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Huang, Junhao; Moghaddam, Saeed Zajforoushan; Thormann, Esben

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Chitosan/Alginate Dialdehyde Multilayer Films with Modulated pH-responsiveness and Swelling

*Junhao Huang, Saeed Zajforoushan Moghaddam, Esben Thormann**

Department of Chemistry, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark

* The author whom the correspondence should be addressed to: esth@kemi.dtu.dk

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Abstract

Oxidation of alginate is a promising method that creates aldehyde groups, which can form stable cross-links with amine groups on chitosan. In this work, it is shown that a systematic variation in the oxidation degree of alginate dialdehyde allows for effective tuning of the swelling capacity of chitosan/alginate dialdehyde multilayer films. Besides, it is demonstrated that the pH-responsiveness of the multilayer films can be regulated by the choice of pH at which the layer-by-layer assembly is conducted. The combination of these two parameters allows designing polysaccharide multilayer films with tunable degree of swelling and stimuli-responsiveness.

1. Introduction

Multilayer films of chitosan (CHI) and alginate (ALG) have drawn increasing attention due to their non-toxicity, biocompatibility, biodegradability, and tunable physicochemical properties.^[1–3] These films are produced using the layer-by-layer (LbL) assembly method, in which a charged substrate is alternately immersed in CHI and ALG solutions.^[4] The electrostatic interactions between the oppositely charged components promote LbL deposition and film growth. LbL assembly itself is a facile, efficient, versatile, and tunable method.^[5] Considering these advantages, CHI/ALG multilayer films are promising candidates for multiple biomedical applications ranging from tissue engineering to drug delivery.^[6–8]

The interior part of the polyelectrolyte multilayer films maintains charge-neutrality at the pH where the LbL assembly is conducted.^{[10],[11]} In other words, the number of positively charged amine groups on CHI and negatively charged carboxyl groups on ALG are roughly identical, showing an approximately 1:1 charge stoichiometry. Changing the pH perturbs the charge-neutrality condition, which can result in excessive swelling and thus dissolution/disintegration of the film. On this basis, CHI/ALG multilayer films have been utilized as drug carriers that afford immediate release when exposed to a specific pH.^{[12],[13]} Nevertheless, some applications, e.g., oral delivery to the gastrointestinal tract, require a more stable multilayer film with moderate swelling and pH-responsivity rather than prompt disintegration.^{[14],[15]}

To address this issue, one can post-cross-link the multilayer film to inhibit the excessive swelling and disintegration.^{[16],[17]} This approach, in general, has several shortcomings though: (i) the common cross-linkers, e.g., glutaraldehyde, are mostly toxic, (ii) the introduced cross-linker could modify the physicochemical properties of the film, (iii) additional post-cross-linking and rinsing steps are required, (iv) diffusion barrier could cause inhomogeneous cross-linking within the film, and (v) controlling the cross-linking density is challenging since it requires changing the concentration of cross-linker, cross-linking time, or cross-linker type.

Oxidation of ALG using sodium metaperiodate produces aldehyde groups that can then directly bind to amine groups of CHI through a Schiff base reaction.^[18–22] Therefore, oxidized alginate, also known as alginate dialdehyde (ADA), allows for simultaneous cross-linking during the LbL deposition. Accordingly, while the chief driving force for the LbL assembly is the electrostatic attractions, the adsorbed polymer chains upon each deposition step can directly cross-link to the beneath layer. Hence, this approach can provide a more homogenous cross-linked network without the need for hazardous chemicals or rigorous post-treatments. We recently showed that CHI/ADA films fabricated at pH 6 respond to pH changes (acidic and alkaline) in terms of reversible swelling/shrinkage without disintegration up to 6 days.^[22]

In this work, we demonstrate that we can effectively modulate the swelling capacity and pH-responsiveness of CHI/ADA multilayer films by (i) changing the cross-linking density through systematically varying the oxidation degree of ADA and (ii) fabricating the films at different pH values. To do so, we prepared CHI/ADA multilayer films at two different pH values (3 and 6) using ADA of different oxidation degrees (0, 5, 25, and 75 %). Quartz crystal microbalance with dissipation monitoring (QCM-D) and spectroscopic ellipsometry measurements were simultaneously conducted to monitor the film properties.

