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Direct Covalent Assembly to Fabricate Microcapsules with Ultrathin Walls and High Mechanical Strength**

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Microcapsules with ultrathin wall and high stability are of both scientific and technological importance. They can provide ideal models for investigations of permeability, elasticity and responsivity on a nanometer scale, and be used as microcarriers and micro-reactors in a confined space. Among the established techniques such as nozzle reactor process, emulsion/phase separation, sol-gel processing and sacrificial templating,[1] assembly of building blocks onto colloidal particles in a layer-by-layer (LBL) manner[2] followed by core-removal is very promising to obtain hollow capsules with precise control over their wall thickness on a scale of ~1 nm.[3] The driving-forces for the LBL assembly applied so far are mostly electrostatic, H-bonding and coordinate interactions: all are of "weak" interactions.[4] Therefore, the stabilities of the resulting microcapsules against high or low pH, high salt concentration and high temperature are not satisfactory.[5] To enhance the binding strength between the building blocks, various post-treatments by glutaraldehyde (GA),[6] oxidization,[7] carbodiimide,[8] UV irradiation[9] and elevated temperature[10] are applied to the pre-formed microcapsules or the core–shell particles, which either transform the ionic bonds into covalent bonds or create new covalent bonds in the multilayer walls.[11]

If direct covalent chemical reaction is adopted as a driving force instead of those "weak" interactions, a same stepwise assembly will yield simultaneously covalently crosslinked multilayer capsules, with no necessity of post-treatments. Covalently assembled multilayers on planer substrates have been fabricated by a reaction between two kinds of multifunctional molecules[12] such as diamine and diisocyanate.[13] However, direct covalent assembly of multilayers on colloidal particles remains still much intriguing to date, though in a broader scope fabrication of covalent microcapsules and nanotubes by a reaction between diazoresin and phenol-formaldehyde resin,[14a] and glutaraldehyde mediated assembly of poly(allylamine hydrochloride) (PAH),[14b] glucose oxidase[14c] and hemoglobin[14d] has been reported. However, except for the structure characterizations many other aspects, in particular physical and chemical properties of these covalent microcapsules are hardly explored due to their structure limitation. These properties are extremely important for demonstrating the merits of the covalent structures, and also for future applications.

In this work, poly(glycidyl methylacrylate) (PGMA) is covalently immobilized onto aminosilanized SiO_2 microparticles (φ 3 μm) via a reaction between the epoxides and the amines to form the first layer. By the same reaction mechanism, a second PAH layer is formed and the surface amino groups are regained. Repeating n cycles will then produce n bilayers of continuous multilayers on the SiO_2 microparticles, leaving behind the hollow capsules composed of $(PGMA/PAH)_n$ upon core-removal by HF etching (Scheme 1). TEM observed that each SiO_2 microparticle is continuously and homogeneously covered by a thin film, as is representatively shown in Figure 1a and undoubtedly ascertained by the magnified image in the inset of Figure 1a. The thickness of 8-layer PGMA/PAH film varies from ~12 nm to ~15 nm. Neither apparent adsorption of larger polymer grains on the particle surfaces nor particle coacervation is observed, as is evidenced by the derived capsules (Fig. 1b). More importantly, Figure 1b and Figure 1c demonstrate that the capsules possess hollow nature and continuous and intact shell structures after template removal. The polygonal shape, creases and folds are characteristics of microcapsules with ultrathin wall thickness, resulting from evaporation of the solvent. AFM images (Fig. 1d and e) reveal flat and smooth morphology, demonstrating again the completeness of the microcapsules.

Using the same technique, multilayer microcapsules with varied layer numbers and SiO_2 diameters were fabricated (Fig. S1–3 in Supporting Information). Moreover, copolymers of GMA and MMA could also be assembled with PAH, yielding intact hollow capsules after core removal (Fig. S4).

