Stable Weak Polyelectrolyte Microcapsules with pH-Responsive Permeability

Weijun Tong,[†,‡] Changyou Gao,*[,†] and Helmuth Möhwald[‡]

Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, China, and Max-Planck-Institute of Colloids and Interfaces, 14424 Potsdam, Germany

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ABSTRACT: Stable weak polyelectrolyte microcapsules were prepared by assembly of branched poly(ethylenimine) (PEI) and sodium poly(acrylic acid) (PAA) followed by glutaraldehyde (GA) cross-linking. By assembly of the building blocks onto polystyrene (PS) latex particles, the variation of the zeta-potentials of the multilayers before and after cross-linking was measured as a function of pH. Charge reversal was observed for all multilayers regardless of their outmost layer composition and cross-linking during a change of pH. The phenomenon is explained by the penetration of the underlying layer. The cross-linked capsules could maintain their macroscopic topology at extreme low or high pH, while reorganizing their microstructure to enable selective permeation or rejection of macromolecules at lower (< pH 4) and higher pH (> pH 6), respectively. Using this property, dextran with a molecular weight of 2000 kDa was successfully encapsulated. Thus, it is possible to produce capsules that are at the same time pH responsive as well as stable over a large pH range.

Introduction

Layer-by-layer (LBL) assembly of oppositely charged polyelectrolytes onto removable colloidal particles has recently been used to create novel nano- and microcapsules with well-controlled size and shape, finely tuned capsule wall thickness, and variable wall compositions.[1]

The resulting capsules may find potential applications in medicine, catalysis, cosmetics, and biotechnology. For various applications, capsules with tunable and reversible permeability are extremely attractive so that encapsulation and subsequent release can be realized. Previous studies have shown that the permeability of the polyelectrolyte microcapsules can be readily tuned by factors such as layer number,[2] pH value,[3] ionic strength,[4] and polarity of the solution[5] as well as annealing[6] and resealing[7] after core removal. In these cases, reversible permeability also has been demonstrated by control of pH[3] or polarity of the solution.[5] These studies mostly focus on multilayer capsules composed of at least one strong polyelectrolyte. Reversible permeability control of capsules composed exclusively of weak polyelectrolytes has scarcely been reported so far.

Great attention has been paid to weak polyelectrolyte multilayers in recent years. On planar substrate detailed investigations have been performed to this class of multilayers, exemplified by poly(allylamine hydrochloride) (PAH) and poly(acrylic acid) (PAA).[8] Pores in the range of hundreds of nanometers have been created in the multilayers by immersing the PAA/PAH multilayers assembled at some pH values in low-pH solution[9] or by exposing the PAA/PAH multilayers prepared from salt-containing polyelectrolyte solution to pure water.[10] Production of hollow weak polyelectrolyte microcapsules templated on diverse microparticles has been reported as well.[11] These capsules show unique pH-responsive properties. For example, the PAA/PAH capsules can be dissolved by exposure to low pH.[11b] The poly(methacrylic acid) (PMA)/PAH capsules show reversible pH-responsive swelling behavior.[11c] The pH-responsive properties of these capsules provide an additional opportunity to tune the permeability, loading, and release properties for many potential applications.

On the other hand, the stability of hollow microcapsules against environmental alterations such as pH, osmotic pressure, and temperature is a critical issue for practical applications. This is especially important for weak polyelectrolyte capsules, whose instability at extreme conditions may greatly restrict their applications. One of the promising pathways to improve the stability is covalent cross-linking of the capsule walls. For example, by incorporation of photosensitive diazoresin (DAR) in a LBL manner followed by UV irradiation, cross-linked capsules are obtained with improved stability against solvent etching and osmotic pressure.[12] By water-soluble carbodiimide chemistry, weak polyelectrolyte capsules have been similarly cross-linked,[11c,13] resulting in stable capsules against solvent etching and pH alteration.

The aforementioned techniques are largely based on a reaction between the functional groups of the two components in the multilayers. Neutron reflectivity shows that there is a large overlap between segments of the adjacent layers.[14] Therefore, it is possible to improve the multilayer stability by cross-linking just one component. For example, stability of the hydrogen-bonded multilayer microcapsules is improved by carbodiimide chemistry using ethylenediamine as a foreign cross-linking reagent for the PMA component.[15] The amino groups of fourth-generation poly(amidoamine) dendrimer (4G PAMAM) in sodium poly(styrenesulfonate) (PSS)/4G PAMAM multilayers have also been cross-linked and activated by glutaraldehyde (GA) treatment for biological applications.[16] More recently, we have demonstrated that multilayer capsules assembled from PAH and sodium poly(styrenesulfonate) (PSS) can be considerably stabilized by cross-linking of only the PAH component with GA.[17] After cross-linking, the chemical and thermal stability as well as the mechanical strength are all greatly improved.

