Sustained Release Control via Photo-Cross-Linking of Polyelectrolyte Layer-by-Layer Hollow Capsules

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Received December 4, 2004. In Final Form: March 25, 2005

We describe the formation and permeability of polyelectrolyte multilayer hollow-shell capsules by photo-cross-linking and controlled-release (fluorescence) studies. The hollow shells were prepared by alternate layer-by-layer (LbL) adsorption of photo-cross-linkable benzophenone modified poly(allylamine hydrochloride) and poly(sodium 4-styrenesulfonate) on polystyrene particles, followed by removing the core with tetrahydrofuran. Zeta potential measurements, fourier transform infrared spectroscopy, and transmission electron microscopy were used to verify the LbL process integrity. A model drug, rhodamine B (RB), was successfully loaded into the polyelectrolyte hollow capsules. The release kinetics of RB was investigated using fluorescence spectroscopy. The permeability of RB through the hollow shells was effectively controlled based on UV irradiation time. It was shown that the release of RB molecules can be controlled by the degree of cross-linking induced in the multilayer.

Introduction

The development of drug delivery systems with controlled release is a major challenge in modern medicine and pharmaceuticals. Drug delivery technology using nontherapeutic agents as drug carriers provides microenvironmental protection of drugs and reduced toxicity.[1] Furthermore, the carriers can be manipulated to deliver drugs to a targeted tissue and achieve a sustained or controlled release of drugs.[2] Synthetic polymers are often used as drug carriers because chemical composition and architecture of polymers can be readily tailored to accommodate drugs, i.e., to possess specific delivery information and to control the drug release kinetics. Various polymeric microstructures such as hydrogels,[3] micelles,[4] and nano- and microparticles[5] have been studied. The controlled release of encapsulated drugs can be achieved via delayed dissolution of polymer matrixes that dissolve slower than the drug, diffusion controlled release where drugs exit through cross-linked polymer chains, or drug solution flow control that utilizes osmotic potential gradients across semipermeable polymer barriers.[1]

Recently, the layer-by-layer (LbL) self-assembly technique has been applied to utilize submicrometer- and micrometer-sized, charged colloidal particles as the adsorbing substrates to produce colloid-supported polyelectrolyte multilayer films.[6] A variety of colloidal particles, melamine resin latexes,[7] biological cells,[8] low molecular weight compounds,[9] and organic[10] and inorganic crystals[11] have already been used as templates for the capsule preparation. Multilayer shells of polyelectrolytes,[6a,b] conducting polymer,[12] inorganic nanoparticles,[13] or proteins[14] have been deposited onto particle templates, giving rise to novel colloidal entities. An interesting extension of these tailor-made core−shell particles has been the subsequent removal of the templated cores, resulting in hollow capsules.[15] The size of the capsules can be varied from 0.1 to tens of micrometers and is defined by the size of the template. The thickness of the capsule wall depends on the number of assembled polyelectrolyte layers.

One of the significant properties of these capsules is their semipermeability. It has been shown that they are permeable for small molecules such as dyes and ions while they exclude compounds with a higher molecular weight.[15b,16] Recently, several studies have been devoted to poly(styrene

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10.1021/la047008x CCC: $30.25
Published on Web 05/11/2005

sulfonate) (PSS)−poly(allylamine hydrochloride) (PAH) microcapsules in an effort to control their permeability properties. Antipov and co-workers were able to obtain sustained release of fluorescent materials by adjusting the number of PAH/PSS multilayers.[10a] At least 8−10 layers of polyelectrolytes were needed to sustain fluorescein release. Also, increasing the number of layers prolonged the release for several minutes. Later, it was found that these PAH/PSS microcapsules are closed or open to high molecular weight polymers depending on the pH of the solution.[17] However, the long-term stability of such multilayer shells under various pH and buffer conditions and its effect on sustained release are unknown.

Recently, we have reported the preparation of polyelectrolyte multilayer films using LbL assembly of photo-cross-linkable benzophenone-modified PAA and PAH.[18,19] It has been shown that the permeability of the multilayer depended on the number of layers and the degree of photo-cross-linking between benzophenone and C−H groups of nearby polymer chains. The permeability depending on the degree of photo-cross-linking was investigated by cyclic voltammetry using anionic $Fe(CN)_6^{3-}$ as a redox probe molecule. Due to the cross-linking of the multilayer films and the change in charge density, the pore size of the film became smaller; therefore the charge-transfer resistance increased and peak current density values also increased. Moreover, by control of the pH environment, ion permselectivity can be manipulated to allow positive or negative ion transport and in specific conditions bipolar behavior.

