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Microencapsulation of Uncharged Low Molecular Weight Organic Materials by Polyelectrolyte Multilayer Self-Assembly†

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Two uncharged microcrystalline substances, pyrene (PYR) and fluorescein diacetate (FDA), were rendered water dispersible by treatment with various amphiphilic substances and subsequently encapsulated by exposure to an alternating sequence of cationic and anionic polyelectrolytes. The amphiphilic compounds employed to charge the microcrystals were ionic surfactants, phospholipids, and polyelectrolytes with an amphiphilic nature. Polyelectrolyte layers were self-assembled onto the pre-charged microcrystalline templates by means of electrostatic layer-by-layer deposition, thus forming a multilayered polymeric shell around the crystalline cores. The semipermeable nature of the polymer multilayer shell was thereafter exploited to remove the templated core by exposure to a mild organic solvent. The release behavior of solubilized PYR and FDA from the crystalline core was examined by monitoring their fluorescence after dissolution with ethanol. Complete removal of the core yielded hollow polymer capsules of micrometer dimensions. The capsule porosity was found to be influenced by the amphiphile used to pre-charge the microcrystal surface. The strategy presented is expected to be a general approach for the encapsulation of hydrophobic, low molecular weight compounds such as drugs, as well as providing a novel and facile pathway to the fabrication of polymer multilayered microcapsules with controlled release properties for drug delivery.

Introduction

In recent years, microcapsules have received considerable attention because of their technological importance in the fields of medicine, pharmaceutics, agriculture, and cosmetics.[1−7] The vast majority of applications are associated with the controlled release of encapsulated active ingredients (e.g., drugs, vaccines, antibodies, hormones, pesticides, and fragrances) under well-defined conditions. Despite the array of encapsulation technologies available, including those based on liposomes, microparticles, and microemulsions, there has been an intense interest in strategies to encapsulate and deliver water-insoluble pharmaceutical drugs in stable and aqueous forms.[8,9] Methods to achieve this have commonly included the incorporation of drugs into micelles and microspheres, emulsification of the drug with oils, the use of concentrated solutions of water-soluble polymers, and solubilization or suspending the drug with nonionic detergents. An alternative and recent approach has been to coat water-insoluble crystalline drugs with a membrane lipid, thus allowing dispersion of the crystal in an aqueous medium.[9] This represents an elegant method to prepare injectable forms of water-insoluble substances. The advantages of this process are the significantly higher concentrations (up to 40% w/v) of the injectable drug afforded (compared with other methods) and the stability of the dispersion.

The concept of using a solid core as a template on which to layer-by-layer assemble polymer layers to effect encapsulation of the core material has been studied extensively.[10] We have previously demonstrated that the combination of self-assembly and colloidal templating strategies provides a versatile means to fabricate core−shell materials and to encapsulate biological macromolecules.[11−17] The method is based on coating colloidal particles dispersed in aqueous solutions by the electrostatic self-assembly of charged polymeric and/or inorganic materials. The charge on the colloidal entities is utilized to facilitate the adsorption of subsequent layers. The colloids employed have included *charged* polymer lattices[11−16] and biological templates, e.g., cells[10] and protein crystals.[17]

In the current study, we have extended our colloidal templating approach to *uncharged* microparticles in order to achieve the encapsulation of hydrophobic low molecular weight compounds. As model (drug) systems, two poorly

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water-soluble crystalline materials have been employed, pyrene (PYR) and fluorescein diacetate (FDA). The first and significant step in their encapsulation involved imparting a charge on the crystal surface by self-assembly of ionic surfactants, phospholipid, or charged polymer that is amphipathic. Next, the assembly of polymer multilayers onto the coated microcrystal templates was achieved by the layer-by-layer adsorption of cationic and anionic polyelectrolytes. Release experiments of the encapsulated low molecular weight compounds were undertaken by monitoring their fluorescence as a function of time after dissolution of the microcrystal core by exposure to ethanol. The type of amphiphile used to disperse the uncharged microcrystalline templates and its influence on the resulting properties of the hollow microcapsules formed (after removal of the microcrystalline core) were also examined. Microelectrophoresis was employed to follow the microcrystal coating process, while confocal laser scanning microscopy (CLSM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) were used to characterize the hollow polymer capsules produced.

