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Alternating Silica/Polymer Multilayer Hybrid Microspheres Templates for Double-shelled Polymer and Inorganic Hollow Microstructures

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Alternating silica/polymer tetra- and penta-layer hybrid microspheres were first prepared via combined inorganic sol−gel reaction and distillation-precipitation polymerization. pH-responsive poly(methacrylic acid) (PMAA) hollow microspheres with asymmetric double-shells were produced after HF etching of the silica layers in the SiO_2/PMAA tetra-layer microspheres with different degrees of cross-linking in the two PMAA layers. On the other hand, silica "core−double shell" hollow microspheres were obtained by calcination of the alternating silica/PMAA penta-layer microspheres. The resulting hollow polymer and silica microspheres with hierarchical structures were characterized by field-emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), energy-dispersive X-ray (EDX) analysis, dynamic laser scattering (DLS), and confocal laser scanning microscopy (CLSM) measurements.

1. Introduction

Core−shell micro- or nanoparticles and their corresponding hollow structures with unique morphology are of great interest, because of their potential applications in drug and gene delivery, hydrogen storage, catalysis, and encapsulation of cosmetics and paints.[1−8] Combined inorganic and polymer synthesis holds great promise to novel core−shell hybrid micro- and nanostructures.[9−11] Silica is a major constituent of modern industrial materials and has diverse applications. It is an essential element of living species, human beings included. Furthermore, silica has been approved as safe by the U.S. Food and Drug Adminstration (FDA). Silica-based micro- or nanomaterials with hierarchical structures have been widely investigated to broaden their applications in adsorption and separation, catalysis, sensors and nanomedicine.[12−18] For instance, stable Pt/mesoporous silica (Pt@mSiO_2) core−shell nanoparticles have been synthesized for high-temperature catalytic reactions.[19] Yolk/SiO_2 shell structures with encapsulated Au and Fe_2O_3 nanoparticles have been developed.[20] Accordingly, fabrication of functional silica systems with tailored structure, shape, size, size distribution, and morphology remains a challenge and of great interest.

On the other hand, stimuli-responsive polymer micro- and nanoparticles have been of great interest because of their unique physical and chemical properties which are suitable for applications in drug and gene delivery, chromatography, diagnostics, and biosensors.[21−24] The polymers in stimuli-responsive particles can change their chain conformation in direct response to stimuli, such

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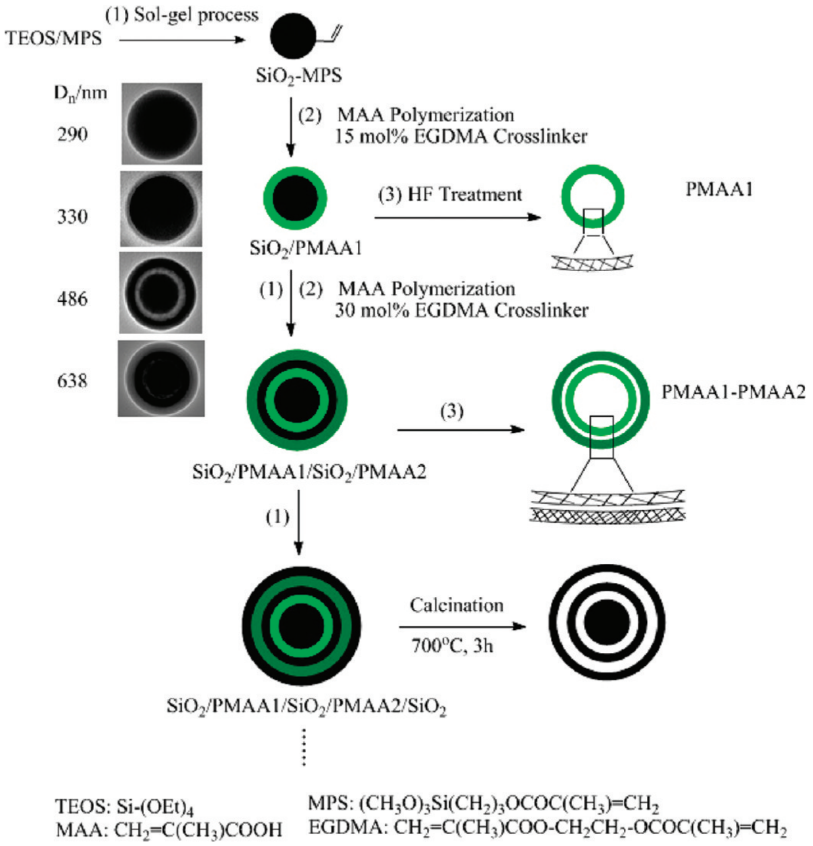
Scheme 1. Schematic Illustration of the Synthesis of PMAA1-PMAA2 Hollow Microspheres with pH-Responsive Asymmetric Double Shells and Silica "Core−Double Shell" Hollow Microspheres



as pH, ionic strength, temperature, and magnetic field.[25−27] An ideal controlled-release device should be able to sustain the drug concentration in the desired therapeutic range in response to physiological stimuli. To date, synthetic stimuli-responsive materials for drug delivery systems (DDS) mainly include hydrogels,[28] micelles,[29] and hollow spheres.[30−33] For improvement in the treatment of numerous diseases, the design and synthesis of more sophisticated microstructures and materials with novel molecular architecture for DDS is an ongoing effort.

In this report, we describe the preparation of poly(methacrylic acid) (PMAA) double-shelled hollow microspheres of well-defined (nearly monodispersed) structure and morphology via combined inorganic sol−gel process and polymerization reaction (Scheme 1). The PMAA double shells with different degrees of cross-linking allow hierarchical pH-response when the microspheres are used, for example, in DDS for the controlled or sustained release and represent an overall improvement over the conventional single-shelled microspheres. Alternatively, calcination of the alternating silica/PMAA penta-layer hybrid microspheres from the combined sol−gel and polymer synthesis in Scheme 1 affords the inorganic "core−double shell" hollow microspheres.