In this study, we report our results on the controlled release of a model encapsulated drug through a polyelectrolyte multilayer hollow shell (barrier) via photo-cross-linking. Core−shell particles were fabricated by the consecutive deposition of benzophenone-modified PAH (PAH-BP) and PSS onto polystyrene (PS) particles. Hollow PAH-BP/PSS capsules were subsequently produced from the precursor core−shell particles by dissolution and removal of the PS core by treatment with THF. The model drug, rhodamine B (RB), was loaded into the hollow shells. The sustained release of RB depending on the degree of cross-linking was then studied using fluorescence spectroscopy. The study demonstrates the potential and advantages of photo-cross-linkable polyelectrolyte hollow capsules as drug carriers in controlled drug release applications.

Experimental Section

Materials. Poly(sodium 4-styrenesulfonate) (PSS), M_w = 70 000 was used without further purification (Aldrich). Benzophenone modified poly(allylamine hydrochloride) (PAH-BP) was synthesized as described in a previous paper.[18] The degree of substitution of the benzophenone group was found to be 9.8%, which was calculated from elemental analysis. The chemical structures are shown in Figure 1. The negatively charged sulfonate-stabilized polystyrene (PS) particles (498 nm diameter) were purchased from Microparticles GmbH, Berlin. Sodium chloride (NaCl) and rhodamine B were purchased from Aldrich. The water used in all experiments was prepared in a Milli-Q Academic system equipped with a 0.22 μm Millistack filter at the outlet and had a resistivity higher than 18.2 MΩ cm.

Multilayer Assembly on Colloidal Particles. The PAH-BP/PSS multilayer-coated PS particles were prepared as follows: 1 mL of a 1 mg/mL aqueous PAH-BP solution (containing 0.5 M NaCl) was added to an aqueous suspension of PS particles (1 wt %). The PAH-BP was allowed to adsorb on the colloids for 10 min. The dispersions were then centrifuged for 10 min at 7000 rpm followed by replacement of the supernatant solution with water. The PAH-BP coated particles were redispersed by shaking, followed by gentle sonication for 10 s. Prior to the next coating cycle, the cleaning process (centrifugation/supernatant exchange/redispersion) was repeated an additional two times to remove nonadsorbed polyelectrolyte. Then subsequent deposition of PSS (1 mg/mL solution containing 0.5 M NaCl) on PAH-BP coated particles was prepared in identical fashion. The desired number of PAH-BP/PSS multilayers was assembled by repeated consecutive assembly of PAH-BP and PSS using this method.

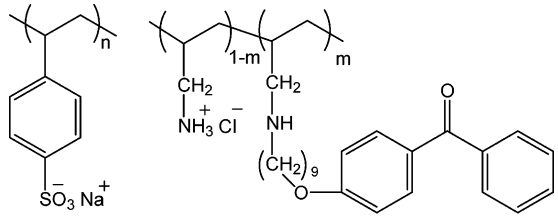

Figure 1. Chemical structures of (a) poly(sodium 4-styrenesulfonate) (PSS) and (b) benzophenone modified poly(allylamine hydrochloride) (PAH-BP).

Hollow Capsule Production. For the production of hollow capsules from polyelectrolyte-coated PS particles, 0.2 mL of the coated PS particles was exposed to 1 mL of THF for 12 h. The capsules were then centrifuged at 7000 rpm for 15 min and redispersed in THF, and the supernatant was exchanged for THF. To ensure complete core removal, the THF treatment and washing steps were repeated an additional two times.

Loading Rhodamine B. The capsules were centrifuged and redispersed in methanol to exchange the supernatant for methanol. A 1.5 mL portion of RB solution in methanol (50 mg/mL) was added to the hollow capsules that were collected from three centrifugation tubes. The mixture was well-stirred and stored in a refrigerator (∼ 4 °C) for 3 days.

Photo-Cross-Linking. An aqueous suspension of RB loaded PAH-BP/PSS multilayer capsules were irradiated with a 150 W Xe lamp (Oriel) without filter at a distance of 15 cm from the source. The irradiation intensity based on the distance, area, and intensity of the lamp was calculated to be 190 mW/cm^2.