In this paper, GA cross-linking is performed on exclusively weak polyelectrolyte capsules assembled from branched poly(ethylenimine) (PEI) and PAA. The PEI molecules possess

[†] Zhejiang University.
[‡] Max-Planck-Institute of Colloids and Interfaces.
* Corresponding author: e-mail cygao@mail.hz.zj.cn; Tel +86-571-87951108; Fax +86-571-87951948.

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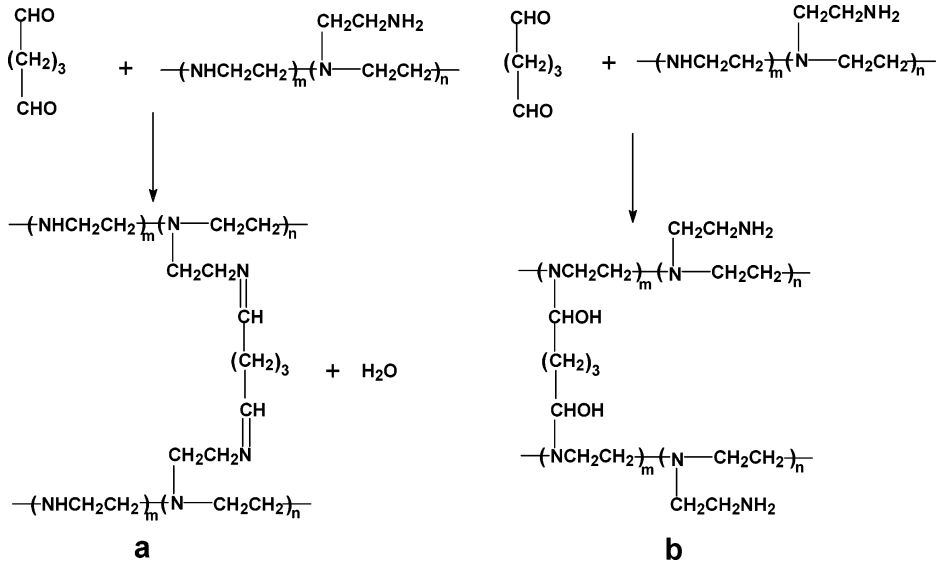
Scheme 1. Reaction Schemes of GA with (a) Primary and (b) Secondary Amines of PEI[a]



[a] Moreover, it is also possible that one −CHO group reacts with primary amine, while the other reacts with the secondary one.

amine groups which can readily react with the aldehyde groups of GA (Scheme 1) at very mild conditions.[18] The cross-linked weak polyelectrolyte microcapsules show good stability against high or low pH and reversible pH-controlled permeability for macromolecules. Using this feature, encapsulation of FITC-dextran with a high molecular weight is also demonstrated. Thus, we can combine seemingly contradictory features of responsiveness and stability.

Experimental Section

Materials. Branched poly(ethylenimine) (PEI, $M_w \sim 25$ kDa), FITC-dextran ($M_w \sim 2000$ kDa), manganese sulfate hydrate ($MnSO_4 \cdot H_2O$), disodium ethylenediaminetetraacetate dihydrate (EDTA), ammonium hydrogen carbonate (NH_4HCO_3), and glutaraldehyde (GA, 30 wt % solution in water) were all obtained from Sigma-Aldrich. Sodium poly(acrylic acid) (PAA, $M_w \sim 20$ kDa) was purchased from Polyscience. All chemicals were used as received. The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 MΩ. Spherical $MnCO_3$ microparticles with a diameter of ~8 μm were synthesized by mixing $MnSO_4$ and NH_4HCO_3 solutions.[19] FITC-PAH was prepared by labeling PAH with fluorescein isothiocyanate (FITC) according to the literature.[20] Polystyrene (PS) microparticles with an average diameter of 925 nm were purchased from Microparticles GmbH, Berlin, Germany.