2. Experimental Section

2.1. Synthesis of Alternating Silica/Poly(methacrylic acid) (SiO_2/PMAA) Multilayer Hybrid Microspheres. The SiO_2/PMAA1/SiO_2/PMAA1 tetra-layer hybrid microspheres were prepared by a combined approach of sol−gel process (Stöber method)[34,35] and distillation−precipitation polymerization.[36] About 9 mL of tetraethyl orthosilicate (TEOS, 98%, Aldrich Chemical Co.) was added to a mixture of 150 mL of ethanol, 15 mL of double distilled water, and 3 mL of ammonia (25 wt %). The mixture was stirred vigorously at room temperature for 24 h. About 2 mL of 3-(trimethoxysilyl)propylmethacrylate (MPS, 98%) was then introduced dropwise into the silica sol over a reaction period of 24 h, to introduce the carbon−carbon double bonds onto the surface of silica template cores. The MPS modified silica particles (SiO_2-MPS) were purified by five cycles of centrifugation (at 8000 rpm in an Eppendorf 5801 Centrifuge) and redispersion in a 1:1 (v:v) mixture of ethanol and water.

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After each cycle, the microspheres were dried in a vacuum oven at 50 °C until a constant weight was obtained (after a total of 5 washing/purification cycles).

To prepare the SiO_2/PMAA1 core–shell microspheres, we dispersed about 0.2 g of the SiO_2-MPS seeds into 80 mL of acetonitrile under ultrasonication in a 100 mL flask equipped with a fractionation column, a condenser, and a receiver. A mixture of methacrylic acid (MAA, 0.82 mL or 0.01 mol, Aldrich Chemical Co., purified by vacuum distillation), ethylene glycol dimethylacrylate (EGDMA, cross-linking agent, 0.28 mL, or 15 mol % relative to MAA), and 2,2′-azobisisobutyronitrile (AIBN, 0.02 g) was then introduced into the flask to initiate the polymerization. The reaction was allowed to proceed under reflux condition. The reaction was stopped in about 2 h after distilling off 40 mL of acetonitrile. The resultant SiO_2/PMAA1 core–shell microspheres were purified by extraction with acetonitrile and ethanol five times to remove the unreacted monomers and oligomers. The degree of cross-linking in the PMAA shell was tuned by adjusting the concentration of cross-linking agent (EGDMA) in the reactant feed. The SiO_2/PMAA2 core–shell microspheres were prepared via the distillation-precipitation polymerization process described above with an EGDMA feed concentration of 30 mol %.

The SiO_2/PMAA1/SiO_2 trilayer hybrid microspheres were synthesized by coating of an outer silica-MPS layer on the resultant SiO_2–PMAA1 core–shell particles via the sol–gel process described above. About 0.15 g of the SiO_2–PMAA core–shell microspheres and 2.4 mL of ammonia were introduced into a water/ethanol (20 mL/160 mL) mixture under vigorous stirring. Then 0.8 mL of TEOS was added dropwise into the flask at room temperature and the reaction mixture was stirred for 24 h. About 0.2 mL of MPS was then introduced dropwise into the silica sol and the reaction mixture was stirred for another 24 h to introduce the carbon–carbon double bonds onto the surface of silica outer shell. The resultant SiO_2–PMAA–SiO_2 trilayer hybrid microspheres were purified and dried using procedures similar to those described for the SiO_2-MPS seeds. For the preparation of mesoporous silica shell, cetyltrimethyl ammonium bromide (CTAB, 0.24 g) surfactant was added to the above reaction system to produce the CTAB/silica composite outer layer in the sol–gel process, followed by repeated calcination at 550 °C for 6 h or 700 °C for 3 h.

The SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer hybrid microspheres were synthesized by distillation-precipitation polymerization from the trilayer hybrid microspheres in acetonitrile with an increased concentration (30 mol %) of the EGDMA cross-linking agent. The procedures were similar to those used for the synthesis of PMAA1 layer in the presence 15 mol % cross-linking agent, as described above. For the PMAA2 layer, the distillation–precipitation polymerization process was performed twice to achieve a high monomer conversion and desired thickness.

The SiO_2/PMAA1/SiO_2/PMAA2/SiO_2 penta-layer hybrid microspheres were synthesized via the sol–gel process described above, using TEOS feed concentration of 0.025 or 0.04 M to further coat another silica layer on the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres.

2.2. Synthesis of Concentric PMAA Double-Shelled Hollow Microspheres and Silica "Core–Double Shell" Hollow Microspheres. PMAA hollow microspheres and concentric PMAA hollow microspheres with asymmetric double shells for differential pH response were prepared by removal of the silica core and layer from the respective SiO_2/PMAA1, SiO_2/PMAA2 and SiO_2/PMAA1/SiO_2/PMAA2 hybrid microspheres in 10% HF for 48 h. The hollow polymer microspheres were cleaned with a 1:1 (v:v) mixture of ethanol and water. The etching process was repeated two times to remove the silica layers completely. The concentric silica "core–double shell" hollow microspheres were obtained by selective removal of the PMAA1 and PMAA2 layers of the SiO_2/PMAA1/SiO_2/PMAA2/SiO_2 penta-layer hybrid microspheres during repeated calcination at 700 °C for 3 h.