Experimental Section

Materials. Pyrene (PYR) was purchased from Aldrich and fluorescein diacetate (FDA) from Sigma. The polycation, poly(allylamine hydrochloride) (PAH), M_w 15 000, and the polyanion, poly(sodium 4-styrenesulfonate) (PSS), M_w 70 000, were obtained from Aldrich. The positively charged surfactants didodecyldimethylammonium bromide (DDDAB), hexadecyltrimethylammonium bromide (HDTAB), dodecyltrimethylammonium bromide (DTMAB), myristyltrimethylammonium bromide (MTMAB), and the negatively charged surfactant sodium dodecyl sulfate (SDS) were all from Aldrich. Dipalmitoyl-DL-α-phosphatidylcholine (DPPC) was purchased from Sigma. All reagents were used as received, except for the PSS, which was dialyzed against Milli-Q water (M_w cutoff 14 000) and lyophilized before use. Fluorescein isothiocyanate labeled PAH (PAH−FITC) was synthesized as follows: FITC was dissolved in dimethyl sulfoxide (final concentration of 2 mg mL^{-1}) and protected from light by wrapping the tube in aluminum foil. The FITC solution (40 μL) was then added to each milliliter of a 2 mg mL^{-1} PAH (M_w 15 000) solution of pH ≈ 10, so that the FITC to $-NH_2$ monomer ratio was 1:100. The mixture was gently stirred and allowed to react at 4 °C overnight. The derivative was then purified by gel filtration using a Sephadex G-25 M PD-10 column (Amersham Pharmacia Biotech AB) and further dialyzed. The water used in all experiments was passed through a Millipore Milli-Q Plus 185 purification system.

Assembly of Polyelectrolyte Multilayers onto Organic Microcrystals. The layer-by-layer assembly of polyelectrolytes onto FDA or PYR microcrystals was carried out as follows: 50 mg of finely milled core particles (FDA or PYR) was first thoroughly mixed with 12 mL of 0.2−0.4 wt % of the dispersing agent (ionic surfactant, lipid, or charged polymer). The crystals were suspended by their immediate sonication for 5 min. The suspension was allowed to stand for 30 min, thus allowing the larger crystals to sediment, or gently centrifuged. The turbid white supernatant was then extracted, centrifuged, washed two times with water, and finally resuspended in water. The resulting microcrystal particles were then layer-by-layer coated with PSS and PAH.[17] When positively charged surfactants or DPPC were used as the first layer, 1 mL of PSS solution (5 mg mL^{-1}, containing 0.5 M NaCl) was added first. PAH solution (1 mL of 5 mg mL^{-1}, containing 0.5 M NaCl) was added first when PSS or SDS were adsorbed onto the microcrystals. After an adsorption time of 15 min for PAH or PSS adsorption, the suspension was centrifuged at 3000 g for 5 min. The supernatant was then removed, and three cycles of water washing and redispersing were applied to remove the excess unadsorbed polyelectrolyte in solution. Polyelectrolyte layers, bearing an opposite charge to that already adsorbed on the particle, were deposited in identical fashion to produce multilayer-coated microcrystals. In some cases, the fluorescently labeled polyelectrolyte, PAH−FITC, was applied (as a 2 mg mL^{-1} solution containing 0.5 M NaCl) to form a fluorescent layer on the microcrystal surface.

Release Experiments. Twelve milliliters of solvent (ethanol or ethanol/water mixtures) were dispensed into 15-mL tubes. The coated microcrystal suspension (0.1 mL) was then quickly added to each tube, and after defined times (2, 5, 10 min etc.) the suspension was centrifuged at 3000 g for 5 min. A portion of the supernatant was removed and tested for the presence of PYR or FDA by fluorescence. For PYR, the fluorescence emission intensity of the supernatant was measured directly by using an excitation wavelength (λ_{ex}) of 350 nm and monitoring the emission (λ_{em}) at 373 nm. FDA was first hydrolyzed into fluorescein either by treatment with esterase or dilute base prior to fluorescence measurement (λ_{ex} = 492 nm, λ_{em} = 513 nm). As control experiments, the release characteristics of uncoated particles were also studied as outlined above.

Hollow Polymer Capsule Production. The microcrystal core was removed by exposing 0.2 mL of the coated particle suspension to 1 mL of ethanol (or chloroform) and allowing 30 min for core dissolution. The resulting hollow polymer capsules were then centrifuged at 10000 g for 10 min, exposed to ethanol again, washed an additional two times with water, and finally resuspended in water.