The chemical compositions of the microcapsules were characterized by FTIR spectroscopy (Fig. 2). The absorbance of esters at 1725 cm^{-1} confirms the presence of PGMA in the capsules, while the absence of epoxide groups (1482 cm^{-1} and 1337 cm^{-1}) reveals the complete reaction of PGMA. This re-

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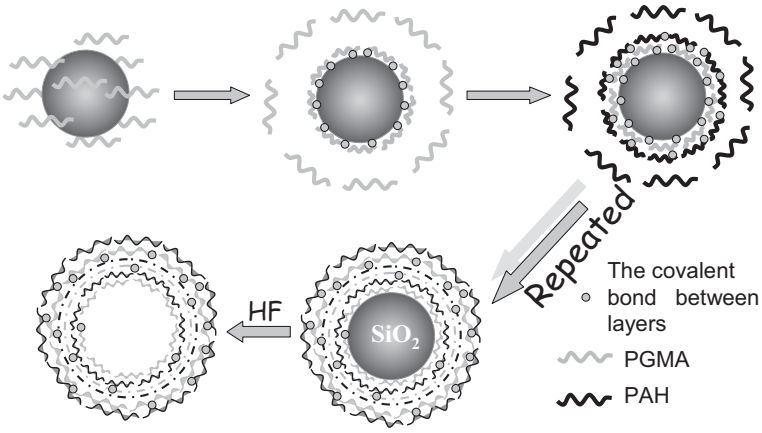

Scheme 1. Schematic illustration to show the process of direct covalent LBL assembly on a silica particle, and fabrication of hollow capsule by etching out the template core.

action incorporates the PAH component into the microcapsules, which is confirmed by the absorbance at 1650 cm^{-1} (N–H deformation vibration in amine) and 746 cm^{-1} (N–H wagging vibration in secondary amine). Thus the assembly is surely driven by the amino-epoxide reaction, which results in the covalent combination between layers.

In order to verify the LBL growth mechanism, silicon wafers were used as substrates to build up the films under the same conditions. Ellipsometry recorded a total thickness of 4.2 nm for 8 layers of PGMA/PAH (Fig. 1f), which is smaller than that of the TEM observation (Fig. 1a, inset). The surfaces of silicone wafers are extremely smooth, leading to less adsorption of the building blocks than the SiO_2 particles. The effective rinsing by sonication to thoroughly remove the physically adsorbed blocks may be another reason. Detailed analysis reveals that the first layer (~1 nm) has a double thickness of the subsequent ones (0.44 ~ 0.55 nm), which is attributed to the more abundant reactive amino groups on the silicone wafers brought by the aminosilanizing reaction. According to Figure 1f, an overall linear increase of film thickness as a function of layer number can be concluded. The linear growth behavior is also confirmed by UV-vis spectroscopy by depositing the films on quartz slides with rhodamine-labeled PAH (Fig. S5). All these results demonstrate that the film was surely assembled in a LBL manner.

Since the assembly was conducted alternatingly in water and tetrahydrofuran (THF), the successful production has already demonstrated the intrinsic stability of these covalently-bonded multilayers and microcapsules against polar solvents. To further elucidate the stability of this crosslinked structure, the microcapsules were exposed to extreme pHs, e.g., alkaline solution (pH 12.8) and acid solution (pH 1.2) for 24 h. All the microcapsules kept their round shape with no

