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Soluble Microcapsules Assembled Stepwise from Weak Polyelectrolytes Using Acid-Decomposable Cores**

By Changyou Gao,* Helmuth Möhwald, and Jiacong Shen

Hollow capsules are of both scientific and technological interest because of their potential applications as new colloidal structures in areas such as medicine, drug delivery, artificial cells or viruses, and catalysis.^[1] Layer-by-layer (LBL) assembly of oppositely charged polyelectrolytes^[2] onto removable colloidal particles has been used to create novel hollow nano- and microcapsules.^[3] This fabrication technique allows control of the capsule size and shape, the capsule wall thickness, and the capsule wall composition. Microcapsules with customized physicochemical properties can be obtained by incorporating one or more functional components such as nanoparticles, biomacromolecules, lipids, photosensitive dyes, inorganic crystals, and multivalent ions onto the capsule wall or into the capsule interior.^[4]

The typical hollow capsules produced so far are composed of poly(styrenesulfonate sodium salt) (PSS)/poly(allylamine hydrochloride) (PAH), PSS/poly(diallyldimethyl ammonium chloride) (PDADMAC), or PSS/chitosan. Weakly crosslinked melamine formaldehyde (MF) colloidal particles or red blood cells have often been employed as sacrificial templates. After the desired number of layers has been deposited, the MF cores or the red blood cells are routinely decomposed in a solution of low pH (<1.6) or deproteinizer, respectively.^[3a,5] These harsh conditions may destroy the multilayers if the association between the negatively and positively charged species is not strong enough. Hence, at least one strong polyelectrolyte in the oppositely charged pairs is generally employed to obtain capsules with high integrity.

Much effort has been devoted to the nanoscale encapsulation of drugs, minerals, dyes, proteins, enzymes, and genes.^[6]

However, entities with large geometric size and/or rigid structure such as nanoparticles and macromolecules of ultrahigh molecular weight are difficult to incorporate unless one takes specific measures to open the capsules. To create microcapsules with controllable permeability, attention has been paid to microcapsules of weak polyelectrolytes, where the charge density on the capsule wall can be readily controlled by adjusting the pH values of the bulk solutions. With this class of systems, exemplified by poly(acrylic acid) (PAA) and PAH, pH-modulated permeability can be expected as a result of conformation alteration of the macromolecular chains.^[7] Moreover, it has been reported that pores in the range of hundreds of nanometers on PAA/PAH multilayers assembled at some pH values have been created as a result of phase separation induced by pH change or salt exposure.^[7a,8] Due to the weak bonding, dissolution of the formed capsules at mild pH conditions is also possible. Therefore, one obtains greater control over the physical state of the assembled capsules, such as pH-tuned opening or closure, surface texture, and solubility.

In this communication we describe the successful fabrication of weak polyelectrolyte microcapsules by consecutive adsorption of PAA and PAH onto MF colloidal particles, followed by decomposition of MF cores in 0.1 M HCl solution. Given the fast core decomposition rate, the technical problem of shell dissolution was solved by precise control of the time of treatment in acid solution. The resulting microcapsules are readily soluble at low pH. Microcapsules with porous wall texture were achieved by depositing PAA and PAH stepwise onto fluorescein diacetate (FDA) crystals at pH 3.5 and 7.5, respectively, followed by treatment at pH 2.5 and then dissolution of FDA by acetone.

To monitor the process of film formation, i.e., charge reversal at each step, by electrophoresis, MF particles with a diameter of 500 nm were alternately coated with PAA (molecular weight M_w 5100) and PAH in 0.5 M NaCl solution (without adjusting pH values).^[9] After adsorption for 10 min, three washings were carried out to remove excess polyelectrolytes. Figure 1 summarizes the ζ -potential recorded upon layer deposition for PAA/PAH pairs. The ζ -potential alternates between positive and negative values, indicating the successful recharging of the particles coated with the adsorbed polyelectrolyte multilayers upon each layer deposition.