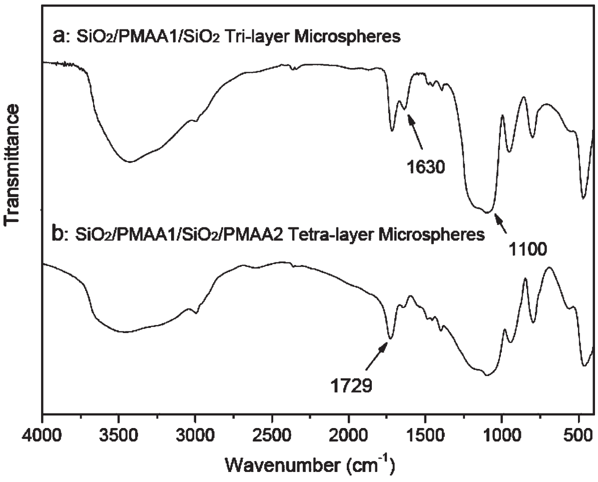

Figure 1. FT-IR spectra of the (a) SiO_2/PMAA/SiO_2 trilayer microspheres, (b) SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres.

2.3. Controlled Delivery from PMAA Hollow Microspheres. Doxorubicin hydrochloride (DOX)-loaded hollow microspheres were prepared by dispersing about 2 mg of the hollow microspheres in 10 mL of 0.1 mg/mL aqueous solution of DOX. The loading of DOX into the hollow microspheres was allowed to proceed, under gentle agitation at pH 7 and room temperature, for 48 h. The DOX-loaded hollow microcapsules were collected by centrifugation at 8000 rpm and washed twice with water of pH below 4 to completely remove the free and adsorbed DOX on the PMAA shell, prior to being freeze-dried. For the release of DOX, 3 mL of phosphate-buffered solution (PBS) containing 2 mg of the DOX-loaded microcapsules was introduced into the dialysis membrane bag with a molecular-weight cutoff of 12 000–14 000 (Spectra/Por, Spectrum Laboratories, Inc.). The dialysis bag was then immersed in 50 mL of PBS at pH 7.4 and 37 °C. A portion of the solution was removed periodically from the dialysis cassette and characterized by UV–visible absorption measurement at the wavelength of 486 nm to determine the concentration of DOX released. The solution was then returned to the dialysis cassette. The percentage of DOX released was calculated from the ratio of the absorbance of DOX released into solution and the initial absorbance of the colloidal dispersion of microspheres loaded with DOX.

2.4. Materials Characterization. Field-emission scanning electron microscopy (FESEM) images were obtained on a JEOL JSM-6700 SEM. Transmission electron microscopy (TEM) images were obtained on a JEOL JEM-2010 TEM and a JEOL JEM-2100F field emission TEM (FETEM). Confocal laser scanning microscopy (CLSM) image was obtained from a Nikon Digital Eclipse C1 Plus confocal system. The dynamic laser scattering (DLS) measurements were performed on a Brookhaven 90 plus laser light scattering spectrometer at a scattering angle of $\theta = 90°$. The UV–visible absorption spectra in the wavelength range of 200–800 nm were obtained on a Shimadzu UV-3101PC spectrophotometer. The porosity of the mesoporous shell structure was characterized by nitrogen

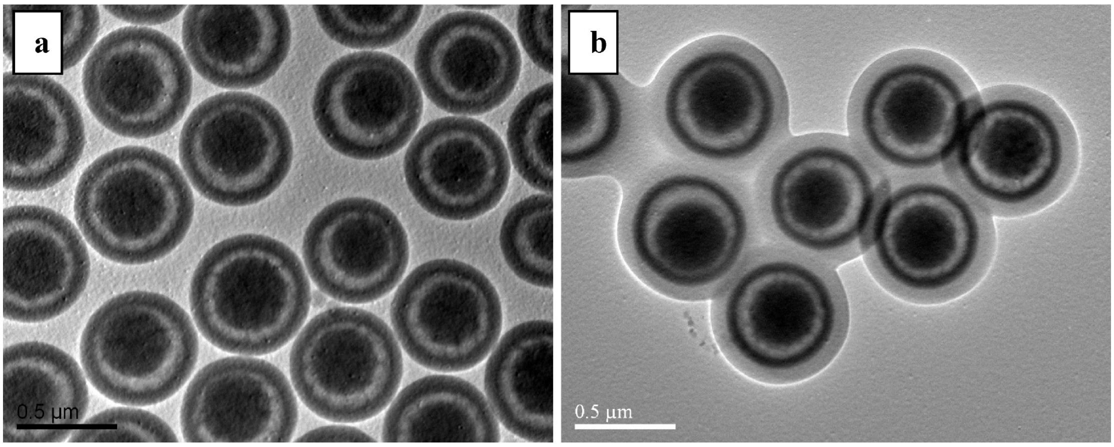

Figure 2. TEM micrographs of the (a) SiO_2/PMAA/SiO_2 trilayer microspheres, (b) SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres.