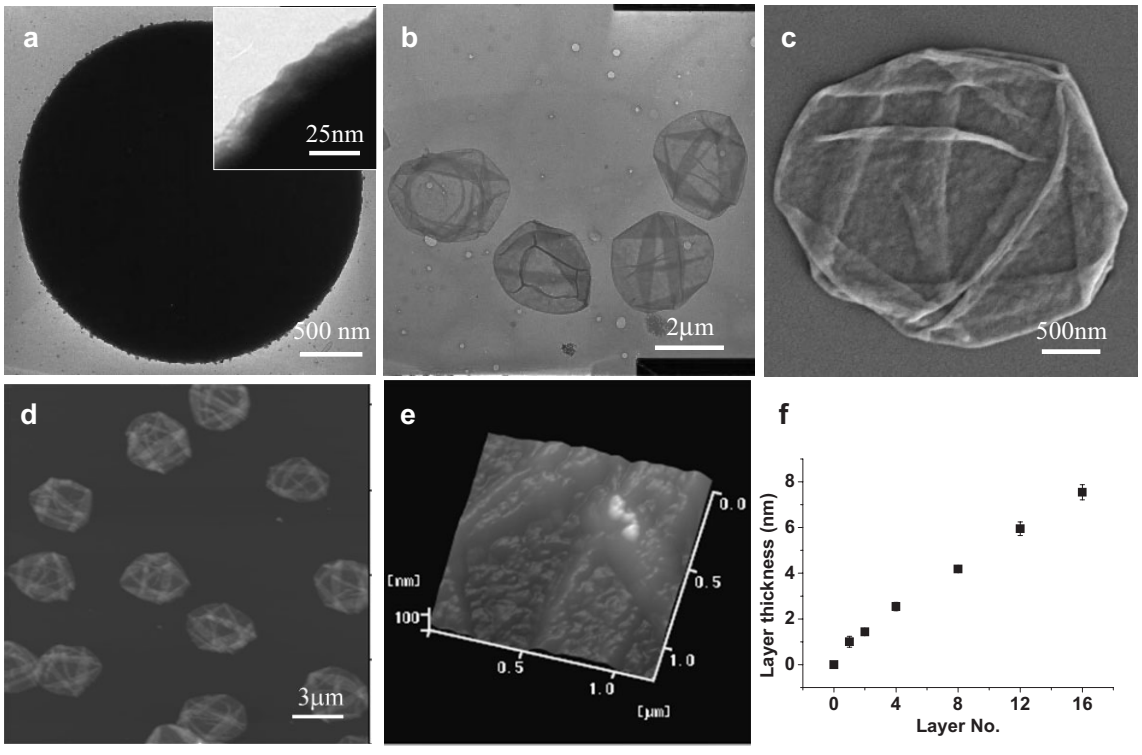

Figure 1. TEM images of 8 layer PGMA/PAH microcapsules before (a) and after (b) core decomposition. The inset in (a) is higher magnification showing the particle edge. c) SEM image of the microcapsules. AFM images of d) the microcapsules and e) higher magnification of a flat region on a microcapsule. f) Multilayer thickness on silicone wafer as a function of layer number recorded by ellipsometry.

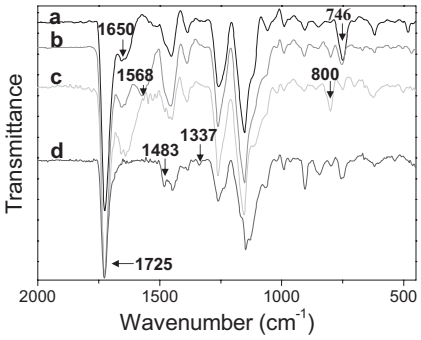

Figure 2. FTIR spectra of a) 8-layer PGMA/PAH microcapsules, and after (b) alkaline and c) acid treatments. Silica particles with an average diameter of 1μm were used as the template. d) FTIR spectrum of PGMA.

measurable change of their size (Fig. 3a and d). In dry state, microcapsules after treatments did not show any detectable changes on their morphology (Fig. 3b and e) and fine structures (Fig. 3c and f) in comparison to the control (Fig. 1d and e), demonstrating that these capsules can not only survive harsh conditions, but also maintain their geometric structure in such cases. By contrast, the microcapsules based on electrostatic force or hydrogen bonding with much thicker walls are readily dissolved in the alkaline solution of the same pH.[15] The absorptions in the FTIR spectra were mostly preserved after acid or alkaline treatment (Fig. 2b and c), revealing again the rather stable chemical structure. Since the amines were protonated after acid treatment, the absorption peak at 746 cm^{-1} shifted to 800 cm^{-1} (NH_2^+ rocking vibration). While after base treatment a new absorption peak appeared at 1568 cm^{-1}, which is assigned to the amide II of secondary amide, demonstrating the occurrence of aminolyzation of the ester groups by the primary amines (yields also covalent bonds). Nonetheless, one can still conclude that higher stability of the microcapsules has been achieved by this covalent assembly in spite of their slight changes in chemical structures.

Thermal stability is of much concern. For example, an elevated temperature can cause either shrinking or swelling of the polyelectrolyte multilayer microcapsules depending on their compositions.[5c,16] This phenomenon is understood as a result of breakage and re-formation of the ion pairs at an elevated temperature. In our case, however, the direct covalent assembly creates stable covalent chemical bonds between layers, which are not destroyable below 200 °C. Therefore, high stability of the layer structure against elevated temperature can be expected. It is experimentally shown that no change of the capsule diameter was observed after the capsules were incubated at 85 °C for 20 h (~(2.90±0.07) μm before and (2.88±0.09) μm after, averaged from >20 microcapsules). Inspection of the surface morphology by AFM did not reveal any change either (Fig. S6).

