polyelectrolyte multilayer assemblies at physiological pH, see: (a) Qiu, X.; Leporatti, S. Donath, E.; Möhwald, H. *Langmuir* **2001**, *17*, 5375−5380. (b) Shi, X.; Caruso, F. *Langmuir* **2001**, *17*, 2036−2042. (c) Antipov, A. A.; Sukhorukov, G. B.; Donath, E.; Möhwald, H. *J. Phys. Chem. B* **2001**, *105*, 2281−2284.
(7) Lynn, D. M.; Langer, R. *J. Am. Chem. Soc.* **2000**, *122*, 10761−10768.
(8) (a) Pei, R.; Cui, X.; Yang, X.; Wang, E. *Biomacromolecules* **2001**, *2*, 463−468. (b) Chluba, J.; Voegel, J.; Decher, G.; Erbacher, P.; Schaaf, P.; Ogier, J. *Biomacromolecules* **2001**, *2*, 800−805.
(9) Shiratori, S. S.; Rubner, M. F. *Macromolecules* **2000**, *33*, 4213−4219.
(10) Polymer **1** is insoluble in aqueous media at pH 7.4, suggesting that degradation or erosion is occurring via hydrolysis rather than decomplexation and dissociation of layers of **1** at higher pH. We continue to investigate the factors controlling film erosion in these systems.
(11) Lvov, Y.; Decher, G.; Mohwald, H., *Langmuir* **1993**, *9*, 481−486.

JA026405W