Methods. a. Layer-by-Layer Assembly, GA Cross-Linking, and Hollow Capsule Fabrication. The pH values of both PAA and PEI solutions were adjusted to 6.5 with 0.1 M HCl or 0.1 M NaOH. Adsorption of the polyelectrolytes (2 mg/mL) onto the $MnCO_3$ microparticles (~1% w/w in suspension) was conducted in 0.2 M NaCl solution for 10 min followed by three washings in 0.2 M NaCl. The excess polyelectrolytes were removed by centrifugation at 300*g* for 5 min. After assembly of a desired layer number of PEI/PAA, the coated particles were incubated in 2% GA solution for a desired time at room temperature. After washing with water five times, they were then incubated in 0.1 M HCl solution for 30 min under continuous shaking. The resultant capsules were centrifuged at 1500*g* for 5 min and washed three times with 0.01 M EDTA solution to rinse off the Mn^{2+}. Finally, the capsules were washed three times with water. To test the chemical stability, the capsules were incubated in 0.1 M HCl or 0.1 M NaOH for 2 h and then washed three times with water. For the ζ-potential measurement, 925 nm PS particles were used as templates in order to avoid quick sedimentation. They were coated and cross-linked in the same way as that for $MnCO_3$ microparticles.

b. Scanning Force Microscopy (SFM). The capsules were incubated overnight in solutions with different pH to investigate the change of their surface morphology. A drop of the sample suspension was applied to freshly cleaved mica. After the capsules were settled down, the liquid phase was gently blown away and dried under a nitrogen flow. The images were obtained by a Digital Instruments nanoscope IIIa multimode SFM (Digital Instruments Inc., Santa Barbara, CA) in air at room temperature using the tapping mode.

c. Confocal Laser Scanning Microscopy (CLSM). Confocal images were taken with a Leica confocal scanning system mounted to a Leica Aristoplan and equipped with a 100× oil immersion objective with a numerical aperture (NA) of 1.4. For visualization, FITC-PAH was used to stain the capsules. To investigate the pH influence on permeability, equal volumes of capsule suspension and FITC-dextran ($M_w \sim 2000$ kDa, 2 mg/mL) with the same pH values (adjusted with 0.1 M NaOH or 0.1 M HCl solution) were mixed and observed after 20 min.

d. ζ-Potential Measurement. The ζ-potentials of the coated PS microparticles were measured at different pHs by a Zetasizer Nanoinstrument Nano Z equipment. Each value was averaged from three parallel measurements.

Results and Discussion

ζ-Potentials of Multilayers on PS Particles. The branched PEI used here contains 25% primary, 50% secondary, and 25% tertiary amines, each with the potential to be protonated. Its capability being assembled into multilayers in a LBL manner has previously been demonstrated.[21] Here a pH value of 6.5 was adopted for multilayer deposition because at this condition a relatively thin and flat PEI/PAA film can be assembled;[21] thus, serious aggregation can be avoided. After assembly, the PEI/PAA multilayer-coated PS particles with PEI or PAA as the outmost layer were dispersed in GA solution for 2 h to cross-link the PEI component. The reaction between PEI and GA is normally employed to produce stable cross-linked PEI coatings on planar substrate as well as on inorganic/organic beads.[18,22] It has been confirmed that both the primary and the secondary amines can react with GA, although the reactivity of the latter is lower than that of the former.[23] As depicted in Scheme 1, the reaction between the aldehyde and the primary amine groups will produce −C═N− bonds (Schiff base) (Scheme 1a),[24] while the reaction between the secondary amines and GA will result in −C−O− bonds (Scheme 1b).[18b] This reaction mechanism has been confirmed previously by IR spectra.[25]

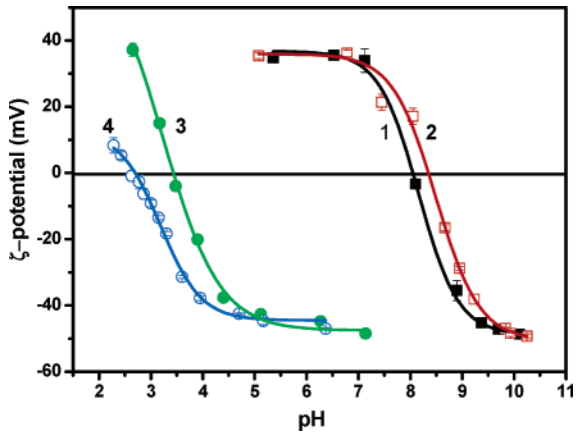


Figure 1. ζ-potentials of polyelectrolyte multilayer-coated PS particles as a function of pH: (1) PS-(PEI/PAA)$_4$PEI (solid squares), (2) PS-(PEI/PAA)$_4$PEI GA 2 h cross-linking (open squares), (3) PS-(PEI/PAA)$_5$ (solid circles), and (4) PS-(PEI/PAA)$_5$ GA 2 h cross-linking (open circles).