Using a method of osmotic induced invagination,[17] the mechanical property of the as-prepared and acid or base treated microcapsules was quantified. For clear visualization in polyelectrolyte solution, a layer of FITC-albumin was

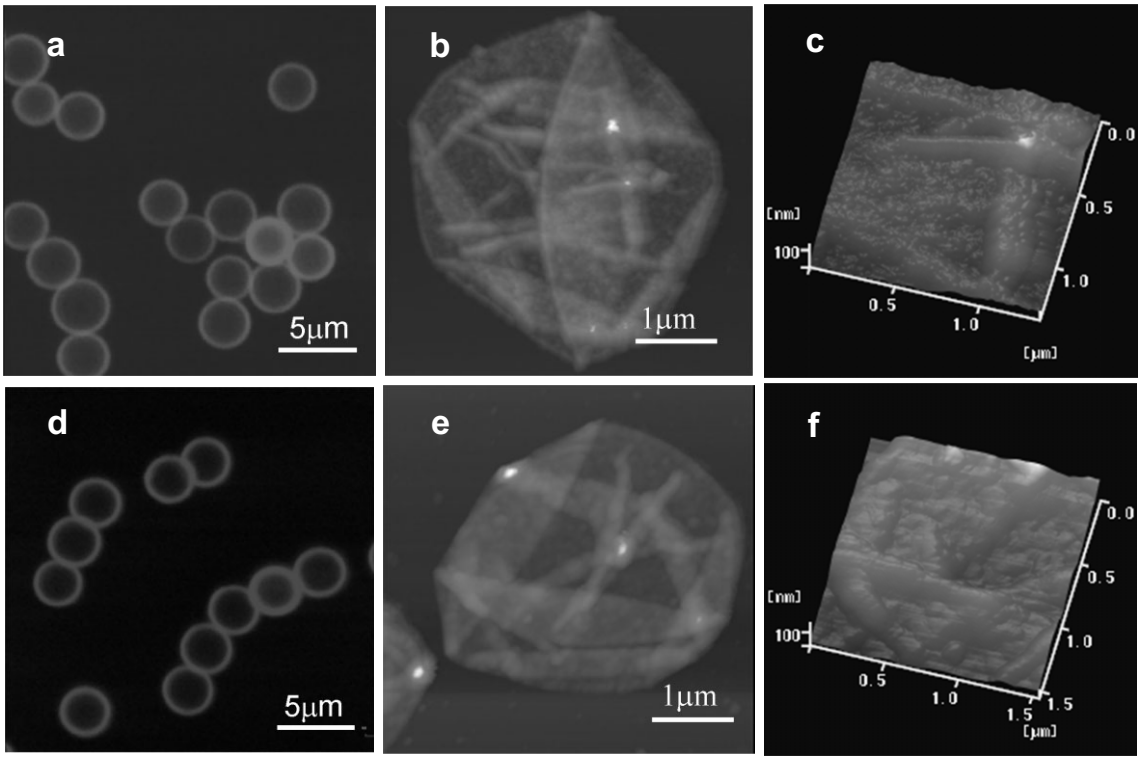

Figure 3. CLSM (a,d) and AFM (b,e) images of 8 layer PGMA/PAH microcapsules after treatment in (a,b) acid (pH 1.2) and (d,e) alkaline (pH 12.8) solutions for 24 h. (c) and (f) are higher magnification of (b) and (e), respectively.

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adsorbed onto the microcapsules. At a critical osmotic pressure (P_c), a sudden invagination of the capsule shells would occur. According to the relation of $\mu = P_c(R/\delta)^2/4$, where μ denotes the elasticity modulus of the shell material, while R and δ denote the radius and shell thickness respectively, the mechanical strength of the shell can be thus obtained. To determine the P_c, the percentages of deformed capsules are plotted as a function of PSS concentration (Fig. 4). In the typical sigmoidal curves, the P_c is defined as the concentration at which the invagination of 50 % of the intact capsules occurs. By referring to a calibration curve,[17a] the critical PSS concentrations of 4.08 % (control), 4.71 % (acid treated) and 4.60 % (base treated) correspond to P_c values of 3.02×10^5 N m^{-2}, 3.57×10^5 N m^{-2} and 3.47×10^5 N m^{-2}. Using the realistic parameters of the microcapsules ($\delta = (13.2 \pm 0.4)$ nm, obtained from AFM images with a sample number of 10; $R = 1.45$ μm), the elasticity modulii are 910 MPa, 1070 MPa, and 1040 MPa for the control, acid-treated and base-treated microcapsules, respectively. These values are much higher than that of the traditional electrostatic PSS/PAH multilayers (290 MPa), and even the GA crosslinked PSS/PAH multilayers (680 MPa),[6b,17a] demonstrating that the covalent PGMA/PAH multilayers have higher stiffness. Unlike the ionic pairs in water which can transiently dissociate,[18] the covalent bonds can not dissociate regardless of the solvent quality, which endows the microcapsules with better stability and larger mechanical strength. Figure 4 and the obtained modulii confirm that even the extreme pH treatments can not weaken the mechanical strength of the microcapsules.