2. Experimental Section

2.1. Materials

Sodium alginate (NaAlg, viscosity ≥ 2000 cP), chitosan (CHI, degree of deacetylation of 75–85%, viscosity 20–300 cP), sodium metaperiodate (NaIO_4 , $\geq 99.5\%$), sodium cyanoborohydride (NaBH_3CN , 95%), ethylene glycol (99.8%), 3-glycidoxypropyltrimethoxysilane (GPS, $\geq 98\%$), sodium hydroxide (NaOH , $\geq 97\%$), dibasic sodium phosphate (Na_2HPO_3 , $\geq 99\%$), sodium dihydrogen phosphate (NaH_2PO_3 , $\geq 99\%$), hydroxylamine hydrochloride ($\text{HONH}_2\cdot\text{HCl}$, 99.99%), sodium bicarbonate (NaHCO_3 , $\geq 99.7\%$), citric acid ($\text{C}_6\text{H}_8\text{O}_7$, $\geq 99\%$), sodium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$, $\geq 99\%$), methyl orange reagent (85%), and sodium chloride (NaCl , $\geq 99\%$) were

purchased from Sigma-Aldrich and used as received. Degassed ultrapure water (Sartorius, Arium Pro, resistivity of 18.2 M Ω cm) was used to prepare all the solutions.

2.2. Preparation of ADA samples

ADA with different oxidation degrees was obtained according to the previously reported method.^{[24],[25]} In brief, different molar ratios of NaIO₄ (5, 20, 75 mol%) were added to NaAlg solution (1 wt%), then left stirring in dark for 24 h. To quench the reaction, excess amount of ethylene glycol was added and left stirring for 0.5 h. ADA was then precipitated by adding copious amounts of ethanol and the precipitate was dialyzed against water for 3 days, followed by lyophilization. Detailed characterization data of the oxidized products, including degree of oxidation using titration, FTIR, and NMR spectra, are provided in the Supporting Information (Section S1).

2.2. LbL Assembly and pH-responsiveness

In-situ QCM-D (Q-Sense E1, Biolin Scientific, Gothenburg, Sweden) and ellipsometry measurements (M2000U, J.A. Woollam Co., Inc.) were conducted to monitor the LbL assembly and swelling behavior of the multilayer films. The measurements were carried out using the Q-Sense Ellipsometry Module (QELM 401, Biolin Scientific, Gothenburg, Sweden). Silica-coated sensors (QXS 335, Biolin Scientific) were used as the substrate for the LbL assembly of films. The sensor was rinsed with copious amounts of acetone, ethanol, and ultrapure water, then plasma-cleaned (PDC-32G plasma cleaner, Harrick Plasma, air pressure ~ 0.5 Torr, 5 min). To ensure firm attachment of the films to the substrate, the silica surface was modified using GPS, so the first deposited CHI layer is covalently grafted to the surface.^{[26],[27]} ADA (200 ppm) and CHI (100 ppm) solutions were prepared in citric buffer (15 mM, pH 3) and PBS (15 mM, pH 6). The polymer solutions were sequentially loaded (150 μ l min⁻¹) into the liquid cell for 40 min with 20 min rinsing time in between. An overall number of 15 layers were deposited with CHI as the outermost layer; then, a reductive amination reaction was conducted in the same buffer and pH for 1 h to ensure formation of permanent covalent bonds.^[27] The surface topography of

the films was assessed using atomic force microscopy (AFM, NanoWizard 3, JPK Instruments AG, Berlin, Germany) in tapping mode (Supporting Information, Section S2).

