# Hydrophobic Effects in the Critical Destabilization and Release Dynamics of Degradable Multilayer Films

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Recent research has highlighted the ability of hydrolytically degradable electrostatic layer-by-layer films to act as versatile drug delivery systems capable of multiagent release. A key element of these films is the potential to gain precise control of release by evoking a surface-erosion mechanism. Here we sought to determine the extent to which manipulation of chemical structure could be used to control release from hydrolytically degradable layer-by-layer films through modification of the degradable polycation. Toward this goal, films composed of poly($\beta$-amino ester)s, varying only in the choice of diacrylate monomer, and the model biological drug, dextran sulfate, were used to ascertain the role of alkyl chain length, steric hindrance, and hydrophobicity on release dynamics. Above a critical polycation hydrophobicity, as determined using octanol:water coefficients, the film becomes rapidly destabilized and quickly released its contents. These findings indicate that in these unique electrostatic assemblies, hydrolytic susceptibility is dependent not only on hydrophobicity but a complex balance between hydrophobic composition, charge density, and stability of electrostatic ion pairs. Computational determination of octanol:water coefficients allowed for the reliable prediction of release dynamics. The determination of a correlation between the octanol:water coefficient and release duration will enable advanced engineering to produce custom drug delivery systems.

## Introduction

The advent of medical prosthetic implants has revolutionized the field of medicine, enabling the treatment of previously debilitating disorders. Surgical implantation of prosthetic devices such as coronary stents, intraocular lenses, and urinary catheters are a few of the most successful medical approaches applied in clinical treatment, to date. Nevertheless, these devices are associated with significant postoperative complications and subsequent morbidity.[1] To lower the incidence of pathology, drug delivery coatings for medical prostheses have emerged as an active area of research and development. While various methods to coat medical implants for localized drug delivery exist, most rely on diffusion based release from a bulk matrix and do not enable the engineering of drug release profiles. Moreover, state-of-the-art coatings are still limited to the elution of a single therapeutic that can withstand the relatively harsh processing conditions necessary for fabrication. The versatility, mild aqueous processing conditions, and compositional diversity of layer-by-layer (LbL) assembled films represents a powerful means to overcome these limitations and construct superior drug delivery coatings.

Layer-by-layer assembly has enabled the creation of conformal thin films with sequential and controlled release capabilities.[2,3] To extend the capabilities of this approach, it is desirable to work with a family of polymers which can be compositionally varied to achieve a broad range of degradation rates, mechanical properties, and biocompatibility with simple modifications in monomer choice. In conventional hydrolytically degradable polymer films, the design rules have been thoroughly explored;[4] however, the parameters which influence the degradation and stability behavior in electrostatically assembled multilayer films have not been closely examined and are not well understood. To date, there has been no systematic study exploring the impact of chemical composition on release dynamics in this promising and rapidly expanding set of new drug carrier systems; therefore, no correlation between hydrolytically degradable polymer structure, charge density, and release exist to allow for rational design. In examining these properties, a framework for understanding the nature of degradation in hydrolytically degradable layer-by-layer films has been created, generating a knowledge base and rubric for fabrication of films uniquely tailored for their given applications. Utilization of these tools will expand the scope of degradable multilayer films to applications such as microreactors, bioMEMs, agriculture, tissue engineering, and basic scientific research.

Electrostatic LbL deposition utilizes ionic interactions to form stable films with nanometer scale control of composition through the alternating adsorption of oppositely charged

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species.[5] LBL films have the ability to incorporate a wide variety of materials, including functional polymers, inorganic nanoparticles, enzymes, small molecules, proteins, polysaccharides, nucleic acids, and carbon nanotubes.[6−16]The ability to create uniform, conformal coatings at room temperature via a mild aqueous process has fueled the emergence of polyelectrolyte multilayer films in biological applications. A great deal of research has recently focused on the use of polyelectrolyte multilayers as drug delivery vehicles. Caruso, Voegel, and others have highlighted the ability of these films to serve as effective gene and protein delivery vehicles.[6,11,12,17−23] Moreover, Rubner, Thierry, and co-workers have pioneered the release of small molecule therapeutics from these systems.[12,24,25] Still, most research utilizes nondegradable films, which rely on drug diffusion from the bulk polymer matrix, and do not take advantage of the controlled release associated with top down degradation of LBL films. Unlike traditional polymer-based delivery systems, polyelectrolyte multilayer films are constructed one nanoscale layer at a time, alternating between polymer and therapeutic. In this manner, a drug delivery coating can be constructed with precise control over film architecture such that degradation via surface erosion will enable drug release in the inverse order of assembly. As a result, highly tailored release profiles can be achieved. To address this issue, Hammond and co-workers have created hydrolytically degradable polyelectrolyte multilayer films composed of a poly($\beta$-amino ester) and polyanion.[26] Poly($\beta$-amino ester)s are cationic polymers produced through Michael addition polymerization of diacrylate and amine monomers. These polymers were first introduced by Lynn et al. and have shown promise in gene delivery and as tissue engineering scaffolds.[27−30] A library of 2350 poly($\beta$-amino ester)s has been constructed.[31] Hydrolytically degradable LbL films, composed of a poly($\beta$-amino ester), and poly(styrenesulfonate), or the anticoagulant, heparin sulfate, were initially studied. Films were shown to undergo surface erosion by the hydrolysis of the poly($\beta$-amino ester) and subsequent release of the polyanion.[32] Wood et al. demonstrated multicomponent release from hydrolytically degradable films by showing that heparin sulfate and the model drug, dextran sulfate, could be released sequentially or concurrently depending on the presence or absence of a cross-linked barrier layer.[2]