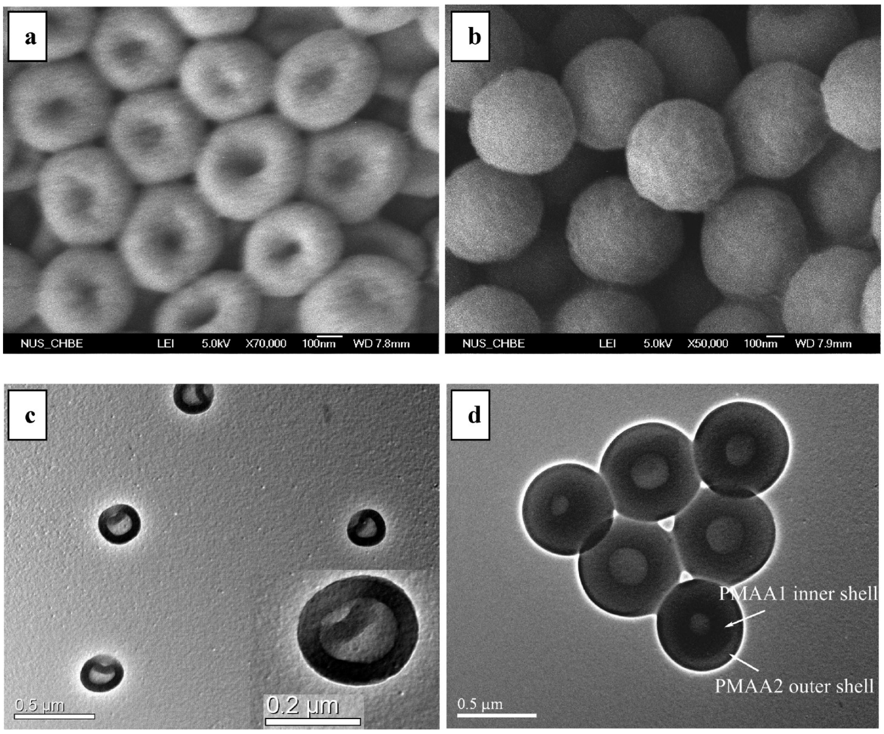

Figure 3. FESEM and TEM micrographs of the (a, c) single-shelled PMAA1 hollow microspheres, (b, d) double-shelled PMAA1-PMAA2 hollow microspheres. The inset in b is the TEM image of the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres.

adsorption−desorption isotherms on a Quantachrome NOVA 4200e porosimeter. The specific surface area (SSA) was determined from the Brunauer−Emmett−Teller (BET) equation in the relative pressure range of 0.05 to 0.35, while the pore size and size distribution were derived from the adsorption branch of the isotherm, using the Barrett−Joyner−Halenda (BJH) model.

3. Results and Discussion

3.1. Alternating SiO_2/PMAA Multilayer Hybrid Microspheres via Combined Sol−Gel Reaction and Distillation−Precipitation Polymerization. Procedures for the synthesis of SiO_2-MPS core, SiO_2/PMAA1 core−shell, SiO_2/PMAA1/SiO_2 trilayer, and SiO_2/PMAA1/SiO_2/PMAA2 alternating tetra-layer microspheres are shown in Scheme 1 (PMAA = poly(methacrylic acid), MPS = 3-(trimethoxysilyl)propylmethacrylate). The silica core and shells were prepared via the sol−gel reaction (Stöber method). The carbon−carbon double bonds of MPS on the surface of silica core and shell serve as the growth sites during the subsequent distillation-precipitation polymerization.[36] The FT-IR spectrum of the SiO_2/PMAA1/SiO_2 trilayer microspheres is shown in Figure 1a. The strong absorption peak at 1630 cm^{-1} is associated with the vinyl group of MPS on the silica. The PMAA layers were produced by distillation-precipitation polymerization. The polymerization technique has been used to synthesize core−shell and hollow micro- or nanospheres of small polydispersity index (PDI).[37−39]

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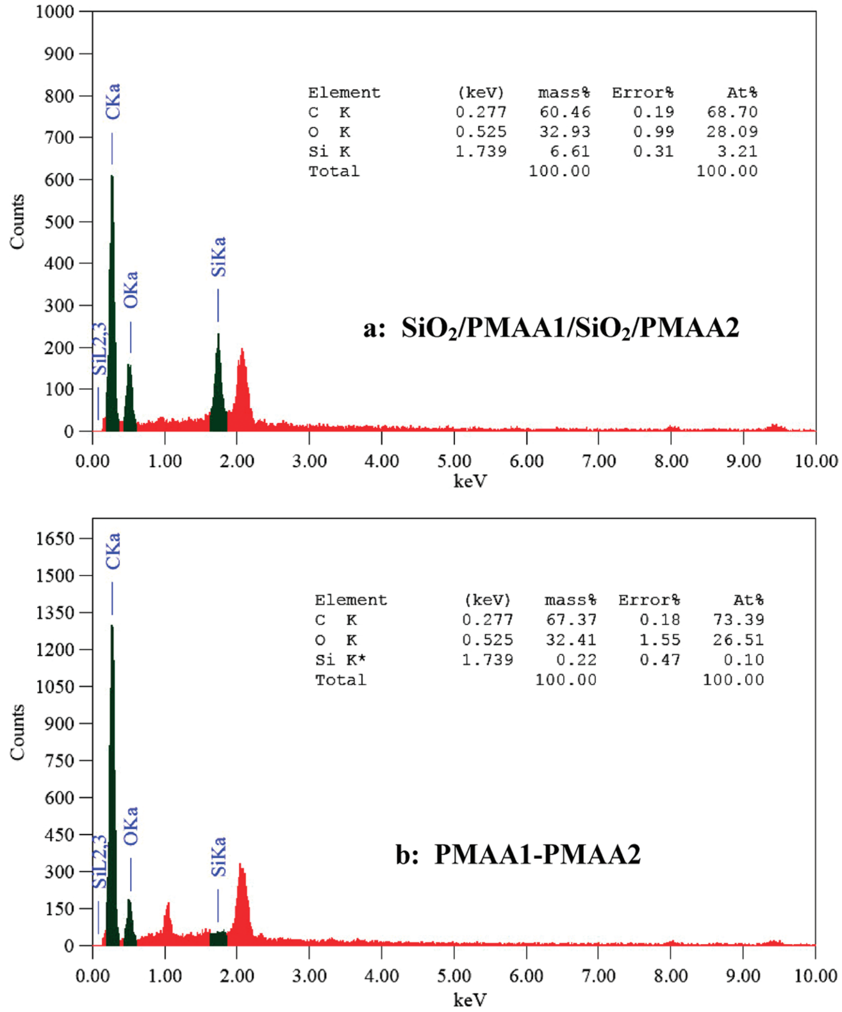

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Element        (keV)   mass%  Error%     At%
C  K           0.277   60.46    0.19   68.70
O  K           0.525   32.93    0.99   28.09
Si K           1.739    6.61    0.31    3.21
Total                 100.00          100.00
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Element        (keV)   mass%  Error%     At%
C  K           0.277   67.37    0.18   73.39
O  K           0.525   32.41    1.55   26.51
Si K*          1.739    0.22    0.47    0.10
Total                 100.00          100.00
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Figure 4. EDX spectra of (a) the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer hybrid microspheres, and (b) the corresponding double-shelled PMAA1-PMAA2 hollow microspheres.