3. Results and Discussion

Figure 1 presents the QCM-D frequency (f) and dissipation (D) shifts (for the third overtone) corresponding to the LbL assembly of the films. The observed decrement in the frequency implies enhanced “sensed mass” while the increment in the dissipation hints to formation of a viscoelastic film. In addition, the ratio of $\Delta D/\Delta f$ is a semi-quantitative measure of film softness/rigidity. Regarding LbL assembly at pH 3 (Figure 1A), the multilayer films possess considerably small $\Delta D(10^{-6})/\Delta f$ ratios (≤ 0.01), indicating a compact and rigid structure with low water content. Increasing the oxidation degree of ADA, in general, does not affect the growth characteristics as rather similar f and D shifts are obtained within the experimental error. Regarding LbL assembly at pH 6 (Figure 1B), the multilayer films are characterized by slightly larger $\Delta D(10^{-6})/\Delta f$ ratios (~ 0.02 - 0.05) that can suggest a somewhat softer and more swollen film structure. Increasing the oxidation degree again has an insignificant effect on the amount of adsorbed polymer and growth kinetics. At pH 3, CHI ($pK_a \sim 6$ - 7) and ADA ($pK_a \sim 3$ - 4) are expected to be strongly- and partially charged, respectively. On the other hand, at pH 6, CHI and ADA are expected to be partially- and strongly charged, respectively. Hence, the multilayer films fabricated at pH 6, in general, should comprise a relatively larger amount of CHI (compared to pH 3), so the charge neutrality condition is fulfilled. It has further been suggested that the adsorbed CHI at neutral pH values has a more coil-like conformation that can produce a less compact interior.^[28]

Next, we discuss how the fabricated films respond to pH changes in terms of charge imbalance and structural variations. To do so, three consecutive pH cycles are performed between pH 2 and 6, as well as between pH 6 and 9. Regarding the films fabricated at pH 3, increasing the pH to around 6 makes ADA more charged, whereas CHI becomes partially charged, which can

create a slight charge imbalance within the film. Further increasing the pH to 9 should produce a more pronounced effect as CHI should be nearly uncharged while ADA is strongly deprotonated. Therefore, the multilayer film becomes negatively charged promoting the adsorption of counterions (Na^+), which creates osmotic pressure and swelling. When the film is not cross-linked, this significant charge imbalance could give rise to excessive swelling, irreversible structural changes, and even dissolution of the film. Introducing chemical cross-links between aldehyde and amine groups prevents immoderate swelling, i.e., the layer swells until a balance between the osmotic effect and the entropy of stretching of chains between the cross-link points is reached. A similar scenario applies to the multilayer films fabricated at pH 6, but with a slight difference. While increasing the pH to 9 should enhance the negative charge in the film, the produced charge imbalance herein (fabricated at pH 6, pH shift: $6 \rightarrow 9$) is expected to be relatively smaller (in comparison to: fabricated at pH 3, pH shift: $3 \rightarrow 9$). This is because the charge neutrality condition is closer to pH 9 and also because a smaller amount of ADA exists in the film. On the other hand, changing the pH to acidic condition makes CHI strongly charged, and ADA partially charged. Therefore, the multilayer film should become positively charged leading to adsorption of counterions (Cl^-) and osmotic swelling. In a similar fashion, the non-cross-linked films are expected to undergo irreversible structural changes, whereas the cross-linked films render controlled swelling/shrinkage.

Figure 2 illustrates the QCM-D data for the non-cross-linked (CHI/ADA-0%) films. Regarding the film fabricated at pH 3 (Figure 2A), increasing the pH to 6 leads to small negative and positive shifts in f and D , respectively. Decreasing the pH to 2 has an inverse effect on f and D with minor hysteresis. Accordingly, the film partly swells when pH is raised to 6 and then collapses when pH is changed to 2; nevertheless, these structural changes are minor considering the insignificant f and D shifts. In contrast, consecutive pH cycles between 6 and 9 demonstrate substantial and irreversible changes in the film structure. Accordingly, large irreversible shifts

in f and D , significant and somehow irregular overtone-dependence, as well as considerable hysteresis is found. This observation might suggest partial disintegration of the film and the formation of aggregated complexes on the surface. Accordingly, the non-cross-linked film fabricated at pH 3 is stable when increasing pH to 6 (modest charge imbalance) but increasing the pH to 9 (drastic charge imbalance) leads to substantial structural changes.