Recently, Zhang et al. proved that the release kinetics of hydrolytically degradable LBL films were dependent on the chemical structure of the polycation.[33,34] Three poly($\beta$-amino ester)s, varying only in alkyl chain length of the diacrylate monomer, were used to show that increasing hydrophobicity could alter the release kinetics of the synthetic polyanion, poly(styrene sulfonate) (SPS). Films composed of each of the three polycations with SPS were found to have unique release profiles, and films constructed of multiple polycations were found to have release profiles intermediate between those constructed of a single polycation.[35] While this study demonstrated the versatility of LBL delivery systems, there remains much more to understand to fully utilize chemical composition to tune release, particularly with respect to the diverse range of biological molecules that can be released using this approach. Work, herein, sought to understand the extent to which structural manipulation could be used to control release of a model biomacromolecule, dextran sulfate, from hydrolytically degradable LBL films. Dextran sulfate (DS) is a good model system because of its similarity to glycosaminoglycans and proteins in macromolecular structure and hydrophobicity. A series of polymers from the poly($\beta$-amino ester) family was investigated by varying the diacrylate monomer used in the polymerization. Diacrylate moieties were altered based on alkyl chain length, steric hindrance, and hydrophobicity. Each polymer was examined for growth, degradation, and release of dextran sulfate from LbL films. Nine polymers were examined in total. These studies revealed a correlation between release dynamics and

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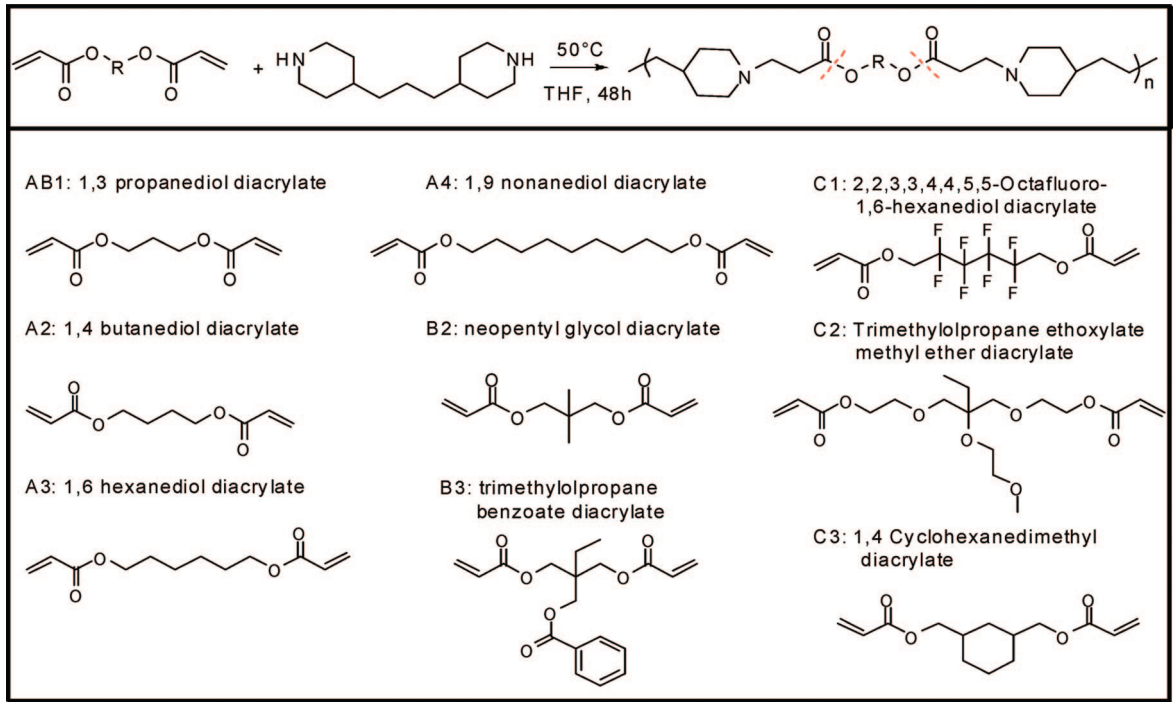


| Polymer | AB1 | A2 | A3 | A4 | B2 | B3 | C1 | C2 | C3 |
|---|---|---|---|---|---|---|---|---|---|
| $M_n$(g/mol) | 20,100 | 15,500 | 9,700 | 16,700 | 7,100 | 9,400 | 14,700 | 6,100 | 15,800 |

**Figure 1.** Reaction scheme for the synthesis of the poly($\beta$-amino ester)s and the diacrylate monomers used. Dashed lines indicate hydrolyzable bonds. Letters are used to designate the categories of monomers investigated. All monomers with A were used in the examination of alkyl chain length, B stands for steric bulk, and C for mechanism clarification. In categories A and B, increasing number corresponds to greater alkyl chain length or bulk, respectively. Polymer number average molecular weights ($M_n$) determined via GPC and are included in the table.

the octanol:water coefficient (LogP) of the diacrylate monomer. This correlation indicated that there is actually an optimum in hydrophobicity with respect to sustained release kinetics due to LbL film destabilization at high degrees of hydrophobicity. The destabilization of multilayers beyond the optimum was rapid, marked, and highly reproducible. The finding of a correlation between LogP and sustained release profiles will enable the creation of custom drug delivery coatings specifically designed to address the necessary biological, chemical, and mechanical requirements of a given application. Furthermore, this paper presents an observation of multilayer destabilization as a systematic function of hydrophobic content and charge density for the first time.