Characterization. ζ-potential analysis was carried out with Brookhaven ZetaPALS dynamic light scattering equipment with a BI-9000AT digital autocorrelator at λ = 656 nm. All studies were done at a 90° scattering angle and temperature controlled at 25 °C; standard 50 μL cuvettes were used for size distribution analysis. All ζ-potential measurements were performed on coated PS particles redispersed in air-equilibrated pure water (pH = 5.6). Transmission electron microscopy (TEM) images were obtained using a Hitachi transmission electron microscope (H-7000). Samples for TEM were prepared by depositing an aqueous solution of the coated PS particles on a carbon-coated copper grid. The solution was then allowed to air-dry for 1 min, and the extra solution was blotted off. Fourier transform infrared (FT-IR) spectra of PAH-BP/PSS coated PS particles were obtained using a Digilab FTS7000 series spectrometer. The dispersion of polyelectrolyte-coated PS particles was dried under vacuum. The samples of each bilayer of PAH-BP/PSS coated particles (10 mg) were prepared by grinding powdery samples with KBr powder (100 mg) and then pressing the mixtures into pellets. Fluorescence emission spectra were measured by exciting at 550 nm using a Perkin-Elmer spectrofluorometer (LS50B) equipped with a Xe lamp and a front-face mirror configuration. For RB release kinetic studies, the increase in the fluorescence intensity at 576 nm was monitored as a function of time.

Results and Discussion

PAH-BP and PSS Multilayer Assembly on PS Spheres. Several studies have been devoted to investigate the multilayer formation and permeation properties of PAH/PSS core−shell particles.[10b,15a,17] Since 9.8% of the

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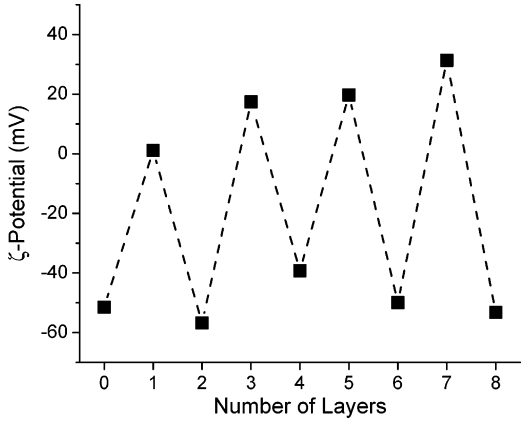

Figure 2. ζ-potential of PAH-BP/PSS multilayers on 498 nm PS latex particles as a function of the number of layers. The odd layer numbers correspond to PAH-BP and the even layer numbers to PSS adsorption.

PAH used in this study is modified with benzophenone, PAH-BP has a lower linear charge density than the degree of ionization. (PAH-BP, pK_a 8−9, is fully ionized at the pH range we used in this study). Thus, the structure and composition of multilayers can be different compared with the combination of the unsubstituted PAH/PSS. Therefore it was important to first investigate the multilayer formation of PAH-BP/PSS on PS colloidal particles and ensure layer integrity.

First, the ζ potential measurement was used to study the assembly of PAH-BP/PSS multilayers on PS particles (Figure 2). Starting from a value of −51.5 mV, corresponding to uncovered PS particles, the ζ potential alternates according to whether PAH-BP or PSS formed the last adsorbed outer layer of the shell. The first PAH-BP layer yielded a ζ potential of about 1 mV. This is probably due to the incomplete coverage by PAH-BP of the PS colloidal particles. After the first layer, PAH-BP as the outermost layer yielded ζ potential values ranging from 17 to 31 mV. When PSS is the outermost layer, ζ potentials ranged from −57 to −39 mV. Therefore the alternating ζ potential data between PAH-BP and PSS suggest stepwise growth of the multilayer films on PS colloidal particle core.[6]