Regarding the film fabricated at pH 6 (Figure 2B), pH cycles between 6 and 2 demonstrate reversible structural changes. Accordingly, decreasing the pH to 2 results in a decrement in f and increment in D , confirming a partially positively charged state and film swelling. Increasing the pH back to 6 leads to partial collapse of the film as a charge-neutral condition is reached. pH cycles between 6 and 9 demonstrate similar trend but in a more pronounced manner. Accordingly, increasing the pH to 9 leads to relatively larger shifts in f and D , which implies a marked charge imbalance condition and more substantial swelling. This leads to some irreversible structural changes in the film as a large hysteresis is found in the f and D shifts following each cycle. Therefore, the non-cross-linked film seems stable when pH is changed between 2 and 6, whereas increasing the pH to 9 results in structural changes with notable hysteresis. Next, we check how cross-linking can affect the pH-induced structural changes in the films.

Figure 3 provides the QCM-D data for the pH cycles performed on the cross-linked films. When fabricated at pH 3 (Figure 3A), the films undergo insignificant structural changes when pH is changed between 2 and 6, whereas increasing the pH from 6 to 9 has a substantial effect in terms of f and D shifts. Increasing the oxidation degree of ADA leads to smaller f and D shifts, meantime the shifts become more reversible. Accordingly, CHI/ADA-5% demonstrates relatively large f and D shifts with significant hysteresis after the pH cycles. This is, however, not the case for CHI/ADA-20% and CHI/ADA-75% films where f and D shifts are relatively smaller, and the hysteresis becomes almost negligible. Accordingly, while all the films are

responsive to alkaline pH, their swelling capacity is controllable by the oxidation degree of ADA.

Regarding the films fabricated at pH 6 (Figure 3B), we observe structural variations when pH is changed to both acidic and alkaline conditions, while the latter effect is more distinguished. Increasing the oxidation degree of ADA has a similar effect in terms of diminishing the f and D shifts and affording more reversible structural changes. Accordingly, CHI/ADA-5% multilayer renders reversible shifts when pH is changed between 6 and 2, but the pH cycle between 6 and 9 displays a minor degree of hysteresis. CHI/ADA-20% demonstrates smaller f and D shifts with minor hysteresis, while CHI/ADA-75% exhibits even smaller shifts with almost no hysteresis. Therefore, all the films are responsive to both acidic and alkaline conditions, while increasing the oxidation degree effectively modulates the degree of swelling and hysteresis. To further examine the pH-responsiveness and swelling of the films, we performed in-situ ellipsometry measurements to ascertain the variations in the film thickness.

Figure 4 illustrates the variations in the estimated thickness of the multilayer films as a function of pH. A two-component optical model (Bruggeman's effective medium approximation) comprising dry polymer (Cauchy parameters: $A = 1.6$, $B = 0.005$) and pure water is used herein. It is noteworthy that these two thin-film analysis methods (ellipsometry and QCM-D) are sensitive to different properties of the film.^{[30],[31]} A thin polymeric film generally comprises a polymer-rich zone close to the substrate with dilute tails on top. In general, ellipsometry is more sensitive to the structural variations in the dense region of the film, whereas QCM-D is sensitive to the dangling polymer chains at periphery of the film, as well.