The ζ-potentials of the PS particles coated with PEI/PAA multilayers before and after GA cross-linking were investigated at different pH. Since the ζ-potential of colloids is mainly decided by their surface charge, this study may reveal the change of surface property brought by the cross-linking. Four types of samples were checked: (1) PS particles coated with 4.5 bilayers of PEI/PAA with PEI as the outmost layer (PS-(PEI/PAA)$_4$PEI); (2) sample 1 treated with GA for 2 h (PS-(PEI/PAA)$_4$PEI GA 2h-cross-linking); (3) PS particles coated with 5 bilayers of PEI/PAA with PAA as the outmost layer (PS-(PEI/PAA)$_5$); and (4) sample 3 treated with GA for 2 h (PS-(PEI/PAA)$_5$ GA 2h-cross-linking).

The ζ-potential measurement in Figure 1 shows that the surface charge of the polyelectrolyte multilayers on the PS particles regardless of the outmost layer, and the GA cross-linking was reversed by variation of the pH value. When PEI was the outmost layer (samples 1 and 2), an increase of the pH value from neutral to alkaline had changed the surface charge from positive to negative. The sharpest change was observed between pH 7 and pH 9. On the other hand, when PAA was the outmost layer (samples 3 and 4), a decrease of the pH value from neutral to acidic had changed the surface charge from negative to positive. The phenomena must result from the interpenetration of the underlying layer. It has been reported that in a similar weak PAA/PAH polyelectrolyte system a significant number of chain segments of the previously adsorbed layer penetrates into the outermost surface layer no matter which polyelectrolyte is the outermost layer.[26] Therefore, when the outmost layer is greatly decharged at high (for PEI being the last layer) or low pH (for PAA being the last layer), the interpenetrated segments will dominate the surface charge and thus cause the charge reversal. This is consistent with previous results; i.e., for PAA/PAH multilayer-coated PS particles, a similar charge reversal is observed.[11a]

It was unexpected that when PEI was the outmost layer, compared with the un-cross-linked sample, the ζ-potentials of the cross-linked multilayers were not decreased but were even enhanced a little. A possible explanation would be that although cross-linking can reduce the number of primary amines, the total number of charged groups is not greatly decreased since primary amines are only 25% of the total amine groups. Reaction of secondary amines results in tertiary amines (Scheme 1b). When a primary amine group is reacted with GA, the neighboring secondary or tertiary amines are more easily charged at relatively high pH due to the elimination of the electrostatic influence.[27] This effect may compensate for the reduction of the primary amines. When PAA was the outmost layer, the ζ-potentials of the cross-linked sample were lower than that of the un-cross-linked one. Because of the highly branched structure of PEI, primary amines should be the main interpenetrating groups on the layer surface. A reaction with GA may then greatly reduce the positively charged groups at low pH. Another reason could be that the branched and cross-linked PEI is more difficult to reorganize its configuration to diffuse outside as that of the linear PAA.

Formation and Stabilization of Hollow Microcapsules. For the ease of characterization, bigger spherical $MnCO_3$ particles with an average diameter of 8 μm were employed as templates. The 2 h cross-linked five-bilayer PEI/PAA capsules with PAA as the outmost layer were obtained after core removal. Figure 2a shows that the cross-linked capsules were still dispersible in water. At neutral pH, the outmost PAA layer has negative charge (Figure 1) and endows the capsules with hydrophilicity, which favors the dispersion of the capsules. The SFM image (Figure 2b) reveals that the capsules collapsed as a result of evaporation of the water content during the drying procedure. Similar to other techniques, cross-linking by GA cannot produce capsules with hard enough wall structure to resist collapse. The double wall thickness of the cross-linked capsules is $\sim$19.8 $\pm$ 1.3 nm, which corresponds to about 1 nm for each layer.