## Experimental Methods

**Materials.** All monomers were purchased from Dajac Laboratories, Inc. (Feasterville, PA), except 1,4-butanediol diacrylate, 1,6-hexanediol diacrylate, and 4,4-trimethylenedipiperidine, which were obtained from Alfa Aesar (Ward Hill, MA). Poly(sodium 4-styrenesulfonate) (SPS, $M_n = 70\,000$) and dextran sulfate ($M_n = 8000$) were purchased from Sigma Aldrich (St. Louis, MO). Dulbecco's PBS buffer and glass substrates were obtained from VWR Scientific (Edison, NJ). Linear polyethyleneimine (LPEI, $M_n = 25\,000$) and $^{14}$C-dextran sulfate sodium salt (100 $\mu$Ci, 1.5 mCi/g, $M_n = 8000$) was purchased from Polysciences, Inc. (Warrington, PA) and American Radiolabeled Chemicals, Inc., respectively.

**Synthesis.** Poly($\beta$-amino ester)s were synthesized as previously described.[29] Briefly, in a typical experiment, a solution of 4,4-trimethylenedipiperidine (34.1 mmol) in anhydrous THF (50 mL) was added to the diacrylate monomer (34.1 mmol) dissolved in anhydrous THF (50 mL). The reaction mixture was stirred for 48 h at 50 °C under nitrogen. After 48 h, the reaction was cooled to room temperature and precipitated in cold stirring hexanes. Polymers were collected and dried under vacuum prior to NMR and GPC analysis. The resulting polymer molecular weights along with their identification, based on diacrylate monomer, can be viewed in Figure 1.

**Film Fabrication.** LBL films were constructed on 1.5 cm$^2$ glass substrates using a Carl Ziess HSM series programmable slide stainer. The glass substrates were plasma etched in oxygen using a Harrick PDC-32G plasma cleaner on high RF power for 5 min to generate a uniform, negatively charged surface prior to deposition. After loading onto the robotic arm, the glass substrate was dipped into 2 mM aqueous polycation solutions for 10 min and then washed with agitation for 10, 20, and 30 s in three different water baths to remove all physically absorbed polymer. This process was repeated with the 2 mM polyanion solution to form a bilayer. All degradable polymer films were constructed on 10 bilayers of linear polyethylenimine and poly(styrene sulfonate) to ensure uniform adhesion of degradable layers to the surface. These films were constructed from a pH 4.2 solution of LPEI and pH 4.7 solution of SPS. Degradable films were prepared with 10 mM polymer solutions in 100 mM acetate buffer at pH 5.0 to avoid the conditions at which poly($\beta$-amino ester)s degrade rapidly. Following deposition, the films were dried thoroughly under a stream of dry nitrogen.

**Release Studies.** Release profiles were investigated by monitoring the release of $^{14}$C-dextran sulfate and the degradation of non-radiolabeled films. For drug release experiments, 20 bilayer radiolabeled films were constructed using $^{14}$C-dextran sulfate solution. The radiolabled deposition solutions were prepared by combining $^{14}$C-dextran sulfate (1.5 mCi/g, $M_n = 8000$), unlabeled dextran sulfate ($M_n = 8000$), and 100 mM acetate buffer to yield

a total concentration of dextran sulfate (unlabeled plus labeled) of 2 mg/mL (1 $\mu$Ci/mL 14C). After fabrication, each 20 bilayer film was immersed in 30 mL of phosphate buffer solution (pH 7.4, 137 mM NaCl, 2.7 mM KCl, 10 mM $Na_2HPO_4$). A 1 mL sample was extracted at various time points and analyzed via scintillation counting. Scintillation counting was performed on a Tricarb liquid scintillation counter (model U2200), and the amount of radiolabel in each sample vial was measured using $^{14}C$ protocol. Degradation vials were tightly capped between sample extractions to prevent evaporation of the buffer solution. Raw data (disintegrations per minute, DPM) were converted to micrograms ($\mu$g) of drug released using the conversion factor $2.2 \times 10^6$ DPM = 1 $\mu$Ci, the specific radioactivity of the drug, and knowledge of the ratio of total drug to labeled drug in the deposition solution. Degradation studies were performed with nonradiolabled 20 bilayer films. Films were immersed in 20 mL of phosphate buffer solution (PBS) in a screw top glass vial and tightly sealed. At various times, films were removed and dried thoroughly under a stream of dry nitrogen, and thickness was measured using profilometry at five predetermined locations on the film surface. Profilometry measurements were performed on a Tencor 21-profilometer. Following measurements, films were reimmersed in buffer solutions and resealed. All release and degradation studies were performed in triplicate. Surface morphology of the LbL film was observed by using Nanoscope IIIa AFM microscope (Digital Instruments, Santa Barbara, CA) in tapping mode in air. All surface roughness measurements are root mean squared measurements.