The assembly of polyelectrolytes on PS particles was then investigated using FT-IR spectroscopy. Figure 3a shows the FT-IR spectra of $(PAH\text{-}BP/PSS)_n$ coated PS particles as a function of the number of bilayers (n = 1, 2, 3, and 4) in the fingerprint region (1800−1000 cm^{-1}). The spectrum was obtained from a mixture of the colloidal sample (10 mg) with KBr (100 mg) matrix in a pellet form. Since the same amount of particles was used for each sample, the intensity of peaks related to PS particles, the C=C ring stretch at 1492, 1450 cm^{-1}, remained constant. The C=C ring stretch at 1601 cm^{-1} showed some increase due to the contribution from benzophenone. The peak at 1601 cm^{-1} for benzophenone is strong due to the conjugation between the carbonyl group and the aromatic ring.[20] On the other hand the characteristic benzophenone peak at 1632 cm^{-1} (C=O stretch) of PAH-BP increased as the number of bilayers increased. Also, the intensity of peaks related to PSS, O=S=O symmetric stretch at 1180 cm^{-1}, increased.[21] Although the peaks from sulfonated groups functionalized on PS surface were overlapped with peaks from PSS, it clearly showed incremental increases as the

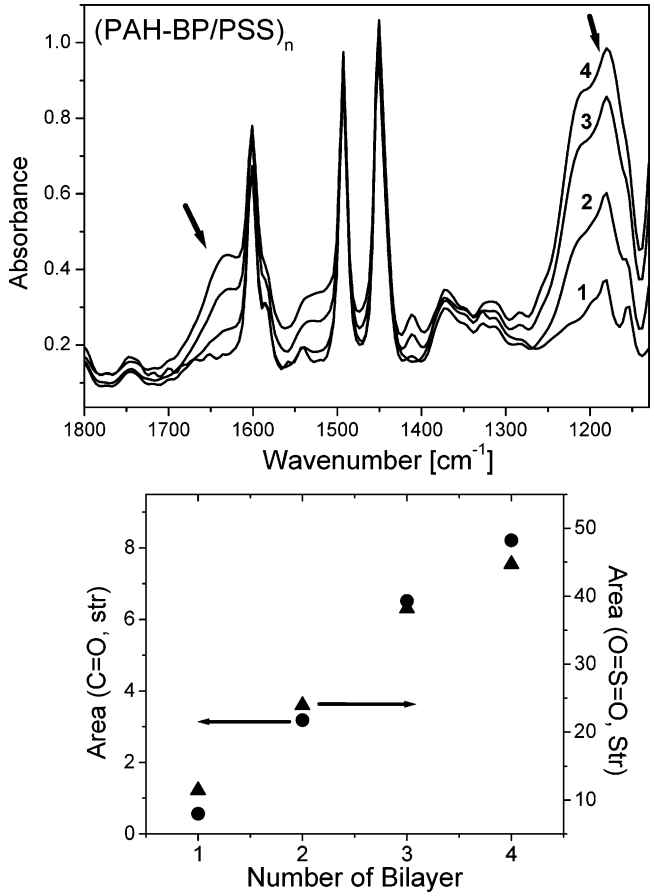

Figure 3. (a) FT-IR spectra of $(PAH\text{-}BP/PSS)_n$ coated PS colloidal particles (n = 1, 2, 3, and 4). The spectrum was obtained from a mixture of sample with KBr in pellet form. (b) Plot of the integrated area under the peak at 1632 cm^{-1}(C=O stretch) (●, left) and the integrated area under the peak at 1180 cm^{-1}(O=S=O symmetry stretch) (▲, right) as a function of the number of PAH-BP/PSS bilayers deposited.

number of bilayers increased. To have more quantitative information of the PAH-BP/PSS multilayer growth on the PS colloidal particles, the integrated areas under the peaks at 1632 cm^{-1} and at 1180 cm^{-1} were plotted as a function of bilayers deposited (Figure 3b). Both integrated areas under the peak increased with the number of bilayers, confirming the growth of PAH-BP/PSS bilayers on the PS colloidal particles.

Direct visualization of PAH-BP/PSS coated PS particles was provided by TEM measurements. Figure 4a shows the TEM micrograph of an uncoated PS colloid (average diameter = 498 nm, inset), and $(PAH\text{-}BP/PSS)_4$ coated PS particles. The coated particles showed increased surface roughness while the PS particle exhibited a smooth surface. As the number of layers increased, the overall diameter of particles also increased. The average diameter of $(PAH\text{-}BP/PSS)_4$ coated PS particles was 541 nm, respectively (determined from measuring the diameters of 15 particles, error range is about 10%). For a four-bilayer deposition, the diameter increase is about 43 nm, corresponding to a film thickness of 21.5 nm. The average layer thickness for PAH-BP/PSS bilayer is ca. 5.4 nm. This value is considerably higher than 2.5−3.3 nm observed for the PAH/PSS bilayer deposited from the same solution condition (1 mg/mL, 0.5 M NaCl).[6c,22] This is probably due to the lower charge density of PAH backbone