As cross-linking can produce covalent bonds acting besides charge interaction in the capsule walls, the stability of the capsules could be improved. Incubation of the cross-linked capsules in 0.1 M HCl or in 0.1 M NaOH for 2 h, they could be still well dispersed in water and keep their intact structures (Figure 3) as those initially exist in pure water (Figure 2a). Normally, the un-cross-linked weak polyelectrolyte capsules will be dissolved at extreme pH due to the decharging of their polyelectrolyte components, leading to disassembly of the multilayer film.[11b] Apparently, GA cross-linking provides additional covalent bonding, which can maintain the macroscopic topology of the capsules after breakage of the electrostatic interaction at extreme pH.

pH-Controlled Permeability of the Cross-Linked Capsules. The permeability of 2 h cross-linked hollow capsules consisting of five PEI/PAA bilayers was monitored by CLSM using FITC-dextran ($M_w \sim$ 2000 kDa) as a fluorescent probe. Representative CLSM images at low or high pH are presented in Figure 4. At alkaline conditions, e.g., pH 10 (Figure 4b), the interiors of the capsules remained dark at least for 20 min, implying that the capsule walls were impermeable for the FITC-dextran. By contrast, at pH 3 the capsule interiors had the same fluorescence intensity as the bulk (Figure 4a), implying that the capsules were now open for permeation of the FITC-dextran. One has to mention that this "open" and "close" state at low and high pH, respectively, was observed for more than 90% of the capsules. The open state for the FITC-dextran was observed in the pH region below 4. Above pH 6, most of the capsules were closed. At pH 5, both open and closed capsules were observed. This behavior is similar to that of PAH/PSS capsules, although the pH value of the transition between the close and the open states shifted 2 units toward the acidic region.[3] Compared with the 2 h cross-linked capsules, the 30 min cross-linked capsules showed similar pH-controlled permeability, except that the pH value of the transition shifted about 1 unit toward neutral pH; i.e., the capsules were open below pH 5 and closed at pH $\geq$ 6.

These results reveal the important fact that the polyelectrolyte chains can preserve their mobility and responsivity to the pH change after GA cross-linking. It has been suggested that the

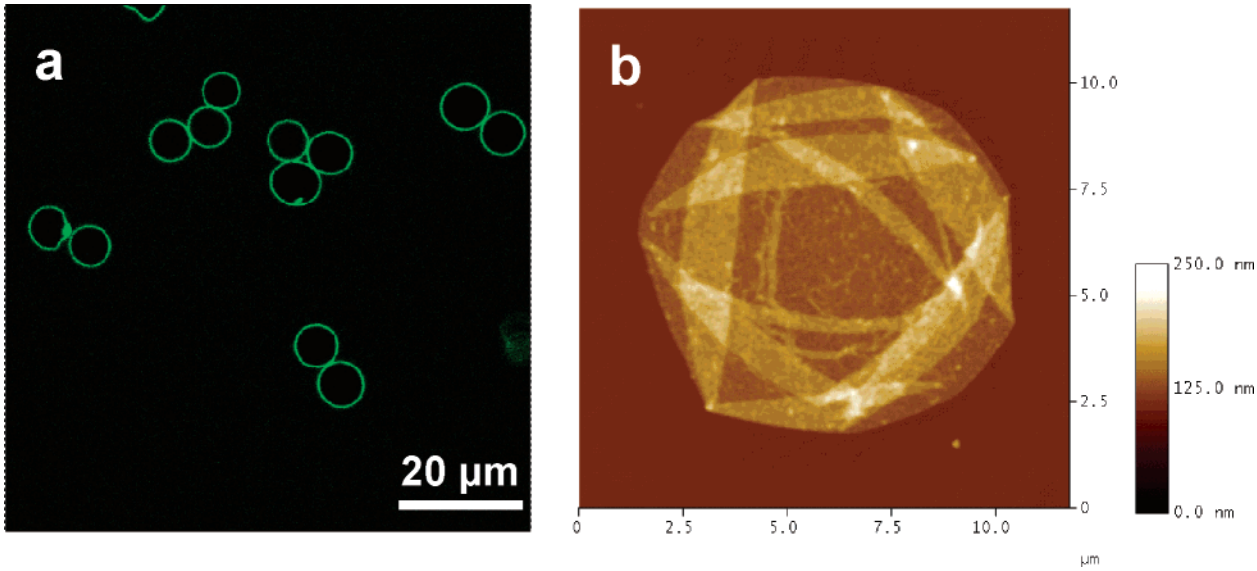


Figure 2. (a) Fluorescence CLSM and (b) SFM images of cross-linked $(PEI/PAA)_5$ hollow capsules via 2 h GA treatment.