**Calculation of Octanol:Water Coefficient.** Octanol:water coefficients used in this work were an average of well-known computational models based on group contribution approaches.[36,37] In general, these methods break compounds into atoms/fragments that are associated with a given constant determined from a database of structures. Correction factors are used to account for atom/fragment interactions. These estimated values are summed to produce the octanol:water coefficient in logarithmitic form (LogP). The eight methods utilized differ in both database and computational constants used, which lead to differences in LogP values.[38] On the basis of previous approaches in the literature, the average was calculated to provide a "consensus" value (Supporting Information, S1); this has been shown to lead to better stability of prediction.[37,39] Advanced Chemical Development, Inc., ALOGPS 2.1, and Actelion open access software were used to calculate LogP. The following computational models were used in LogP determination: ALOGPS, IALogP, AB/LogP, miLogP, KOWWIN, XLogP, ACD/LogP, and CLogP.[39]

## Results and Discussion

Poly($\beta$-amino ester)s composed of 4,4-trimethylenedipiperidine and diacrylate monomers varying in alkyl chain length, steric bulkiness, and other modulators of hydrophobicity were synthesized to explore the impact of structure. Polymers were named based on their diacrylate monomer, which were grouped according to the aspect of structural control the monomers were used to explore. All monomers were placed in at least one of three categories: alkyl chain length (A), steric bulkiness (B), and mechanistic character (C). Mechanistic character refers to the mechanism of film degradation. The structure of the diacrylate monomers and the molecular weights of their corresponding polymers can be seen in Figure 1.

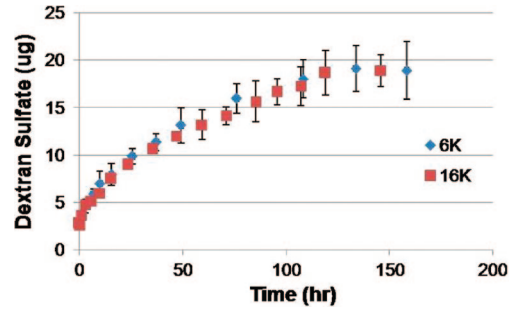


**Figure 2.** Effect of Poly A2 molecular weight on the release of $^{14}C$-dextran sulfate from (Poly A2/dextran sulfate)$_{20}$ films. Poly A2 with $M_n$'s of 6100 and 16 000 were examined. Release studies were performed at 25 °C in PBS buffer.

The molecular weights of the poly($\beta$-amino ester)s range from 6000 to 20 000 g/mol. These differences can be attributed to the fact that molecular weight in step-growth polymerization is highly dependent on stoichiometry and monomer reactivity. Attempts were made to modulate reaction time and stoichiometry to create polymers with similar molecular weights; however, this could not be achieved for all polymers. To determine the effect of molecular weight differences, release studies were performed on dextran sulfate containing multilayers of Poly A2 with $M_n$ of 6000 and 16 000 g/mol, as shown in Figure 2. Because no differences in release kinetics were observed, it was assumed that small differences in molecular weight between the poly($\beta$-amino ester)s would not substantially affect their degradation and release dynamics; polymers were studied as synthesized.

Although numerous methods to control degradation of polymers exist, modulation of hydrophobicity has proven to be an effective regulator of degradation rate for polyesters. Hydrophobicity can control degradation via a number of mechanisms, many of which are a result of reduced exposure to water. In short, the local concentration of water around the scissile bond able to undergo hydrolytic cleavage is decreased with increasing hydrophobicity; because ester hydrolysis is dependent on the effective water concentration, the degradation rate of polyesters can be modulated in this manner. Furthermore, increasing steric bulk around esters can make the bonds less susceptible to hydrolysis. Both methods of controlling degradation rate were utilized to determine the extent to which structural modulation could be used to control degradation of films.

**Effect of Alkyl Chain Length on Release.** To determine the extent to which local hydrophobicity around the ester could be used to control release, four polymers with varying alkyl chain lengths were investigated. The polymers examined, Poly AB1, A2, A3, and A4 contained 3, 4, 6, and 9 methylene units, respectively. Drug release and degradation profiles of these polymers can be seen in Figure 3. As expected, altering alkyl chain length extends dextran sulfate release; however, the most hydrophobic polymer, Poly A4,

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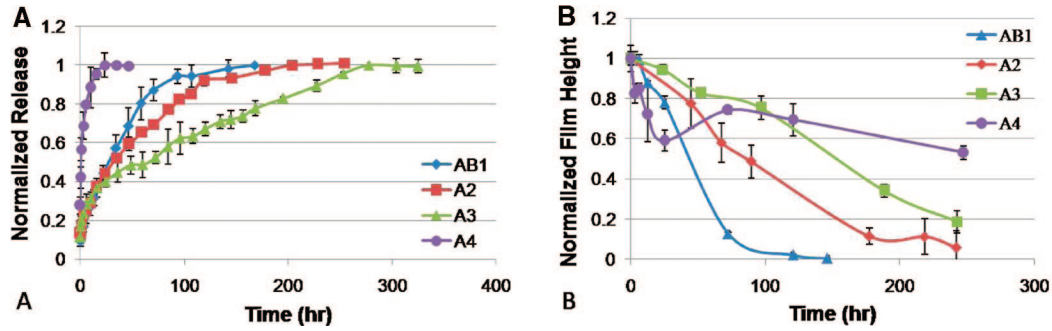


**Figure 3.** Effect of alkyl chain length on $^{14}$C-dextran sulfate release and film degradation. Release and degradation studies were performed on (Poly X/dextran sulfate)$_{20}$ films at 25 °C in PBS buffer. (A) Normalized release of $^{14}$C-dextran sulfate versus time. Release was normalized by the total amount of dextran sulfate released for each system. (B) Normalized film height of (Poly X/dextran sulfate)$_{20}$ over time. Films were normalized by the film height a time zero.

did not exhibit the longest release as anticipated. (Poly A4/DS)$_{20}$ films were found to be unstable, with 80% of the total amount of dextran sulfate released in less than 10 h.