Acid-decomposable MF particles with an average size of 3.7 μm were employed as templates to prepare PAA/PAH hollow microcapsules. All coatings and washings were continuously conducted in 0.2 M NaCl solution with polyelectrolyte concentration of 2 mg/mL, where the natural pH values for PAA (M_w 20000) solution and PAH solution are 7.7 and 4.7, respectively.^[10] A lower salt concentration would be favorable to obtain denser multilayers on the colloidal particle surface. Moreover, by using PAA with larger molecular weight, a shell structure more stable against acid dissolution during the core removal procedure is expected, owing to the higher chance of entanglement between molecular chains.

After five bilayers of PAA/PAH had been deposited, the coated particles were treated with 0.1 M HCl solution. How-

[*] Prof. C. Y. Gao, Prof. J. C. Shen
Department of Polymer Science and Engineering, Zhejiang University
Hangzhou, 310027 (P.R. China)
E-mail: cygao@mail.hz.zj.cn
Prof. H. Möhwald
Max Planck Institute of Colloids and Interfaces
D-14424, Potsdam (Germany)

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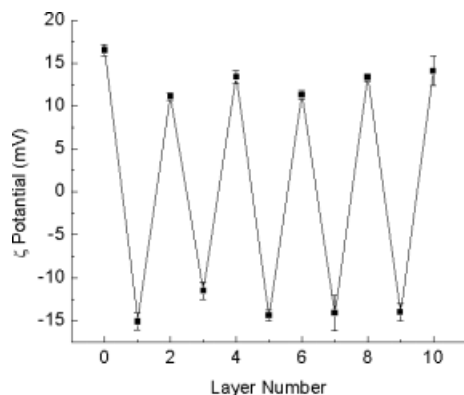


Fig. 1. ζ -potential as a function of layer number for MF particles coated with alternately PAA (odd) and PAH (even) as the outer layer. The line is to guide the eye and has no physical meaning.

ever, only a clear solution was obtained when membrane filtration apparatus was used to wash off the excess acid and the MF degradation products. Dynamic observations of the core removal by confocal laser scanning microscopy (CLSM) yielded that a typical shell swelling existed at the initial stage, followed by the disappearance of the shells afterwards. The explanation of this observation is apparently the dissolution of the shells due to the long time in acid. It takes 5–10 min to wash off acid by membrane filtration, depending on the filter size. This time, as will be proved later, is long enough to destroy the shell structure.

Although the PAA/PAH complex is intrinsically unstable at lower pH because of the full decharging of the PAA molecular chains (pK_a for free PAA, 4.5–5.5, but shifted to much lower value for PAA in the multilayer),^[7a] we suppose that the complete dissociation between PAA and PAH should last for some time because of the shielding of polymer chains. Therefore, we may utilize this time to solve the problem since core decomposition is completed in 20–25 s.^[11] By addition of an equal amount of 0.1 M NaOH solution to the reaction system after 30 s, by which time the core decomposition had finished, the further interaction of HCl on the PAA/PAH shells was terminated to avoid destruction of the shell. Figure 2 shows that this protocol yields hollow PAA/PAH capsules both in solution and out of solution. However, both CLSM and scan-

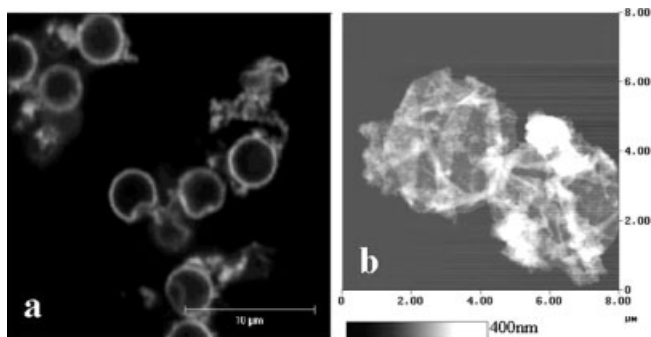


Fig. 2. a) CLSM and b) SFM images of PAA/PAH microcapsules fabricated by the neutralization protocol after incubation of the coated MF particles in 0.1 M HCl for 30 s.

ning force microscopy (SFM) have proved that the capsules obtained were rather dirty, owing to the precipitation of the MF decomposition products. The contaminants could not be separated or removed afterwards.