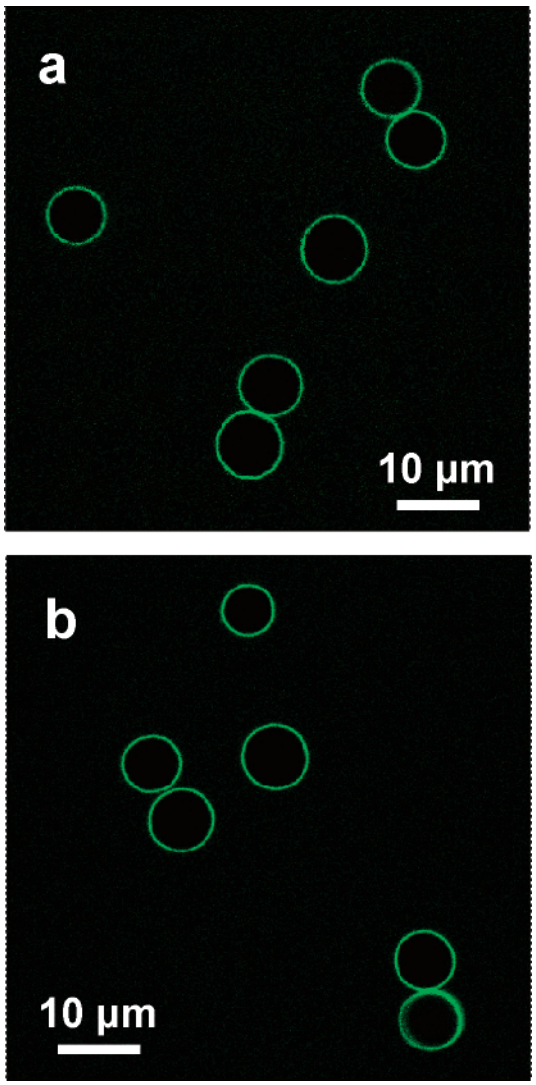


Figure 3. Fluorescence CLSM images of 2 h cross-linked $(PEI/PAA)_5$ capsules after incubation in (a) 0.1 M HCl and (b) 0.1 M NaOH solutions for 2 h, followed by washing with water.

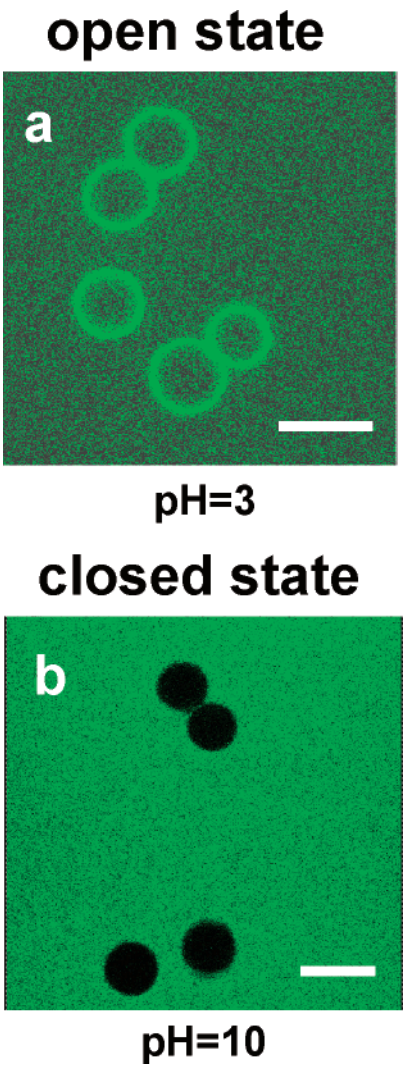


Figure 4. Permeability switch of the cross-linked capsules for FITC-dextran ($M_w \sim 2000$ kDa) with the change of pH. (a) pH 3 and (b) pH 10. Scale bar = 10 μm.

change of the polyelectrolyte charges upon pH variation might induce pore formation or loosen the polyelectrolyte networks, thus enabling the macromolecules to penetrate.[3b] Moreover, it is also reported when weak polyelectrolyte multilayer films (linear PEI/PAA,[28] PAH/PAA[9]) assembled at certain pH are incubated in acidic solution with a pH 2−3, they undergo a transition from a continuous to a nanoporous morphology due