Previous research has highlighted the influence of hydrophobicity on the rate of hydrolysis for poly($\beta$-amino ester)s.[33,40] Zhong et al. showed that for a series of hyperbranched poly($\beta$-amino ester)s more hydrophobic polymers degrade at a slower rate.[40] Additionally, Lynn et al. showed that erosion of films composed of a poly($\beta$-amino ester) and polystyrene sulfonate was dependent on hydrolysis of the polymer backbone by utilizing polyamide structural analogues of the poly($\beta$-amino ester)s. Films composed of the polyamides, which contained amide linkages instead of esters, did not erode under physiologically relevant conditions.[33] The paper concluded that polymer chain scission via hydrolysis of the ester bonds is necessary for surface erosion of the films; however, Poly A4, which is very hydrophobic, is unlikely to have completely hydrolyzed over the time scale necessary to explain the rapid release of DS from (Poly A4/DS)$_{20}$, especially since more hydrophilic polymers degraded over several days. It is improbable that the rapid release kinetics of (Poly A4/DS)$_{20}$ is due to chemical degradation of Poly A4.

Thus, to ascertain whether (Poly A4/DS)$_{20}$ films were in fact undergoing an abnormal destabilization phenomenon via bulk erosion or normal surface erosion, film degradation and surface roughness were monitored by profilometry. Here, bulk erosion is defined as degradation that occurs throughout the polymer matrix or includes more than the surface of the film. All films except (Poly A4/DS)$_{20}$ were found to be surface eroding with fairly linear degradation profile and constant roughness profiles (Supporting Information, S2). For (Poly A4/DS)$_{20}$, 40% of the total film thickness was removed within 24 h, while the remaining film did not fully degrade after 240 h. Reduced film stability may be attributed to reduced ionic interaction resulting from the low charge density of Poly A4. This suggests that alkyl chain modulation can be used to control release within a certain charge density threshold, at which point it exhibits a maximum release time. If this is the case, chemical control of release via the addition of hydrophobic units is mediated by loss of polymer charge density and the ability of the polymer to form sufficient ionic cross-links to maintain film stability.

**Effect of Steric Bulk on Release.** To investigate the effect of steric bulk on the release kinetics of hydrolytically degradable LbL films, three polymers, varying only in the substitution on the diacrylate monomers, were explored. The effects of bulkiness were studied using poly AB1, B2, and B3. Poly AB1 is composed of 1,3-propanediol diacrylate and trimethylenedipiperidine (diamine used in all polymer) and serves as a control, since it has no substitution on the $\beta$-carbon of the diacrylate. Poly B2 has intermediate branching with two methyl groups on the $\beta$-carbon, and Poly B3 is the bulkiest of the series, with an ethyl and benzoate moiety. The drug release and degradation profiles of (Poly AB1/DS)$_{20}$, (Poly B2/DS)$_{20}$, and (Poly B3/DS)$_{20}$ can be viewed in Figure 4. As anticipated, change in steric bulk does alter release. However, while the release duration increased from Poly AB1 to Poly B2 as expected, the most hindered polymers, Poly B3, had the fastest release rate. In fact, (Poly B3/DS)$_{20}$ films were found to be unstable; more than 80% of the total amount of dextran sulfate was released in $\leq$8 h.

To determine if (Poly B3/DS)$_{20}$ films were undergoing bulk erosion as result of destabilization or normal surface erosion, film degradation and surface roughness were monitored. Both (Poly AB1/DS)$_{20}$ and (Poly B2/DS)$_{20}$ had fairly linear degradation profiles and steady roughness profiles, which are characteristic of surface erosion. However, almost 50% of the (Poly B3/DS)$_{20}$ film eroded within the first 4 h. The remaining film persisted for more than 250 h, indicating that surface erosion was not occurring, since normal surface erosion (top down chemical degradation) would have yielded degradation kinetics similar to those observed in the first four hours. The reduced film stability of Poly B3 may be attributed to its steric bulkiness, which might interfere with the ability to form ionic cross-links. Since ionic cross-links are noncovalent in nature, they are subject to exchange with free ions in the solution. Traditionally, polyelectrolyte multilayer films are stabilized by the myriad ionic cross-links that form on each polymer chain; however, in hydrolytically degradable LBL films, which erode via chemical degradation of the polycation, the number of ionic cross-links per chain is constantly being reduced by chain breakdown from ester hydrolysis. If sterics hinder the allowed conformational space of the polymer enough to greatly reduce the number of ionic cross-links formed per repeat unit and the number is further reduced by chain cleavage, the film stability might be compromised. Thus, it appears

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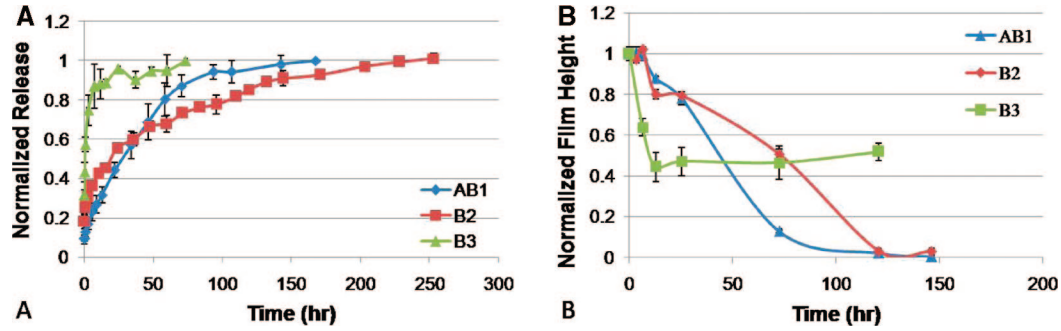


**Figure 4.** Effect of steric bulk on $^{14}$C-dextran sulfate release and film degradation. Release and degradation studies were performed on (Poly X/dextran sulfate)$_{20}$ films at 25 °C in PBS buffer. (A) Normalized release of $^{14}$C-dextran sulfate versus time. Release was normalized by the total amount of dextran sulfate released for each system. (B) Normalized film height of (Poly X/dextran sulfate)$_{20}$ over time. Films were normalized by the film height a time zero.