Microelectrophoresis. The microelectrophoretic mobility of coated organic microcrystals was measured with a Malvern Zetasizer 4 by taking the average of 5 measurements at the stationary level. The mobilities (μ) were converted to the electrophoretic potentials (ζ) using the Smoluchowski relation $\zeta = \mu\eta/\epsilon$, where η and ϵ are the viscosity and permittivity of the solution, respectively.[18] All measurements were performed on microcrystals re-dispersed in air-equilibrated pure water (pH ≈ 5.6).

Confocal Laser Scanning Microscopy (CLSM). CLSM images were taken on a confocal laser scanning Aristoplan microscope from Leica with a 40× oil immersion objective.

Transmission Electron Microscopy (TEM). TEM measurements were performed on a Philips CM12 microscope operated at 120 kV. TEM samples were prepared by deposition of a diluted particle suspension onto a carbon-coated copper grid. The mixture was allowed to air-dry for 1 min, after which time the excess solution was removed by blotting with filter paper.

Atomic Force Microscopy (AFM). AFM images were obtained using a Nanoscope IIIa AFM (Digital Instruments, CA) in tapping mode. Samples were prepared by applying a drop of a diluted solution onto a freshly cleaved mica surface, and air-drying.

Fluorescence Spectroscopy. Steady-state fluorescence spectra were recorded using a Spex Fluorolog 1680 spectrometer. Both excitation and emission bandwidths were set at 1.0 nm. All measurements were performed on air-equilibrated solutions at 25 °C.

Results and Discussion

Microelectrophoresis measurements were utilized to follow adsorption of the layers on the microcrystal templates. The microelectrophoretic mobility of the crystals after exposure to surfactant, phospholipid (DPPC), or polymer (PSS), and subsequently polyelectrolytes of alternating charge, was measured. Figure 1 shows the ζ-potential as a function of the polymer coating layer number for PYR and FDA microcrystals pre-exposed to surfactant (DDDAB or SDS, Figure 1a) or DPPC or PSS (Figure 1b). PYR crystals exposed to DDDAB (positively charged) showed a ζ-potential of +50 mV, while SDS (negatively charged) dispersed FDA crystals exhibited a value of −50 mV. Furthermore, FDA microcrystals dispersed with DPPC yielded a ζ-potential of +20 mV and those exposed to PSS a value of −40 mV. These data confirm charging of the microcrystal surface through adsorption of the amphiphilic substances, explaining the dispersability of the microcrystals in aqueous solution.

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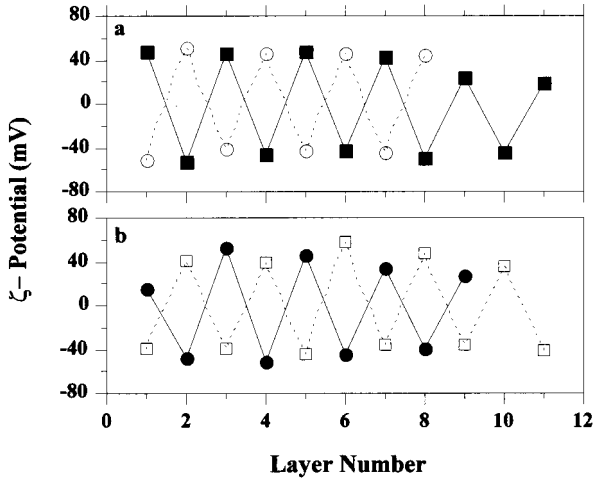

Figure 1. ζ-Potential of amphiphile-stabilized PYR and FDA microcrystals as a function of polyelectrolyte layer number: (a) PYR-DDDAB (filled squares), FDA-SDS (open circles); (b) FDA-DPPC (filled circles); FDA-PSS (open squares). Layer number = 1 corresponds to the amphiphile-coated microcrystals. Surface charge reversal is seen with adsorption of each polyelectrolyte layer. From layer number 2 onward, positive values are for PAH adsorption and negative values for PSS deposition. Layers 9 and 11 for the PYR-DDDAB system and layer 10 for the FDA-PSS system correspond to PAH−FITC adsorption.

The adsorbed layer coats the microcrystal, thus protecting it from aggregation.