Different degrees of cross-linking in the PMAA1 and PMAA2 shells were achieved using different concentrations of the cross-linking agent, ethylene glycol dimethylacrylate (EGDMA), during polymerization. The carboxylic acid groups on the PMAA shells are utilized in the hydrogen-bonding interactions during condensation hydrolysis of TEOS in the sol−gel reaction to form the new silica shell. The absorption peak at 1729 cm^{-1} in the FT-IR spectrum of the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres in Figure 1b is associated with stretching vibration of carbonyl groups of the PMAA segments introduced by distillation-precipitation polymerization. The average diameters of the SiO_2-MPS core, SiO_2/PMAA1 core−shell, SiO_2/PMAA1/SiO_2 trilayer, and SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres are about 290, 330, 486, and 638 nm, respectively, as determined from transmission electron microscopy (TEM) images. TEM images of the well-defined SiO_2/PMAA1/SiO_2 trilayer and SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres are shown images a and b in Figure 2, respectively.

3.2. pH-responsive PMAA Hollow Microspheres with Asymmetric Double Shells. pH-responsive single-shelled PMAA1 hollow microspheres and double-shelled PMAA1-PMAA2 hollow microspheres are obtained, respectively, after removal, by HF etching, of the silica core from the SiO_2/PMAA1 core−shell microspheres, and both the silica core and shell from the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer hybrid microspheres. Because the PMAA1 and PMAA2 shells in the hollow microspheres are synthesized with different degrees of cross-linking (PMAA1 with 15 mol % EGDMA and PMAA2 with 30 mol % EGDMA, both with respect to MAA monomer concentration in the reactant feed), the resulting double shells of the PMAA1-PMAA2 hollow microspheres are structurally asymmetric in terms of degrees of cross-linking.

Field-emission scanning electron microscopy (FESEM) images of the resultant PMAA1 and PMAA1-PMAA2 hollow microspheres are shown in Figures 3a and 3b, respectively. The biconcave shape of the single-shelled PMAA1 hollow microspheres, similar to that of the red blood cells (RBCs) in human beings,[40−42] is readily discernible in Figures 3a. In comparison with the flexible and

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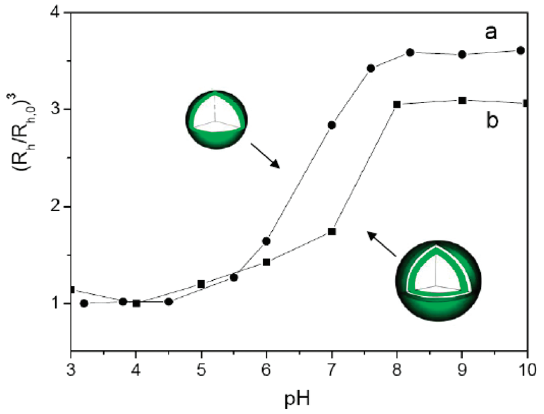

Figure 5. Changes in relative hydrodynamic volume of the (a) single-shelled PMAA1 hollow microspheres and (b) double-shelled PMAA1-PMAA2 hollow microspheres as a function of pH.

deformable PMAA1 hollow microspheres, the PMAA1-PMAA2 hollow microspheres with asymmetric double shells are more robust and more rigid (Figure 3b). The higher degree of cross-linking in the PMAA2 outer shell must have helped to maintain the spherical framework. The hollow structures of PMAA1 and PMAA1-PMAA2 microspheres are discernible from the corresponding TEM images c and d in Figure 3. The shell thickness of the PMAA1 microspheres and combined double-shell thickness (inclusive of the inter-shell spacing) of the PMAA1-PMAA2 hollow microspheres are about 42 and 190 nm, respectively, as deduced from the TEM images c and d in Figure 3 The successful removal of the silica core and layer from the tetra-layer hybrid microspheres is suggested by the disappearance of Si signal in the energy-dispersive X-ray (EDX) spectrum of PMAA1-PMAA2 hollow microspheres (Figure 4).