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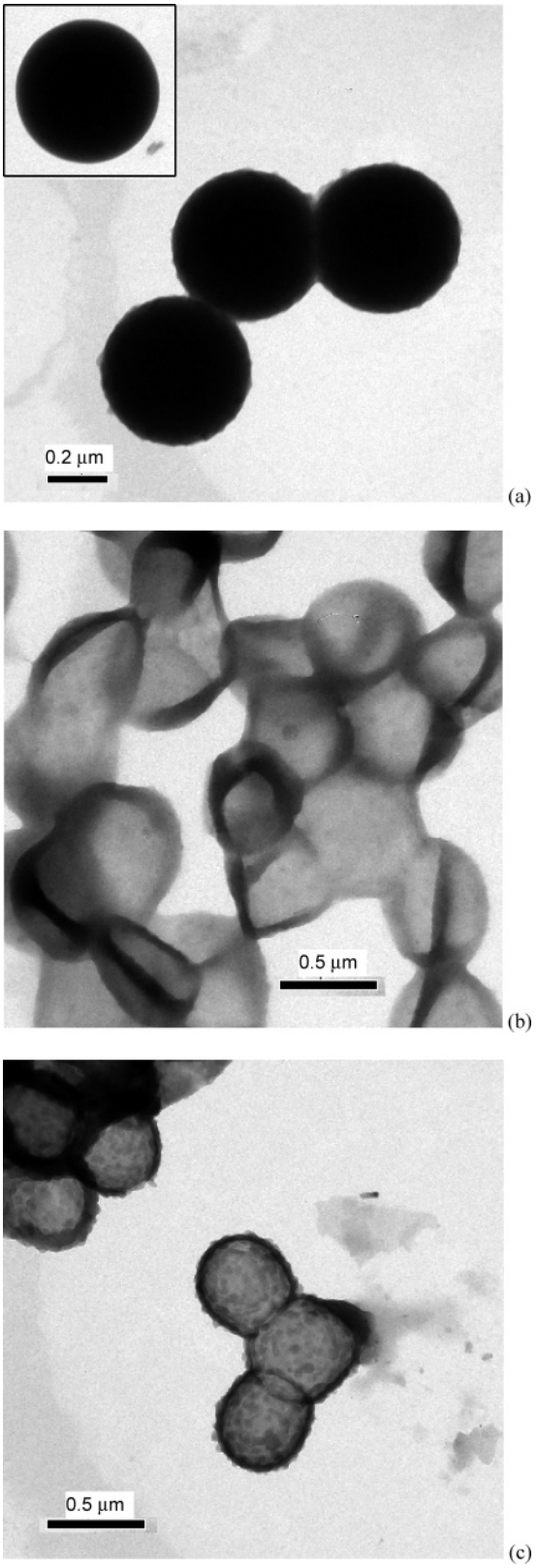

Figure 4. TEM images of (a) $(PAH\text{-}BP/PSS)_4$ coated PS particles. The PS particles used as templates have a diameter of 498 nm (inset), (b) hollow $(PSS/PANI)_5$ capsules, obtained after decomposition of the PS template, and (c) RB-loaded $(PSS/PANI)_5$ capsules after 3 min of UV irradiation.

as well as the bulky benzophenone side groups. In a previous study, it has been shown that the multilayer of poly(acrylic acid) (PAA) and PAH modified with benzophenone formed thicker layers compared to its unmodified PAA/PAH under the same solution conditions.[18]