In summary, we have demonstrated that the direct covalent assembly of PGMA and PAH can be successfully applied onto curved colloidal surfaces. After removal of the sacrificial cores, stable hollow microcapsules with ultrathin shells (in the order of ~10 nm) and good shell completeness are obtained. The microcapsules have better stabilities against extreme pHs and elevated temperature. The elasticity modulus of the PGMA/PAH multilayers is as high as 910 MPa, which is much larger than that of the electrostatic or GA-crosslinked PSS/PAH multilayers. This technique opens a new avenue for obtaining microcapsules with ultrathin shells but high stability, and enriches the family of driving forces for LBL assembly.

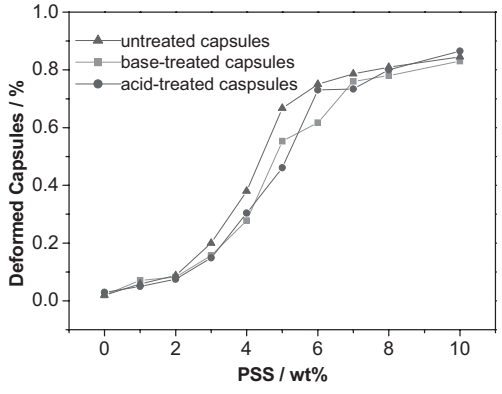

Figure 4. The percentage of deformed capsules as a function of PSS concentration. The microcapsules were pre-adsorbed with FITC-labeled albumin for visualization under CLSM in polyelectrolyte solution. The number of calculated capsules for each point is ~200.

Experimental

Covalent LBL Assembly on Silica Particles and Hollow Capsule Fabrication: The APS-modified silica particles were incubated in 4 mg mL^{-1} PGMA or poly(GMA-*co*-MMA)/THF solution at 65 °C for 4 h in a N_2 atmosphere. Then the solution was centrifuged and the precipitated particles were washed with THF 3 times. The silica particles were transferred to 4 mg mL^{-1} PAH solution with pH ~ 9.1 at 65 °C for 4 h in a N_2 atmosphere. After centrifugation, the particles were washed with distilled water 3 times. The assembly was repeated until the desired layer numbers were reached. The resulting core–shell particles were treated with 0.4 mol L^{-1} HF solution to etch out the silica template, obtaining the covalent LBL microcapsules.

Covalent LBL Assembly on Silicon Wafers and Quartz Slides: The APS-modified silicone wafers were immersed in 4 mg mL^{-1} PGMA/THF solution in glass tubes. After degassed under reduced pressure, the tubes were sealed. The solution was shaken at 55 °C for 4 h. After washed under sonication in THF, the silicone wafers were transferred into 4 mg mL^{-1} PAH solution. After degassed, the tubes were sealed and shaken at 55 °C for 4 h. Then the silicone wafers were washed under sonication in water. The assembly was repeated until the desired layer numbers were reached. Covalent assembly on quartz slides was conducted in the same way, except that the normal PAH was substituted by rhodamine-labeled PAH.

Characterizations: Ellipsometry was performed using an optical null ellipsometer (Multiskop Ellipsometer, Optrel GmbH) with a He-Ne laser (632.8 nm) at an angle of 70°. Silicon wafers were used as the substrates. The film thickness was calculated using a computer program, assuming a refractive index value of 1.5 for the PGMA/PAH multilayers. Each point was averaged from 10 individual measurements. Transmission electron microscopy (TEM) was performed on TECNAL-10, Philips and JEOL JEM-200CX, Japan. Copper grids coated with cellulose acetate films were used to support the samples. The topography of the microcapsules was observed using a Seiko Instruments SPI3800 N atomic force microscope (AFM) with a tapping mode under ambient conditions. The fluorescent image was captured using a Bio-Rad Radiance 2100 confocal laser scanning microscope (CLSM). Scanning electron microscopy (SEM) was performed on SIRION-100 (RAITH). Fourier transform infrared spectroscopy (FTIR) was recorded on a VETOR 22 spectrophotometer. UV-vis spectra of the PGMA/rhodamine-labeled PAH multilayers assembled on quartz slides were monitored by a UV-vis spectrophotometer (UV-2550, Shimadazu, Japan).

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