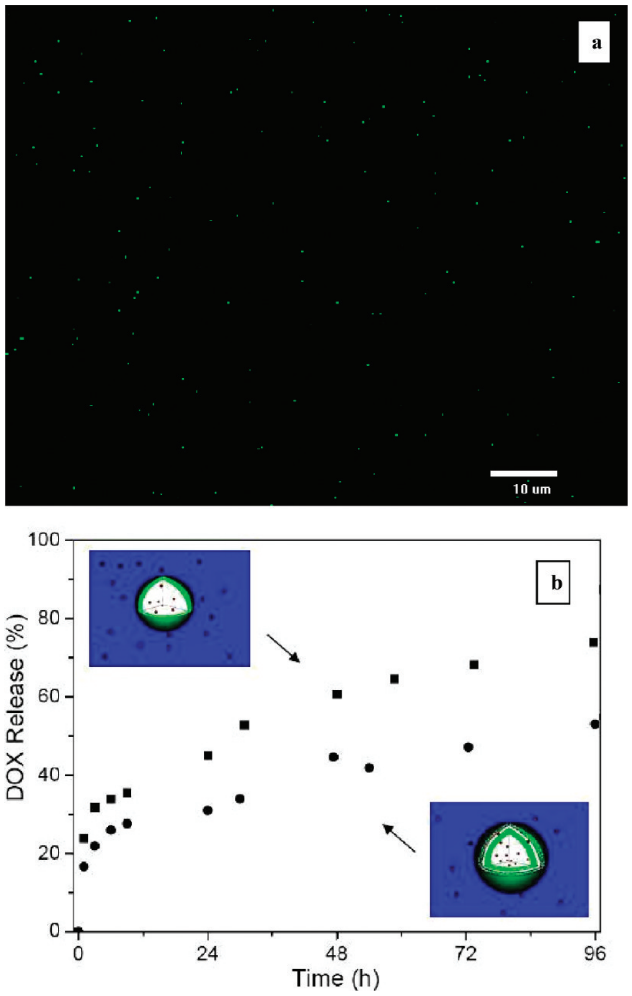

Figure 6. (a) CLSM image of the double-shelled PMAA1-PMAA2 hollow microspheres loaded with doxorubicin hydrochloride (DOX). (b) Release profiles of DOX from single-shelled PMAA1 hollow microspheres and asymmetric double-shelled PMAA1-PMAA2 hollow microspheres.

Table 1. Comparison of the DOX Release Rates from the Single- and Double-Shelled PMAA Hollow Microspheres

type of micro-spheres	degree of cross-linking (as mol % cross-linking agent in the feed)	shell thickness (nm)[a]	percentage of DOX released (%)[b]
PMAA 1	15	42	34
PMAA 2	30	40	31
PMAA1-PMAA2	15−30	190[c]	26

[a] The shell thickness of the hollow microspheres was determined from the TEM images. [b] The percentage of DOX released was calculated from the ratio of the absorbance of the drug in the solution after 6 h of release and the initial absorbance of colloidal suspension of DOX-loaded microspheres. [c] Inclusive of the gap/space between the shells.

Biological systems, such as cell membranes and chameleons, adapt to their surroundings by undergoing reversible structural and functional changes in response to external stimuli. Phospholipids bilayer membranes are structurally and functionally asymmetric.[43] They can prevent useful molecules inside the cell from leaking out and unwanted molecules from diffusing in. Efforts have been made to mimic the biological systems using self-assembly techniques.[44−46] To further investigate the asymmetric shell architecture in the present hollow microspheres, the pH-dependent hydrodynamic diameters of the double-shelled PMAA1-PMAA2 hollow microspheres were characterized by dynamic laser light scattering (DLLS). Figure 5 shows the changes in dimension of the PMAA1 and PMAA1-PMAA2 hollow microspheres induced by pH of the dispersing media. For both types of microspheres, the volume of the microspheres changes considerably as a function of pH. With increasing pH of the medium, the acrylic acid groups are ionized and the capsules assume a swollen or “open” structure. The pH-dependent volume changes are reversible. For the single-shelled PMAA1 microcapsules or the inner shell of the double-shelled PMAA1-PMAA2 microspheres, the hydrodynamic volume ($(R_h/R_{h,0})^3$, $R_{h,0}$ = hydrodynamic radius at pH 4) increases by a factor of 3.6 when the pH of the medium is increased from 4 to 8. Compared to that of the PMAA1 inner shell, the volume of the highly cross-linked PMAA2 outer shell in the PMAA1-PMAA2 hollow microspheres increases only by a factor of 2.9

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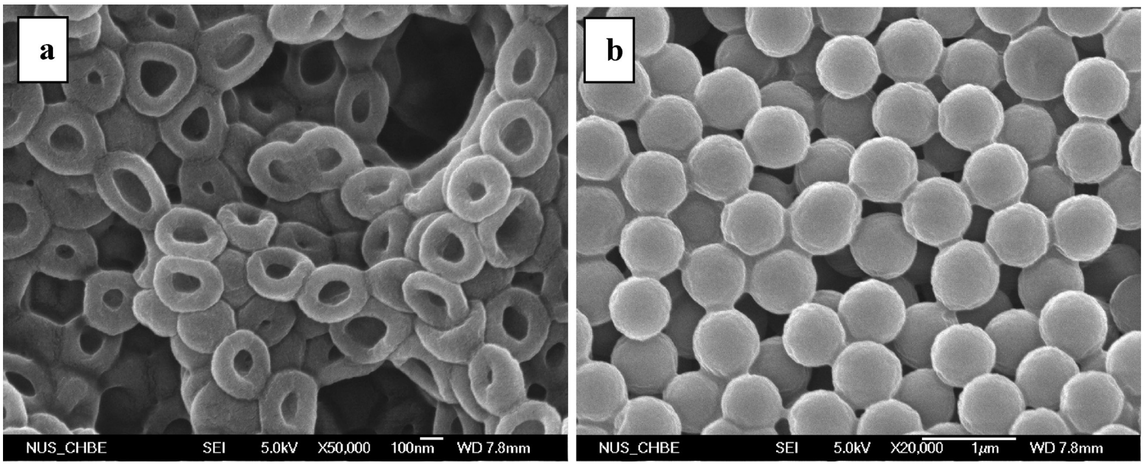

Figure 7. FESEM images of hollow microspheres after loading and releasing of doxorubicin hydrochloride (DOX): (a) single-shelled PMAA1 and (b) double-shelled PMAA1-PMAA2.