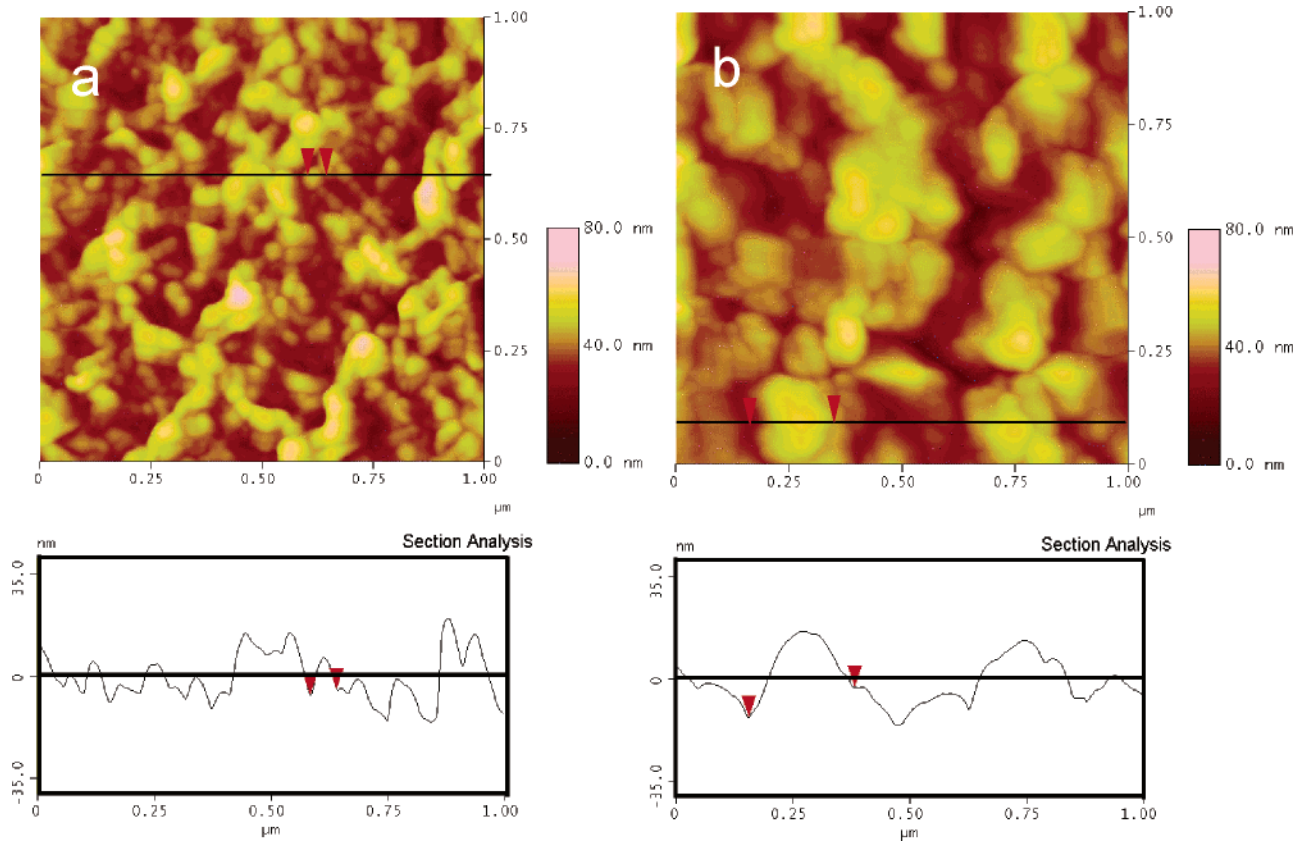


Figure 5. SFM images to show the surface morphology of the capsules dried from (a) pH 3 and (b) pH 10 solutions. Corresponding profiles are shown at the lower parts with the positions indicated in (a) and (b).

to phase segregation upon protonation of the highly charged acid groups. In our previous study a similar pore formation on the PAA/PAH capsule walls has been observed when they are treated with low-pH solution.[11b] It is thus reasonable to deduce that the pH-dependent permeability observed here is most possibly caused by a wall structure change. Observed under SFM (Figure 5), capsules pretreated with pH 3 (Figure 5a) or pH 10 (Figure 5b) show actually different surface morphology. Although both have grains on their capsule wall and the same root-mean-square surface roughness of ~7.7 nm, a much larger domain size is found for capsules dried from pH 10 solution. The mean diameter and height of the domains were revealed to be 260 ± 27 nm and 27 ± 3 nm, respectively. By contrast, at pH 3 a mean diameter of 65 ± 9 nm and height of 13 ± 2 nm were obtained. Some places with thinner wall thickness were also observed for capsules dried from pH 10 solution (Figure 5b). All these results confirm a difference of the capsule microstructure incubated at low or high pH, although no apparent pores are observed as that before for the PAH/PSS capsules.[3b]