The mechanism of microcrystal dispersion and stabilization can be explained by the hydrophobic interactions between the amphiphiles and the microcrystals. Since both PYR and FDA are hydrophobic, the hydrophobic chains of the surfactants and those on DPPC are expected to be associated with the microcrystal surface, while the ionic groups on these amphiphiles project away from the surface.[19] It is worthy to note that neither the PYR nor FDA microcrystals could be readily dispersed with the polyelectrolytes PAH, poly(diallyldimethylammonium chloride) (PDADMAC), or copolymers of DADMAC and acrylamide with varying DADMAC contents (8−73 mol %). In stark contrast, the microcrystals could be dispersed by exposure to PSS. This tends to suggest that the amphiphilic nature of PSS, owing to the aromatic group on the polymer backbone and the charged groups, is responsible for the successful adsorption and consequent charging of the crystal surface. The coated microcrystals are prevented from further growth (i.e., aggregation) by the ionic and/or steric interactions of the thin coating that is associated with each microcrystal particle. These surface-modified microcrystals represent stable and charged colloids suitable for polyelectrolyte multilayer coating.

As depicted in Figure 1, an alternating sign in the ζ-potential was observed when the pre-charged crystals were consecutively exposed to polymer solutions of opposite charge. The sign of the ζ-potential depended on the polyelectrolyte that formed the outermost layer, i.e., the polymer that was last deposited. Regardless of the microcrystal type (PYR or FDA), or the amphiphile used to coat and stabilize the microcrystals, alternating positive and negative ζ-potentials were measured for coated crystals alternately exposed to PAH and PSS, respectively. This suggests stepwise growth of the polymers on the microcrystal template and is characteristic of polymer multilayer formation on charged colloidal particles.[10]

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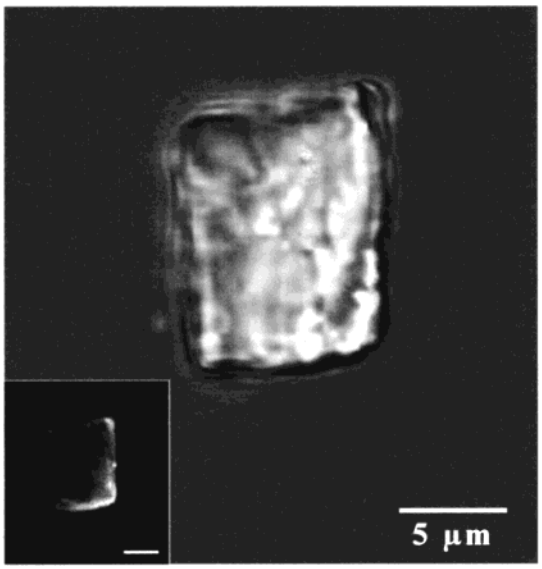

Figure 2. Transmission and fluorescence (inset) CLSM micrographs of an FDA crystal dispersed by adsorption of PSS and further coated with 9 polyelectrolyte layers, with the outermost layer being PAH−FITC, [$(PAH/PSS)_4$/PAH−FITC]. The scale bar in the inset corresponds to 5 μm.

Values of ca. +50 mV were observed when PAH formed the outermost layer and −50 mV when PSS was deposited last. The slightly lower positive values observed for the PAH−FITC layers (ca. +20 mV) is attributed to the presence of negatively charged FITC molecules on the PAH chains. Importantly, the amphiphiles were strongly adsorbed onto the microcrystals allowing the formation of polymer multilayers. However, the formation of small quantities of amphiphile−polyelectrolyte complexes in solution cannot be ruled out. The above data highlights the general nature of the assembly process: charged surfactants, lipids, or amphiphilic polymers can be used to charge hydrophobic crystalline templates, thus facilitating their encapsulation with polyelectrolyte multilayers.

CLSM was employed to investigate the morphology of the microcrystals and to verify their coating with polymer multilayers. Figure 2 displays a CLSM image (in transmission mode) of a FDA microcrystal that has been dispersed as a result of coating with PSS and additionally coated with nine polyelectrolyte layers (the last layer was PAH−FITC). The inset shows the corresponding CLSM fluorescence micrograph. It is evident from the transmission image that the microcrystal possesses a solid core. The microcrystals had various shapes, ranging from near-spherical to rodlike, square and rectangular. Direct evidence for polymer coating of FDA is provided in the CLSM fluorescence image (inset). This displays fluorescence due to PAH−FITC present in the outer layer of the coated microcrystal. Similar CLSM images were observed for pre-dispersed FDA and PYR crystals coated with polymer. Studies showed that the coated microcrystal suspensions were stable for days when stored in an aqueous medium, reflecting the stability of the adsorbed layers.