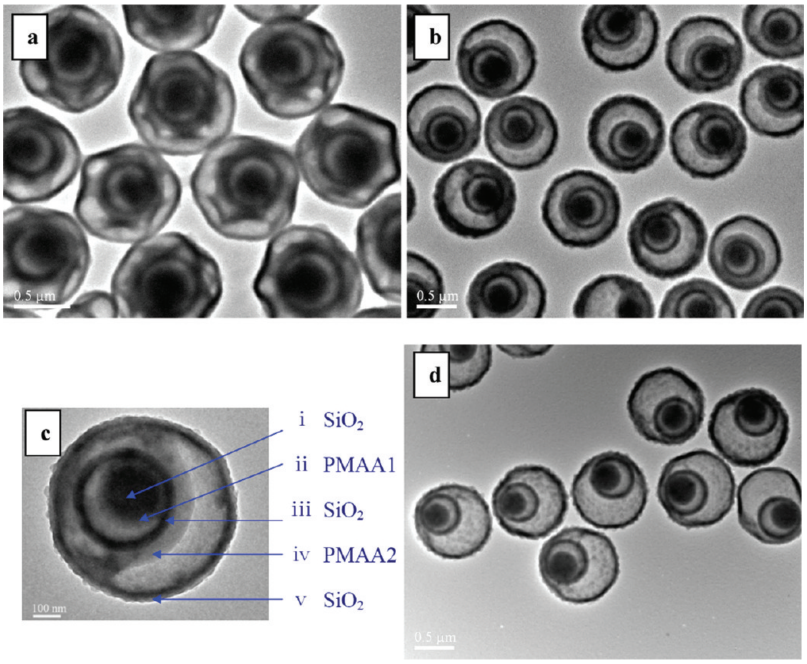

Figure 8. TEM images of the SiO_2/PMAA1/SiO_2/PMAA2/SiO_2 penta-layer hybrid microspheres with different outer SiO_2 shell thickness controlled by TEOS feed concentration of (a) 0.025 and (b) 0.04 M during the synthesis from the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres. (c) The TEM image of an enlarged SiO_2/PMAA1/SiO_2/PMAA2/SiO_2 penta-layer microsphere from b. (d) The silica "core–double shell" hollow microspheres after repeated calcination at 700 °C for 3 h of the penta-layer microspheres in b.

when the pH of medium is increased from 4 to 8. Thus, the more highly cross-linked PMAA2 shell is less responsive to changes in pH of the environment than the PMMA1 inner shell.

The so-obtained PMAA1-PMAA2 hollow microspheres with differential pH-sensitivity of the double shells provide unique structural features to regulate/control the diffusion of guest molecules in and out of the hollow structures. Doxorubicin (DOX) is a well-known antibiotic used in the treatment of a wide range of tumors. However, cardiotoxicity of the drug is a major drawback, limiting its administration.[47] It is thus highly desirable to reduce the accumulation of DOX in the heart muscle. Herein, the anticancer drug of DOX was used and loaded into the single-shelled PMAA1 hollow microspheres and double-shelled PMAA1-PMAA2 hollow microspheres to study the sustained release behavior. The confocal laser scanning microscopy (CLSM) image of the DOX-loaded PMAA1-PMAA2 hollow microcapsules is shown in Figure 6a. The loading capacities of DOX in the PMAA1 and PMAA1-PMAA2 hollow microcapsules are about 16 and 18 μg/mg, as determined from the difference in DOX concentration between the original aqueous solution and the supernatant after the loading process. Figure 6b shows the kinetic of DOX release from single-shelled PMAA1 and double-shelled PMAA1-PMAA2 hollow

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microspheres under physiological conditions (phosphate-buffered solution or PBS, at pH 7.4 and 37 °C). The rate of DOX release from the PMAA1-PMAA2 hollow microcapsules is considerably slower, with half of the drug being released in about 80 h, in comparison to only about 30 h for its single-shelled PMAA1 counterpart.

Polyelectrolyte microcapsules, prepared via the layer-by-layer deposition technique and with permeability properties, have been widely explored for encapsulation and stimuli-responsive controlled release.[48,49] To determine the effect of double layer and degree of shell cross-linking on the DOX release rate, the single-shelled PMAA2 hollow microspheres were also synthesized in the presence of 30% cross-linking agent, using procedures similar to those for the preparation of the outer shell of the double-shelled microspheres. The rate of DOX release from the double-layered (PMAA1-PMAA2) microspheres is compared to those from the corresponding single-layered (PMAA1 and PMAA2) microspheres (Table 1). The percentage of DOX released was calculated from the ratio of the absorbance of the drug in the solution after 6 h of release and the initial absorbance of colloidal suspension of DOX-loaded microspheres. The more highly cross-linked PMAA2 microcapsules showed a sustained release, in comparison with that of the PMAA1 hollow microspheres of a lower degree of cross-linking. The release was further retarded in the PMAA1-PMAA2 double-shelled hollow microspheres with a combined shell thickness (including the intershell spacing) of about 190 nm. Thus, the sustained release rate arises from the combined effects of the double-layered structure[50] and the increased degree of cross-linking[51] and cannot be attributed to the adsorption of DOX on the shell surface. After all, the adsorbed DOX on the PMAA shell would have been removed when the DOX-loaded microspheres were washed/with water of pH below 4. The thickness of each PMAA and silica layer can be tuned, through the simple adjustment of reaction time and monomer/precursor (MAA/TEOS) concentration, to further tailor or control the release properties of the hollow microspheres.

The stability of hollow microspheres is one of the most important criteria governing their practical applications. The FESEM images of single-shelled PMAA1 and double-shelled PMAA1-PMAA2 hollow microspheres, after loading and releasing of DOX, are shown in images a and b in Figure 7, respectively. Although the hollow particles have been subjected to solvent and acid extraction, centrifugation, and drug encapsulation and release, their structure and morphology remain intact. Thus, the polymer hollow microspheres with cross-linked single or double shells exhibit good stability for practical release and delivery applications.