The molecular mechanism of this structure change should be mainly correlated to the charging degree of the polyelectrolytes at different pH. At the pH of capsule preparation, namely pH 6.5, the ionization degree of the adsorbed PAA is close to 100%.[8a] However, only ~50% of the amine groups in PEI molecules are in an ionization state.[21] The charge density will determine the stoichiometric ratio of the polyelectrolyte in the multilayers. Therefore, half of the amines of the adsorbed branched PEI in the multilayers are uncharged (most of them should be tertiary and secondary amines, because they have lower pK_a compared with the primary amines[27]). When the pH is decreased to 3, PAA is largely protonated while charging of PEI occurs. Consequently, net positive charges are created in the multilayer walls. The charge repulsion between the PEI chains will cause the reorganization of the wall structure, most likely in a smaller range because of the cross-linking. This may then create channels or even defects for permeation of the macromolecules with high molecular weight.

By this mechanism, the capsule should also permeable at high pH since PEI is decharged while PAA is fully charged. However, the cross-linked capsules were closed to the polysaccharide even at pH 12. The intrinsic reason is not clear yet. The most possible reason might be related with the unsymmetrical cross-linking of the capsule components, a structure like the semi-interpenetrating polymer networks (semi-IPNs). It is likely that only variation of the cross-linked PEI backbone can induce substantial change of the capsule structure as in the case of lower pH. Although PAA is fully charged at pH 12, the charge repulsion may not be strong enough to conquer the elastic restoring force of the PEI networks to create big enough channels. Therefore, permeation of macromolecules is impossible.

The feature of pH-controlled reversible permeability can be used to encapsulate macromolecules into capsules, which may find potential application for sustained release. Here the capsules were incubated in FITC-dextran solution at pH 3 for 30 min. Then the solution pH was increased to 10. After removal of the bulk solution by centrifugation, strong fluorescence from the capsule interior can be seen, demonstrating the successful loading (Figure 6).

Conclusions

Stable weak polyelectrolyte microcapsules can be prepared by assembly of branched PEI and PAA followed by GA cross-linking. The resultant hollow capsules have a cross-linked wall

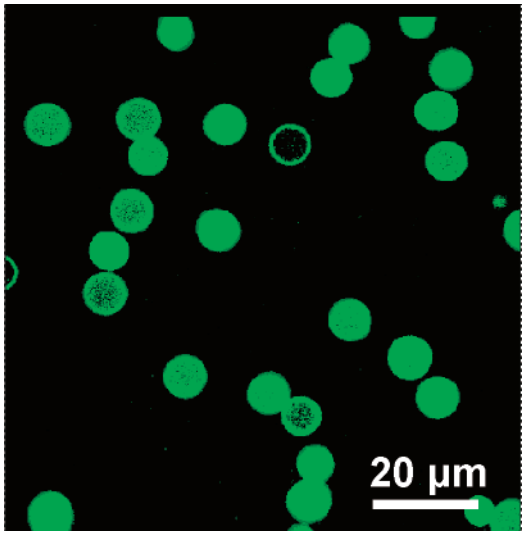


Figure 6. CLSM image to show the loading of FITC-dextran ($M_w \sim$ 2000 kDa) via a pH-controlled permeability switch protocol.

structure like the semi-interpenetrating polymer networks (semi-IPNs) and thus are stable at extreme low or high pHs. The 2 h cross-linked capsules show reversible pH-controlled permeability for macromolecules, exemplified here with dextran ($M_w \sim$ 2000 kDa). They are open below pH 4 and close at pH higher than 6. Using this feature, high molecular weight compounds can be encapsulated. Apparently, it is possible to stabilize the structure at the micrometer level by cross-linking while still maintaining the responsiveness at the nanometer level. With this useful feature, the weak PE capsules with stable structure may find various applications as microcontainers, delivery vehicle, biosensors, and bioreactors in the future. Furthermore, the feasibility of GA cross-linking can be extended to other multilayer systems assembled from amine-containing building blocks such as proteins, enzymes, and polysaccharides, too.

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