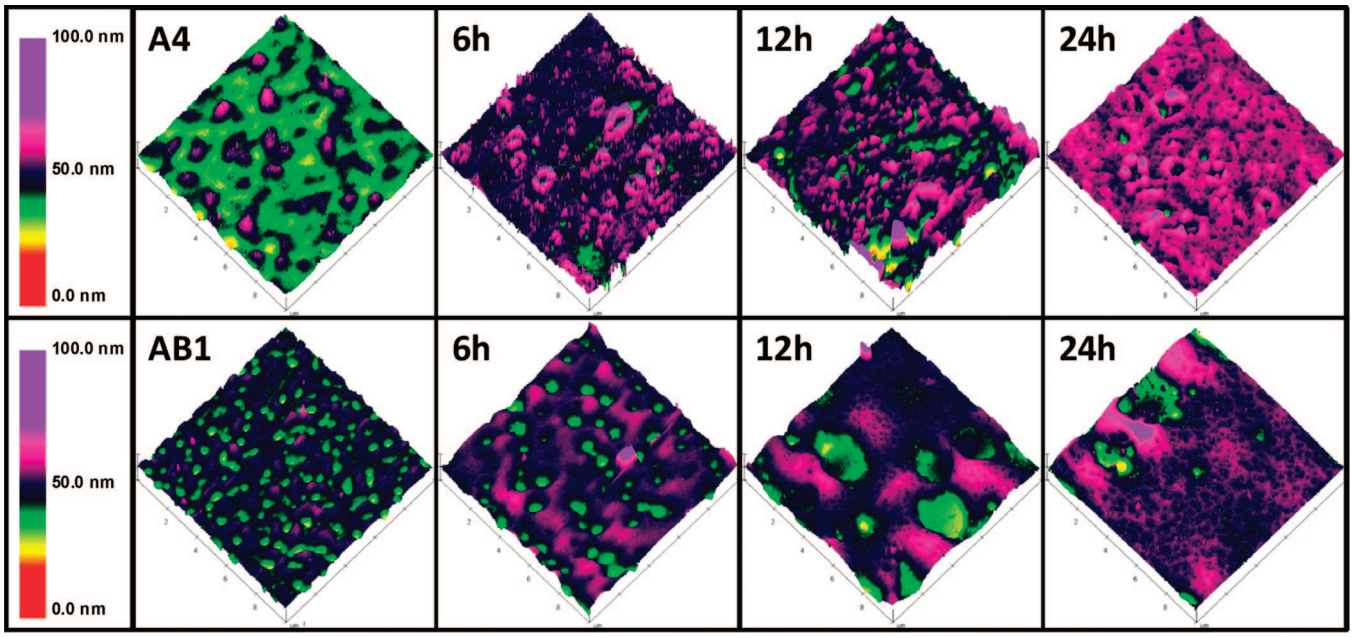


**Figure 5.** Atomic force microscopy images of (Poly A4/dextran sulfate)$_{20}$ (top) and (Poly A/B1 /dextran sulfate)$_{20}$ (bottom) films after 0, 6, 12, and 24 h in PBS buffer at 25 °C.

that the use of steric hindrance to control release rate is limited by the ability of the polymer to form sufficient ionic cross-links to maintain film stability.

Interestingly, in both (Poly A4/DS)$_{20}$ and (Poly B3/DS)$_{20}$ films, a thin slowly degrading film remained after total dextran sulfate release. On the basis of film degradation profiles, it can be hypothesized that some type of structural rearrangement, such as phase separation, is occurring in these films. The presence of a white precipitant remaining on the substrate after complete release is also suggestive of a phase segregation process in which the dextran sulfate escapes from the film. This analysis suggests that films were immediately destabilized, leading to reorganization of polymer within the film as water-soluble dextran sulfate was released into the bath; presumably, following this rearrangement and major film disruption, the poly($\beta$-amino ester), which is not soluble in pH 7.4 water even at low to moderate molecular weights, remains to a large extent immobilized to the substrate surface as a residue. If phase separation occurred in this setting, charge shielding of the poly($\beta$-amino ester) by ions in solution would allow a dense film to remain on the substrate. The hydrophobic nature of Poly A4 and Poly B3 would result in a very slowly degrading film consisting primarily of the poly($\beta$-amino ester).