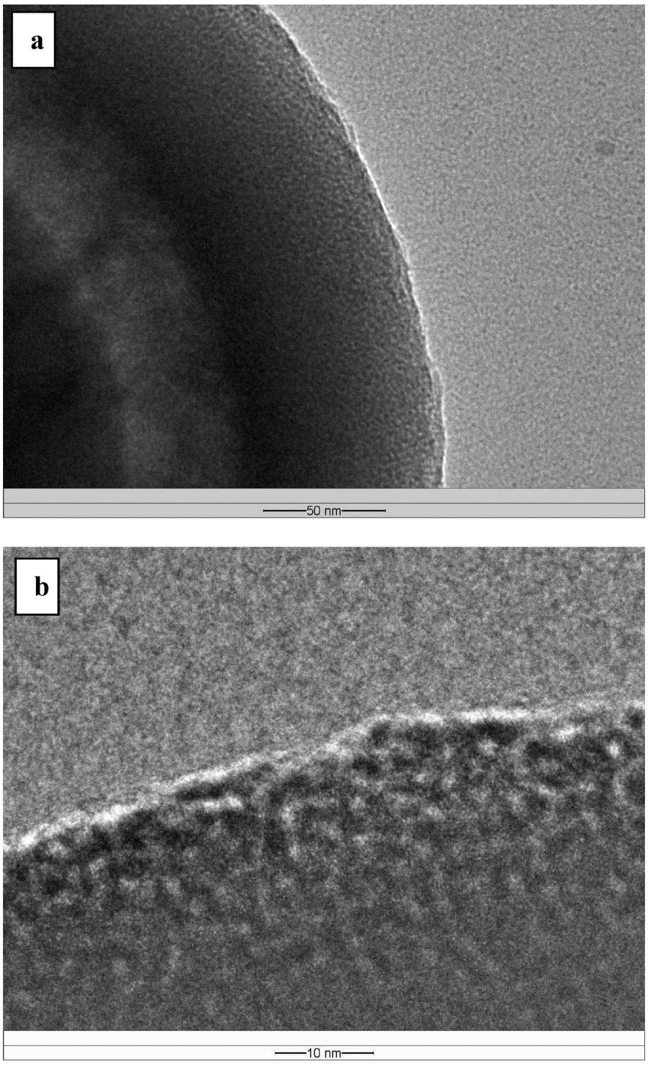

Figure 9. Field-emission TEM micrographs of the mesoporous structure of silica outer shell in the concentric silica “core−double shell” microspheres prepared via repeated calcination at 550 °C for 6 h.

3.3. Hollow Silica Microspheres with “Core−Double Shell” Structures. The combined approach of inorganic sol−gel process and polymer synthesis provides the opportunity for developing more sophisticated microstructure to mimic the complex biological systems. The TEM images of SiO_2/PMAA1/SiO_2/PMAA2/SiO_2 penta-layer hybrid microspheres of different outer silica shell thickness, obtained by using different TEOS feed concentrations (0.025 and 0.04 M) in the sol−gel process to further coat another silica layer on the SiO_2/PMAA1/SiO_2/PMAA2 tetra-layer microspheres, are shown in images a and b in Figure 8, respectively. The enlarged TEM image in Figure 8c shows the distinctive penta-layer structure of the hybrid microspheres of Figure 8b. The void between the PMAA2 layer and the SiO_2 outer layer is probably caused by the different degrees of shrinkage between the soft polymer layer and the hard inorganic silica outer shell during the process of drying.

As an alternative to concentric hollow polymer microspheres from removal, by HF etching, of the inorganic silica layers of the silica/polymer hybrid microspheres, concentric hollow silica microspheres can also be prepared

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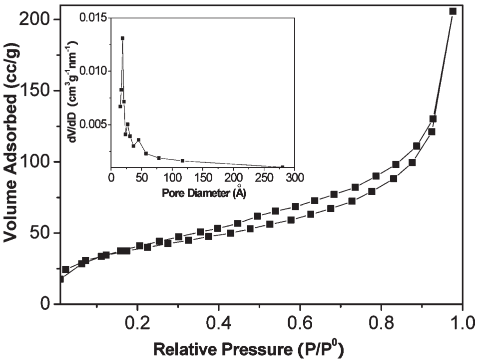

Figure 10. Nitrogen adsorption−desorption isotherms and the corresponding pore size distribution (inset) in the mesoporous silica outer shell of the concentric silica “core−double shell” microspheres.

by removal of the polymer layers via calcination at an elevated temperature. Figure 8d shows the TEM image of silica “core−double shell” hollow microspheres from repeated calcination at 700 °C for 3 h of the penta-layer microspheres of Figure 8b. In comparison with the morphology of the penta-layer microspheres before calcination in Figure 8b, the PMAA1 and PMAA2 layers have disappeared and larger voids have formed between the silica core and the two shells. This unique microstructure can serve as reaction cages, or reactors of micrometer scale, for confined reactions.[52] To facilitate molecules diffusing in and out of the outer silica shell, interconnected mesopores can be introduced into the silica shell via addition of a surfactant, such as cetyltrimethyl ammonium bromide (CTAB), during the sol−gel reaction.[11−14] Well-defined mesoporous structure in the silica outer shell is readily observed in the FETEM images (Figure 9a,b) after decomposition or removal of the CTAB surfactant. The mesoporous silica shell has a specific surface area (SSA) of 29 m^2/g and a mean pore size of 19 Å, as determined from the nitrogen adsorption−desorption isotherms in Figure 10.

4. Conclusions

Combined inorganic sol−gel reaction and polymer synthesis for the preparation of either stimuli-responsive polymer double-shelled hollow microspheres or inorganic “core−double shell” hollow microspheres has been described. The double shells in the stimuli-responsive polymer microspheres can be rendered asymmetric by different degrees of cross-linking while the silica shells in the inorganic microspheres can be rendered porous by the introduction of a surfactant during the sol−gel process. Furthermore, the size, shell number and thickness, core diameter and void dimension of the microstructures can be tailored by varying the sol−gel process and polymerization conditions. For the PMAA1-PMAA2 hollow microspheres illustrated, the outer and inner shells with different degrees of cross-linking can provide differential response to pH of the environment, and are thus potentially useful for controlled release in drug delivery systems (DDS). The silica “core−double shell” hollow microspheres, on the other hand, can probably be utilized as microreactors for confined reactions.

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