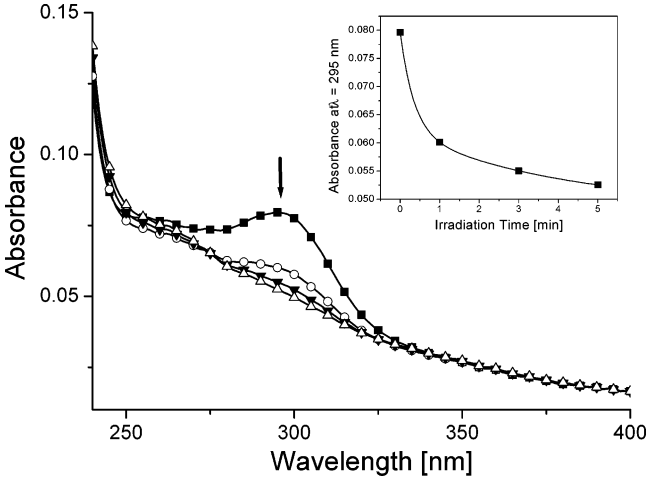

Figure 5. UV−vis spectra of $(PAH\text{-}BP/PSS)_4$ hollow capsules in aqueous dispersion as a function of UV irradiation time (■, 0 min; ○, 1 min; ▼, 3 min; ▲, 5 min). The inset shows the decrease of absorbance at 295 nm with UV irradiation time.

Nevertheless, the increase in the diameter is consistent with the coating of the polyelectrolyte shell on the colloid template in a linear fashion.

PAH-BP/PSS Hollow Shells. For the production of hollow capsules from $(PAH\text{-}BP/PSS)_4$ coated particles, the core (PS) was removed by dissolution in THF. The PAH-BP/PSS capsules were characterized using TEM. A TEM image of $(PAH\text{-}BP/PSS)_4$ hollow capsules is shown in Figure 4b. The numerous folds, creases, and flattening observed are due to the drying procedure prior to the measurements. From the image, it can be seen that hollow spheres are produced, which indicates that by exposing the PAH-BP/PSS coated particles to THF, the PS core were dissolved and extracted from the core via permeation through the semipermeable PAH-BP/PSS multilayer walls.[23] However, it is not possible to quantify the total removal of the PS core without doing further elemental analysis. On the basis of previous reported work using the same procedure[16,17,23] and the fact that the creation of a hollow space or volume was achieved, these hollow shells were deemed sufficient for further photo-cross-linking and permeability studies.

Photo-Cross-Linking of PAH-BP/PSS Hollow Shells. The PAH-BP/PSS hollow capsules were then photo-cross-linked by UV light. The aqueous dispersion of hollow capsules was constantly stirred during the UV irradiation. The cross-linking process was monitored by UV−vis spectroscopy. Figure 5 shows the UV−vis spectra of $(PAH\text{-}BP/PSS)_4$ hollow capsules in water as a function of UV irradiation time. Under UV irradiation, the absorbance at 295 nm decreased and almost disappeared after 5 min. The proton (H) from the C−H bonds present in the polymer multilayer film is easily abstracted by the excited benzophenone ($\pi\pi^*$) upon UV irradiation. Then, the benzophenone ketyl radical and a polymer on-chain radical readily recombine to generate a new C−C bond, causing cross-linking within the polyelectrolyte shell.[24] Further evidence of cross-linking was found in FT-IR studies (Figure 6). After 5 min of UV irradiation, the cross-linked hollow capsules were centrifuged, dried under vacuum, and mixed with KBr in pellet. Due to the cross-linking, two absorbance bands of benzophenone at 1632

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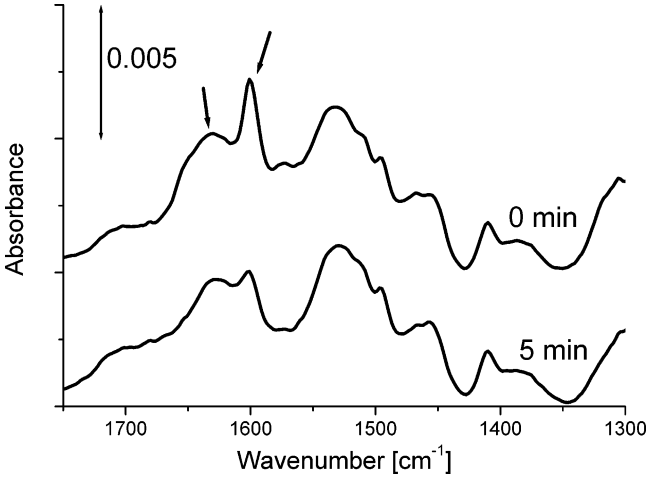

Figure 6. FT-IR spectra of $(PAH\text{-}BP/PSS)_4$ hollow capsules before and after 5 min of UV irradiation time The spectrum was obtained from a mixture of sample with KBr in pellet form.