Nevertheless, the above experiment demonstrates that fabrication of PAA/PAH capsules templated on MF is possible. To avoid the precipitation of MF decomposition products, prior to core removal the particles were adhered to a mica surface by electrostatic binding. After incubation in 0.1 M HCl for 30 s, the capsules adhering to mica were rinsed with a large amount of water. SFM observation revealed that this strategy yielded clean hollow capsules with typical morphology for capsules in the dry state (Fig. 3a). Creases and folds were formed due to the collapse of the capsules after evaporation of the liquid content. No contaminants on the capsule

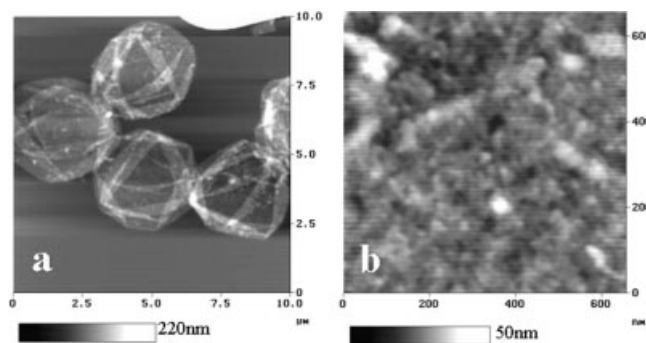


Fig. 3. a) SFM image of PAA/PAH capsules fabricated in situ on mica to show the successful production with high purity (see also Fig. 2b). b) Pores in the capsule wall observed on a high-magnification scanning image.

walls were detected. The average layer thickness measured by SFM, 0.5 nm/layer, is much smaller than that of PSS/PAH capsules (1.5–2.0 nm/layer), demonstrating that the capsule wall is quite thin. An even thinner layer thickness was reported by Shiratori and Rubner at the same pH values and in the absence of electrolyte.^[7c] Hence one can conclude that the presence of salt in the present assembly conditions is indispensable to ensure deposition of sufficient material. Higher magnification of a flat area without folds (Fig. 3b) showed the existence of pores in the capsule wall with diameters of tens of nanometers, which should be attributed to the capsule swelling induced by osmotic difference during core removal^[11] and the partial dissolution of the weak polyelectrolyte complex.

Capsules suspended in water were similarly obtained by controlling the total acid treatment to less than 150 s. A centrifugation protocol was used to remove the acid rapidly after incubation of the coated particles in 0.1 M HCl for < 60 s. Figure 4 shows that the capsules were successfully produced with high purity both in solution and out of solution (see also Fig. 2). It is worth noting that collapsed capsules cannot be returned to their initial shape by any means tried up to now.

The obtained PAA/PAH capsules are readily decomposable by low pH after incubation for a longer time. Figures 5a,b present the SFM top views of the capsules after treatment with 0.1 M HCl for 5 and 10 min, respectively. All capsules

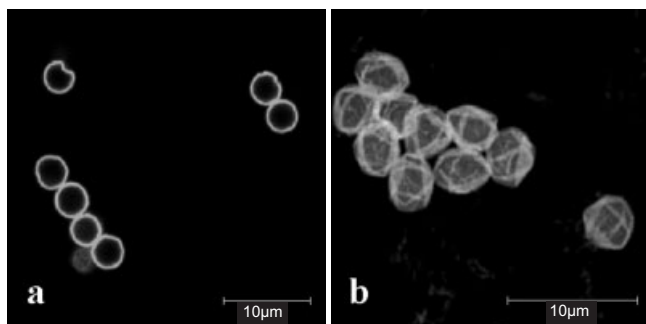


Fig. 4. PAA/PAH capsules with high purity and integrity obtained both in solution (a) and out of solution (b) by strictly controlling the time of treatment with acid.