Regarding the films built at pH 3 (Figure 4A), we see minor variations in the thickness when pH is switched between 2 and 6, meaning that the bulk-like part of the film does not swell significantly, even when the film is not cross-linked. On the other hand, the film thickness undergoes substantial changes when the pH is varied between 6 and 9. For the non-cross-linked

film, the estimated thickness (upon first pH change from 6 to 9) increases to an irrational value of around 400 nm and a water content quite close to 100 vol%. We suggest this is an uncertainty in the modeling procedure; hence, the multilayer film is considered to be disintegrated (the thickness values are not plotted after this point). Increasing the oxidation degree of ADA effectively reduces the swelling. Accordingly, the estimated increment in the thickness of the multilayers with 5, 25, and 75% oxidation degrees is around 120, 55, and 40 nm, respectively. Therefore, increasing the oxidation degree could enhance the cross-linking density, moderate the degree of swelling, and reduce the structural hysteresis.

Regarding the films prepared at pH 6 (Figure 4B), the non-cross-linked film demonstrates an increment in thickness of around 15 nm when the pH is switched between 6 and 2. The cross-linked multilayers, however, do not show a significant change in thickness in this pH range. Accordingly, the observed shifts in QCM-D data might be attributed to the structural variations in the periphery of the film rather than the interior region. On the other hand, pH cycles between 6 and 9 affirm film swelling but in a moderate way (compared to the films built at pH 3). The non-cross-linked film undergoes substantial swelling with considerably large degree of hysteresis, which again suggest irreversible changes in the multilayer structure. Increasing the oxidation degree of ADA reduces the degree of swelling as well as the structural hysteresis. Accordingly, the estimated increase in the thickness of the multilayers with 5, 25, and 75% oxidation degrees are approximately 30, 20, and 10 nm, respectively.

4. Conclusion

We have demonstrated that the pH-responsiveness and swelling capacity of CHI/ADA multilayer films could be effectively tuned. The pH at which the multilayer is fabricated significantly affects the pH-responsiveness. For a film that is built at pH 3, increasing pH to 6 has no significant effect, whereas further increasing the pH to 9 leads to considerable swelling. For a film that is built at pH 6, the film is sensitive to both acidic and alkaline conditions, while

the latter is more pronounced. When the films are not cross-linked, increasing the pH to 9, in general, produces uncontrolled and irreversible swelling/structural changes, yet the films seem to be stable at neutral and acidic conditions. On the other hand, increasing the oxidation degree of ADA was confirmed to control the cross-linking density, which could reduce the swelling and variations in thickness. Therefore, besides the previously discussed advantages of ADA, e.g., being a biodegradable and non-toxic cross-linker, it also allows for effective tuning of the multilayer films properties. Accordingly, depending on the desired application, one can fabricate CHI/ADA multilayer films with optimized (i) pH-responsiveness to acidic, neutral, alkaline conditions and (ii) degree of swelling both in the interior and at the surface of the film.

Conflicts of Interest

The authors declare no conflict of interest.

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Figure 1. QCM-D data for CHI/ADA multilayer films comprising ADA with different oxidation degrees (ALG is referred to as ADA-0%) fabricated in citric buffer at pH 3 (A) and PBS buffer at pH 6 (B).

Figure 2. QCM-D data of consecutive pH cycles on the non-cross-linked multilayer films (CHI/ADA-0%) prepared in citric buffer at pH 3 (A) and in PBS buffer at pH 6 (B).

Figure 3. QCM-D data of consecutive pH cycles on the cross-linked multilayer films prepared in citric buffer at pH 3 (A) and in PBS buffer at pH 6 (B). In each case, three different oxidation degrees of ADA, i.e., ADA-5%, ADA-25%, and ADA-75% are examined.

Figure 4. Variations in the ellipsometry thickness as a function of pH of the multilayer films prepared in citric buffer at pH 3 (A) and in PBS buffer at pH 6 (B). In each case, the initial thickness (estimated thickness at the pH where the layer is fabricated) is subtracted from the data.

Multilayer films of chitosan and alginate dialdehyde demonstrate reversible swelling/shrinkage in response to variations in pH, due to the formation of chemical cross-links during the layer-by-layer assembly. The pH-responsiveness and swelling capacity are tunable by the pH at which the multilayer is fabricated, as well as the degree of oxidation of alginate dialdehyde.

Junhao Huang, Saeed Zajforoushan Moghaddam, Esben Thormann*

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