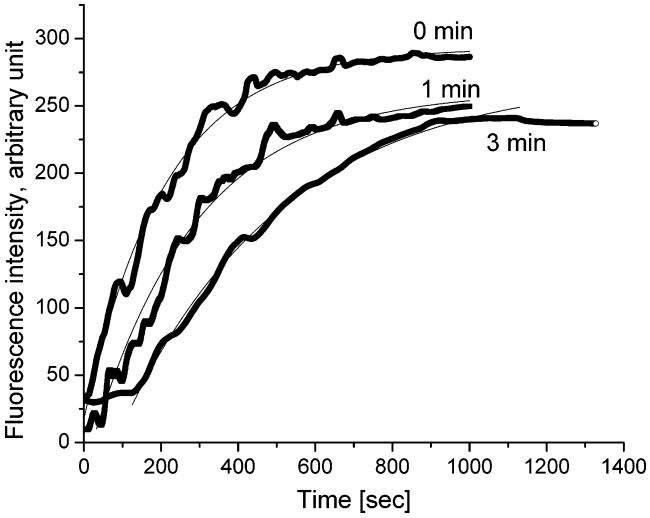

Figure 7. The fluorescence intensity (scatters) increase as a function of time after RB-loaded $(PAH\text{-}BP/PSS)_4$ capsules were added into 2.00 mL of water. The solid lines represent the best fit to the experimental data by eq 3.

cm^{-1} (C=O stretch) and 1601 cm^{-1} (ring C=C stretch) disappeared. The decrease of the latter band is due to the loss of conjugation between the carbonyl group and the aromatic ring because of the conversion of the C=O group.[20] The cross-linking resulted in reduction of thickness of the multilayer films when PAH-BP/PSS bilayers were deposited on a flat surface. The ellipsometric thickness of the multilayer film on silicon substrate in water was measured before and after the cross-linking by the procedure described as in the previous paper.[18] The thickness decreased by about 18% after 3 min of irradiation. However in the case of the particles, the diameter of the hollow shells was not significantly reduced after cross-linking as observed in the TEM. It is worth noting that the temperature of the hollow shell dispersion was slightly increased (~30 °C) after 5 min of UV irradiation. It has been reported that PSS/PAH polyelectrolyte capsules undergo heat-induced shrinkage due to the structural change of individual polyelectrolyte molecules in multilayers after annealing at 70 °C for 2h.[25] However, the heat-induced structural change of polyelectrolyte hollow capsule was ignored in our case considering the significantly lower temperature and short exposure time.

Controlled Release. To investigate controlled-release properties of the hollow shells upon cross-linking of the shells, rhodamine B (RB) was used as a model drug. PAH-BP/PSS hollow shells were loaded with RB before cross-linking. Since RB has better solubility in organic solvents than water, methanol was chosen as a medium. It has been shown that polyelectrolyte capsules form stable colloidal dispersions in different solvents, such as methanol, pentanol, octane, and decane.[26] These solvents do not affect significantly either the structure or the appearance of the surface of the shells. After 3 days of incubation in RB methanol solution, RB-loaded hollow capsules were cross-linked by exposing dispersion solution to UV light for 1, 2, and 3 min. Figure 4c shows a TEM picture of $(PAH\text{-}BP/PSS)_4$ capsules loaded with RB after 3 min of exposure to UV light. The folds and creases observed in the hollow capsules disappeared because of the increase in internal volume due to the loaded RB molecules inside the capsules. Similar features of the shape, such as the dimple and the rim, have been shown in scanning electron microscopy of PAH/PSS polyelectrolyte capsules that were filled with dye precipitates.[27]

Sustained release of the load RB molecules due to the cross-linking in polyelectrolyte capsules was investigated using fluorescence spectroscopy. Fluorescence spectroscopy is a convenient tool for the determination of permeability of hollow capsules because the fluorescence of the RB dye inside the capsules is suppressed as a consequence of the self-quenching of the dye. Upon releasing the dye into the bulk, the fluorescence intensity should increase. RB release kinetics was monitored by following the increase in the fluorescence intensity of RB at 576 nm as a function of time after RB-loaded capsules were mixed with water. In Figure 7, typical time-dependent fluorescence curves are shown. It clearly shows that the cross-linking reduced the permeation of the RB through the polyelectrolyte capsule wall. The cross-linking induced smaller pore sizes within the polyelectrolyte multilayer, which resulted in lower permeability consistent with previous studies. It is important to note that the final fluorescent intensity was reduced to about 12−15% after the cross-linking and remained constant even after 1 h. This is probably because the RB molecules were trapped and cross-linked with benzophenone in the PAH-BP/PSS multilayer. The permeability of PAA-BP/PAH-BP multilayer on gold substrates was also studied using cyclic voltammetry (CV), depending on the degree of cross-linking (not shown). After cross-linking, the peak current decreased and the shape of the CV became broad and plateau shaped, which indicated slower diffusion of redox molecules to the electrode through an array of defects, which do not overlap with each other.[19]