To assess the possibility of a phase separation mechanism, AFM measurements of (Poly AB1/DS)$_{20}$, as a control, and (Poly A4/DS)$_{20}$ during degradation in PBS at 25 °C were taken over a time course relevant for Poly A4 degradation and can be seen in Figure 5. At time zero, (Poly A4/DS)$_{20}$ films were fairly uniform with slight surface roughness, 8% of the total film thickness; however, at six hours, holes on the order of 71 nm—57% of the total film thickness—formed (Supporting Information, S3). At 12 hours, channels appeared, and the film became highly irregular. Then at 24 h, well after DS release is complete, a relatively smooth film with few holes remained. This same morphology persisted for 48 h (Supporting Information, S4). In contrast, (Poly AB1/DS)$_{20}$ films start out fairly smooth, 3% of total film thickness, are swollen at six hours, and flatten out as the film continues to degrade. The findings for (Poly A4/DS)$_{20}$ correlate with a phase segregation mechanism of film destabilization and are consistent with the analysis of roughness over time. The root-mean-square roughness of (Poly A4/DS)$_{20}$ and (Poly B3/DS)$_{20}$ films was monitored over

the time of complete drug release (Supporting Information, S2). Additional details of the erosion AFM study are provided in Supporting Information. (Poly AB1/DS)$_{20}$ was used as an example of surface erosion more typically observed in these films. Significant changes in roughness were observed for both (Poly A4/DS)$_{20}$ and (Poly B3/DS)$_{20}$, two of the systems which undergo rapid destabilization. After just four hours of immersion in PBS buffer, (Poly A4/DS)$_{20}$ films had a roughness of greater than 30% of the total film thickness and (Poly B3/DS)$_{20}$ films reach a roughness of almost 50% of total film thickness in 12 h. The gross changes in film morphology probably account for the short drug release times for (Poly A4/DS)$_{20}$ and (Poly B3/DS)$_{20}$ films, as the soluble DS is released via bulk diffusion from the destabilized films.

**Determination of Boundaries.** Investigation of alkyl chain length and steric bulkiness suggest that charge density and hindrance to the formation of ionic cross-links may serve as limiting phenomena in the structural control of release dynamics. The similar morphological changes observed for both (Poly A4/DS)$_{20}$ and (Poly B3/DS)$_{20}$ suggest a common mechanism for destabilization. In both polymer series, the general hydrophobicity of the polymer is increased. Therefore, it can be hypothesized that film destabilization is caused by a hydrophobicity limit, beyond which film deconstruction and phase segregration occurs. Though the limits of charge density and degree of ionic cross-links have been documented in LbL film adsorption, hydrophobic film disruption has yet to be shown.[41] To assess the validity of the hydrophobic effect on multilayers, octanol:water coefficients were calculated for Poly A4 and B3. Octanol:water coefficients are partition coefficients for solutes in octanol versus water and are often expressed with the logarithmic scale as LogP. The LogP is a distinct physiochemical property of a molecule and used as the standard scale for lipophilicity. In fact, LogP calculations are widely used to determine pharmacological end points, bioconcentration, soil sorption coefficients, and biodegradation rate. While simple experimental methods to determine LogP exist and can be readily applied to many chemicals, they can be difficult or even impossible to perform for certain molecules and macromolecules,[42] and theoretical calculations can also present challenges.[36] For this reason, computational models, which serve as reliable predictive models, are heavily used. In this study, eight widely acclaimed and readily available models of octanol:water coefficients were utilized, to avoid biases that could arise from use of a single method. Using these models, the hydrophobicities of Poly A4 and B3 were found to be similar, indicating that hydrophobicity alone could account for the observed film instability.

To clarify the mechanism of destabilization and ascertain whether the effect is due to loss in charge density or increase in chain hydrophobicity, polymers C1 and C2 were examined. Poly C1, a fluorinated version of Poly A3 with a LogP similar to Poly A4 and B3, was used to determine if

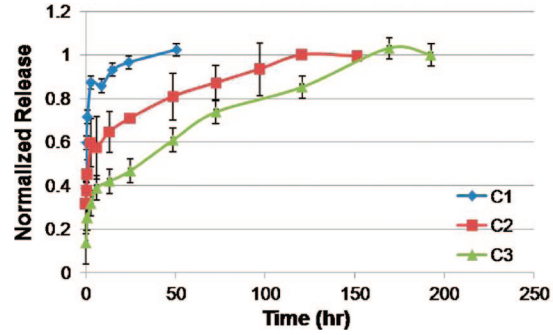


**Figure 6.** Release of $^{14}$C-dextran sulfate release versus time. Release studies were performed on (Poly X/dextran sulfate)$_{20}$ films at 25 °C in PBS buffer, and release was normalized by the total amount of dextran sulfate released for each system.

hydrophobicity alone could destabilize the multilayer films. Since (Poly A3/DS)$_{20}$ was found to be stable and the charge density of A3 and C1 are essentially the same, the destabilization of (Poly C1/DS)$_{20}$ films indicate a mechanism based on hydrophobicity. The release kinetics of multilayers containing Poly C1 can be seen in Figure 6. Films constructed of (Poly C1/DS)$_{20}$ were unstable and released more than 80% of the total amount of the dextran sulfate in less than 8 h, suggesting that hydrophobicity does cause film instability. Still, the effect of sterics and charge density could not be ruled out, so to determine their role, Poly C2 was also investigated as a component in the multilayer films. Poly C2 has a LogP similar to Poly AB1, but its bulkiness and backbone charge density are similar to those of Poly A4 and B3, respectively. (Poly C2/DS)$_{20}$ films did not undergo destabilization, as shown in Figure 6. The relative contributions of charge density and alkyl chain length were clarified by investigating the mechanism clarification (C) series of polymers. Specifically, Poly C1 has the same charge density as Poly A3, which forms stable films. However, Poly C1 has a greater octanol:water coefficient and is thus more hydrophobic than Poly A3. Films composed of Poly C1and dextran sulfate were unstable, indicating that hydrophobicity alone can destabilize films. To determine if charge density was responsible for the destabilization of Poly A4, films composed of Poly C2 were constructed. Poly C2 is more hydrophilic than Poly A4 but has a similar charge density. Poly C2 films were stable, proving that the charge density alone could not disrupt film stability.