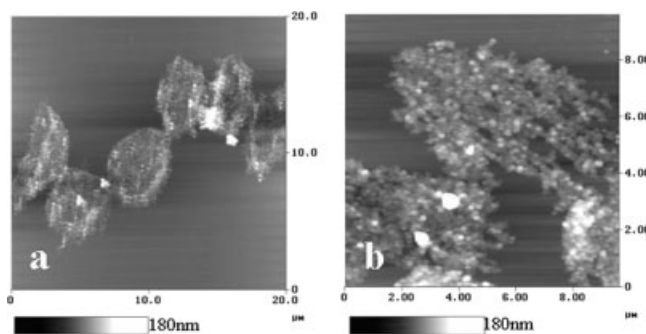


Fig. 5. SFM images of the microcapsules treated with 0.1 M HCl for a) 5 min and b) 10 min to show the decomposable shell structure.

had been destroyed after 5 min, but the contour of the capsules was roughly preserved. Continued treatment, e.g., for 10 min, resulted in complete disappearance of the capsules, leaving only small pieces and remains adhering to the mica substrate. Note that these dissolution experiments were performed in situ on mica.

PAA/PAH capsules with porous wall texture were achieved after deposition of PAA and PAH onto FDA crystals at pH 3.5 and 7.5, respectively, followed by treatment at pH 2.5 for 10 min and then dissolution of the core by acetone. Weakly crosslinked MF cores are unsuitable for this purpose because they cannot be decomposed afterwards due to the further polymerization of the resin at low pH.^[11] The weak polyelectrolyte capsules with flat wall morphology in air were obtained by assembling under the above conditions. A surface roughness of 0.6 nm over an area of $1.2 \mu\text{m} \times 1.2 \mu\text{m}$ was found (Fig. 6a). After incubation at pH 2.5 before core removal, however, pores several nanometers to tens of nanometers in diameter and 4–10 nm in depth on the capsule walls were observed together with an increase in surface roughness to 1.8 nm over an area of $2.5 \mu\text{m} \times 2.5 \mu\text{m}$ (Fig. 6b). This result is consistent with the observation of PAA/PAH multilayers on a flat substrate by Rubner and co-workers, who attributed this alteration to phase separation induced by the chain reorganization.^[7a] The smaller phase separation degree observed here may be attributed to the smaller layer number or/and the special geometric structure. Work is under way to explore the morphology alteration and the influence on cap-

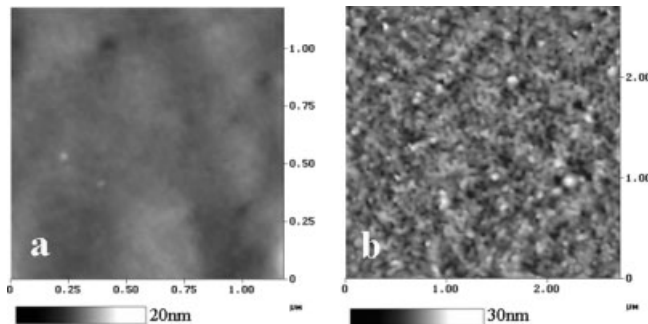


Fig. 6. SFM images to show the surface texture alteration of PAA/PAH capsules templated on FDA crystals. The cores were dissolved by acetone after assembly at pH 3.5 for PAA and pH 7.5 for PAH (a), and after treatment of (a) at pH 2.5 for 10 min before core removal (b).

sule properties, such as permeability and loading properties. One can expect that this alteration of the capsule surface texture will provide an additional opportunity to modulate the capsule properties.

In conclusion, we have shown the successful production of weak polyelectrolyte hollow capsules templated on MF particles. Capsules suspended in aqueous solution with high purity were fabricated by controlling the time of treatment in acid solution and by removing the acid quickly by centrifugation. The pH responsivity and solubility of these novel capsules provides an additional opportunity to tune the permeability, loading, and release properties for many future applications, such as chemical reservoirs, drug control release, and artificial cells.

Experimental

PAA with M_w of 5100 and 20 000 was purchased from Fluka; PAH with M_w of 50 000–65 000 and FDA crystals were from Aldrich. Weakly crosslinked MF particles were a commercial product from Microparticles GmbH, Germany. 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 $18.2 \text{ M}\Omega \text{ cm}$.

A membrane filtration technique was employed to consecutively adsorb PAA and PAH onto MF particles or FDA crystals [12]. The adsorption of polyelectrolytes (2 mg/mL) was conducted in NaCl solution for 10 min, followed by three washings in NaCl solution with the same concentration. Then the respective oppositely charged polyelectrolyte species was adsorbed. To disperse the hydrophobic FDA crystals in water, a PSS layer was adsorbed prior to PAA and PAH deposition.