The fluorescence intensity $I(t)$ as a function of time t is theoretically described using Ding and Liu's equations which described the RB release from polyisoprene-*block*-poly(2-cinnamolylethyl methacrylate) nanospheres[28]

$$n_{out} = n_{tot}(1 - e^{-(pS/V)t}) \quad (1)$$

where n_{tot} is the total number of RB molecules, n_{out} is the number of RB molecules in the bulk aqueous phase at time t, p is the permeability, and S and V denote the surface

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area and the volume of an average capsule. The fluorescence intensity $I(t)$ as a function of time t is described as

$$I(t) = I_\infty - n_{tot}(\varphi_{out} - \varphi_{in})e^{-(pS/V)t} \quad (2)$$

where φ_{out} and φ_{in} are the fluorescence quantum yields in bulk water and the PAH-BP/PSS capsule, respectively, and $I_\infty = \varphi_{out}n_{tot}$ is the fluorescence intensity of RB after it is completely released into the aqueous phase.

We then fit the time dependence by a function

$$I = c + a(1 - \exp^{-At}) \quad (3)$$

where the coefficient $A = pS/V = 3p/r$ and r is radius of hollow capsule.[29] Fitted curves are shown together with the experimental results in Figure 7. Unlike the failed fitting with experimental data using these equations for RB release from copolymer nanospheres as studied by Ding and Liu,[28] in our case, there is very good agreement between eq 3 and the experimental data. The assumption made for this theoretical system is the uniform size distribution of the capsules and the thinness of the shell layer, which is generally true in our system (monodispersed PS core, thickness of polyelectrolytes, 20 nm, is considerably smaller than the diameter of the capsule, 500 nm). Before cross-linking, the coefficient A was calculated at 4.7×10^{-2} s^{-1}, corresponding to a permeability, $p = 4 \times 10^{-8}$ m/s with the radius $r = 2.5 \times 10^{-5}$ m. This value is similar to that determined by means of fluorescence recovery after photobleaching for a similar thickness of PAH/PSS multilayers.[29] After 1 min of UV irradiation, the coefficient A was reduced to 3.7×10^{-2} s^{-1}, corresponding to a permeability, $p = 3 \times 10^{-8}$ m/s. Then the coefficient A was further reduced to 2.4×10^{-2} s^{-1}, after 3 min of irradiation, corresponding to a permeability, $p = 2 \times 10^{-8}$ m/s; i.e., the permeability value was reduced 50%. These values are thus consistent with controlled permeability of the model drug RB based on irradiation time resulting from the increased degree of photo-cross-linking for the polyelectrolyte multilayer shell. Further studies will be made on different sizes of model drugs and the possibility of using pH control on the permeability kinetics.

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Conclusion

This paper has demonstrated that the permeability of polyelectrolyte multilayer capsules can be tuned by cross-linking of the multilayer shell. Hollow shells were successfully prepared by alternating the adsorption of photo-cross-linkable benzophenone-modified PAH and PSS on PS particle and followed by removing the core with THF. Release kinetics of a model drug, RB, was investigated using fluorescence spectroscopy. It was found that the permeability of $(PAH\text{-}BP/PSS)_4$ hollow shells was reduced from 4×10^{-8} to 2×10^{-8} m/s after 3 min of UV irradiation. These findings indicate a novel approach for fabrication of hollow shells with sustained and controlled release properties that can be suitable for drug release systems or other controlled-release applications. Further studies are underway to investigate the location of model dye molecules in the capsule using fluorescence microscopy and mechanical and chemical stability of hollow capsules after the cross-linking.

Acknowledgment. We thank Professor Michael S. Wong and his group at Rice University for zeta potential measurements and Leigh Millican for TEM (High Resolution Imaging Facility at UAB). Partial funding from the Research Division of the University of Houston, NSF-CTS (0330127), and NSF-CHE-0304807 is appreciated.

LA047008X