Therefore structural manipulation can only be used to alter release in hydrolytically degradable LBL films to the extent that polymer hydrophobicity helps to induce film destabilization. Since LogP proved to be an important indicator for film instability, release duration versus LogP was plotted for all of the systems to examine the significance of LogP in the release predictions. The resulting graph in Figure 7 shows a strikingly clear trend between LogP and release with increasing LogP corresponding to increased release duration until film instability occurs at LogP $\geq$ 3.8. As illustrated, increasing LogP resulted in a predictive increase in release duration until a certain threshold value. Beyond this point, hydrolysis of the poly($\beta$-amino ester) no longer dominated the erosion process. At values higher than the threshold, the films become destabilized by the extent of polymer hydrophobicity. The presence of a trend for each computational

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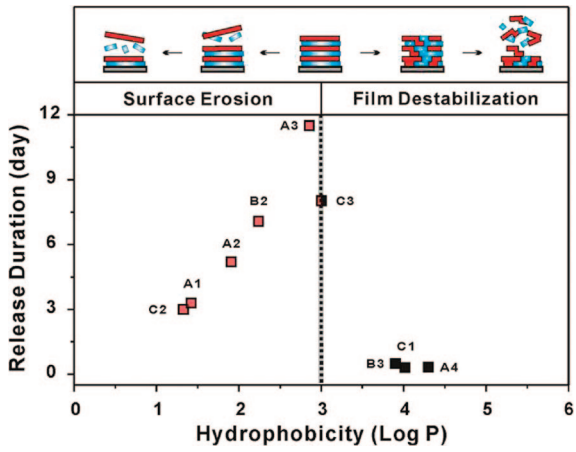


**Figure 7.** Correlation between LogP, release duration, and proposed dissolution mechanism in (Poly X/dextran sulfate)$_{20}$ films. Data labels indicate the corresponding polymer for each observed release time.

method was determined. Though slight differences existed, all methods yielded the same general trend; therefore, averaged values were used to provide a consensus for LogP values and generate a master curve.

To ascertain if Poly A3 served as the true peak of release before destabilization and test the accuracy of the trend, Poly C3 was examined. Poly C3 is composed of a cyclohexanedimethyl diacrylate and has a LogP of 3.1. Films constructed of (Poly C3/DS)$_{20}$ were found to have a release duration lower than (Poly A3/DS)$_{20}$ but did not exhibit film destabilization. Additionally, (Poly C3/DS)$_{20}$ films fell within the trend, suggesting that once a certain LogP is reached some degree of hydrophobic destabilization occurs leading to reduced release duration. Ongoing research is focused on elucidating morphological changes in systems with LogP greater than 3.8. The correlations in Figure 7 suggest that LogP can be used to predict the release duration of poly($\beta$-amino ester)s in LbL films, irrespective of diacrylate monomer structure, and that these relationships can potentially be generalized to include a number of different counterpolyanions.

## Conclusions

Traditional drug delivery coatings are limited by the elution of a single therapeutic, diffusion based release characteristics, and often harsh processing conditions. Polyelectrolyte multilayer films represent a versatile technology for the creation of simple, conformal drug delivery coatings that enable one to engineer release dynamics based on chemical composition as well as thin film heterostructure. Recent research has highlighted the ability of hydrolytically degradable films to deliver a broad range of therapeutics and attain complex release profiles through the selection of film architecture and utilization of top down degradation associated with surface erosion. Still, the formation of an effective delivery system hinges upon the ability to selectively control drug release profiles. Examination of film release dynamics, degradation, and stability as it relates to steric bulk, charge density, and hydrophobicity is unprecedented in the literature. Toward establishment of a framework for degradable multilayer film design, the effect of chemical composition on drug delivery properties in hydrolytically degradable, polyelectrolyte multilayer films was investigated. To determine the effect of chemical structure, several poly($\beta$-amino ester)s, varying only in the diacrylate monomer used in the polymerization, were used to ascertain the role of hydrophobicity, steric hindrance, and charge density on release dynamics. Small changes in hydrophobicity led to substantial increases in release duration until a critical hydrophobicity of the degradable polycation was reached, upon which major film destabilization and rapid release occurred.

A novel correlation between LogP and release duration was revealed. Indeed LogP was found to be a key indicator of release duration and film stability in these systems. Release duration was found to increase proportionally with LogP until a threshold value, at which films becomes rapidly destabilized, was reached. Destabilization was hypothesized to result from phase segregation of very hydrophobic degradable cation and the hydrophilic polyanion. Thus, release dynamics are not only dependent on hydrolytic susceptibility but a complex balance between hydrophobic composition, charge density, and stability of electrostatic ion pairs. Utilization of LogP as a predictive tool for release duration will allow for the selection of polymers based on biological, chemical, and mechanical properties with an understanding of the effect on drug release. The determination of a LogP release duration correlation will also enable the creation of polymers based on the specific demands of the application and implantation site. This correlation and in-depth exploration of the interactions that drive hydrophobic instability in these films may have far reaching implications in electrostatically assembled thin films in general.

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**Supporting Information Available:** Calculated LogP values from the eight methods (S1), roughness analysis of (Poly AB1/dextran sulfate), (Poly A4/dextran sulfate)$_{20}$, and (Poly B3/dextran sulfate)$_{20}$ during degradation (S2), atomic force microscopy images of the (Poly A4/dextran sulfate)$_{20}$ holes formed after 6 h of degradation (S3), atomic force microscopy images of (Poly A4/dextran sulfate)$_{20}$ after 48 and 72 h of degradation (S4) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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