The ζ -potential of the coated MF particles was measured by electrophoresis on a Malvern Zetasizer 4. The electrophoretic mobility u was converted into the ζ -potential using the Smoluchowski relation $\zeta = u\eta/\epsilon_0\epsilon$, where η and $\epsilon_0\epsilon$ are the viscosity and permittivity of the solution, respectively [13]. Confocal micrographs were taken with a Leica TCS NT (Leica, Germany). For the visualization of the capsules, rhodamine 6G (Rd6G) or 6-carboxyfluorescein (6-CF) was used as a fluorescence probe. The capsule solution and the probe solution were mixed on a glass coverslip. The images of capsules in aqueous environment were acquired immediately. The images in the dry state were taken after the water had evaporated. SFM images were recorded in air at 20–25 °C using a Nanoscope III Multimode SFM (Digital Instruments Inc., Santa Barbara, CA). The samples were prepared by applying a drop of the capsule solution onto freshly cleaved mica.

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Templated Nanowire Assembly on the Surface of a Patterned Nanosphere**

By Lorraine Nagle and Donald Fitzmaurice*

The bottom-up assembly of functional nanoscale architectures in solution is a goal shared by researchers in many fields.^[1] Expected benefits include greater control over material properties and innovative technologies that address unmet needs.^[2]

One approach envisaged is the self-assembly in solution of nanoscale architectures from molecular and condensed phase components.^[3]

In considering what molecular and condensed phase components might be suitable,^[4–6] one is immediately attracted to high-information-content molecules,^[7] and to the rapidly growing number of nanoparticles whose properties can be tuned by controlling their size and surface composition.^[8]

There exists a growing number of examples where high-information-content molecules and nanoparticles have been self-assembled in solution to yield novel nanoscale architectures, some with significant technological potential.^[9–11]

Despite this progress, it nevertheless remains the case that the structural diversity and functional complexity of the nanoscale architectures that have been self-assembled in solution fall short of what is needed.

It is in this context that we report findings related to the patterning of nanospheres, specifically, the deposition of a single gold nanoparticle on a silica nanosphere using a nanoporous membrane as template. We also report findings related to the assembly of a gold nanowire on the surface of a silica nanosphere.

Efforts directed at preparing patterned nanospheres have included the deposition of a monolayer of gold nanoparticles on one side of a silica nanosphere using Langmuir–Blodgett techniques.^[12] They have also included the evaporation of a metal onto one side of a latex nanosphere.^[13,14] Recently, we have applied a facile method to pattern nanospheres based on ultrafiltration technology whereby gold nanoparticles were assembled on only one side of a larger silica or latex nanosphere.^[15]

In our current approach (Fig. 1), the nanospheres to be patterned are immobilized on the upper surface of a membrane filter. The nanosphere diameter exceeds that of the membrane pores by one order of magnitude. The nanosphere surface is in direct contact with one, and in proximal contact with relatively few of the membrane pores. The membrane filter is inverted and a dispersion of nanoparticles is filtered through its underside. As a consequence, a column of nanoparticles is trapped inside the nanosphere-sealed membrane pores. The membrane is inverted and washed in order to remove the trapped nanoparticles with the exception of the nanoparticle adsorbed at the surface of the nanosphere. The nanospheres patterned through adsorption of a single nanoparticle are redispersed in ethanol by sonicating the membrane filter.

Shown in Figure 2A are the amine-modified silica nanospheres retained on a membrane filter. Shown in Figure 2B are the patterned silica nanospheres obtained by filtering an aqueous dispersion of citrate-stabilised gold nanoparticles through the underside of the same membrane. The twenty nanospheres shown were spread over one square (90 $\mu\text{m} \times 90 \mu\text{m}$) of a 400 square mesh carbon-coated copper transmission electron microscopy (TEM) grid. Statistical analysis of one hundred silica nanospheres revealed that 63 % were patterned with one gold nanoparticle, 8 % with two and 29 % were unpatterned.

[*] Prof. D. Fitzmaurice, Dr. L. Nagle
Department of Chemistry
University College Dublin
Belfield, Dublin 4 (Ireland)
E-mail: donald.fitzmaurice@ucd.ie

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