The release behavior of the pyrene and fluorescein diacetate molecules, from dissolution of the core templates, through the polymer capsule wall was investigated by using fluorescence spectroscopy. Following centrifugation of the coated microcrystal suspensions that were exposed to ethanol, the supernatant was assessed for either pyrene or fluorescein at regular time intervals. Control experiments for DDDAB-dispersed PYR microcrystals and those

dispersed with PSS revealed rapid release characteristics: Upon addition of ethanol, the pyrene core was removed within about 30 min for both the surfactant- and PSS-coated crystals. The pores in the polymer microcapsules produced in this work are large enough to allow removal of the low molecular weight core molecules (see below). This finding is consistent with earlier reports on the permeability characteristics of polyelectrolyte multilayers: Polymer multilayers are permeable to low molecular weight substances[14,15] but essentially impermeable to polymers larger than 4000 Da.[20] Further experiments showed that the rate of removal was found to be dependent on the first layer adsorbed, the number of polyelectrolyte layers, and the ratio of ethanol to water in the dissolving medium.[21] It is worth noting that up to five polyelectrolyte layer pairs were assembled onto the microcrystal templates in the current work. Slower release rates were observed with increasing polyelectrolyte layer number.[21] The assembly of thicker shells (e.g., more polyelectrolyte layers) may have the effect of smoothing out the outer surface and at the same time reducing the porosity. The layer-by-layer assembly of polycations and polyanions displays a remarkable self-regularity: For films grown on poorly charged and/or rough planar substrates, irregular growth has often been observed for the first few layers with regular growth achieved after the deposition of a number of layer pairs.[22−24]

The CLSM micrographs of polymer-coated FDA microcrystals after being exposed to ethanol solution and dispersed in water are displayed in Figure 3. The transmission image (a) shows a number of the colloidal entities produced. There is no evidence of a solid core, indicating dissolution and removal of the microcrystal. Ethanol solubilizes the core material and the individual molecules are then able to diffuse through the semipermeable polymer capsule walls. The structures seen in the transmission image are due to the contrast of the remaining polymer layers from the original coating of the microcrystals, indicating the successful formation of hollow polymer capsules. The above results are consistent with the visual observation that the polymer-coated microcrystal suspensions lost their turbidity upon the addition of ethanol. Further evidence is provided by the corresponding CLSM fluorescence image (b), which shows the fluorescence from the PAH−FITC layers. The different morphologies observed are due to the diversity of the microcrystal shapes. Some indentations on the polymer capsule walls may also be due to the centrifugation process used in their preparation. There was no evidence of rupturing of the capsule walls as a result of the facile removal of the microcrystal core by treatment with ethanol. The CLSM results demonstrate that polymer multilayers can be deposited onto pre-charged microcrystal templates and that the core can be removed by treatment with an appropriate solvent, leaving behind hollow polymer capsules.

The polyelectrolyte capsules produced were further characterized using TEM and AFM. TEM images of air-dried hollow polymer capsules obtained from SDS-dispersed PYR microcrystals coated with 11 polymer layers and FDA crystals dispersed with PSS and additionally coated with 9 polyelectrolyte layers are illustrated in Figure 4 (a and b, respectively). The insets show higher magnifications of the capsule walls. The folds and creases seen in the polymer capsules are a result of evaporation of the aqueous content by air-drying.[10] The striking difference between the images in Figure 4a and Figure 4b is the wall porosity. Capsules produced when the microcrystals were dispersed with surfactant (either positively or negatively charged) exhibit a much smoother texture and lower porosity than those produced from PSS-dispersed microcrystals. Pores of diameter from 20 nm to larger than 100 nm were observed for hollow capsules derived from polymer-coated PSS-dispersed microcrystals. In contrast, it was difficult to discern pores in the very smooth textured polymer capsules when surfactant was used to disperse the microcrystals, suggesting an average pore size of less than about 10 nm. These findings were confirmed by AFM measurements. The differences seen

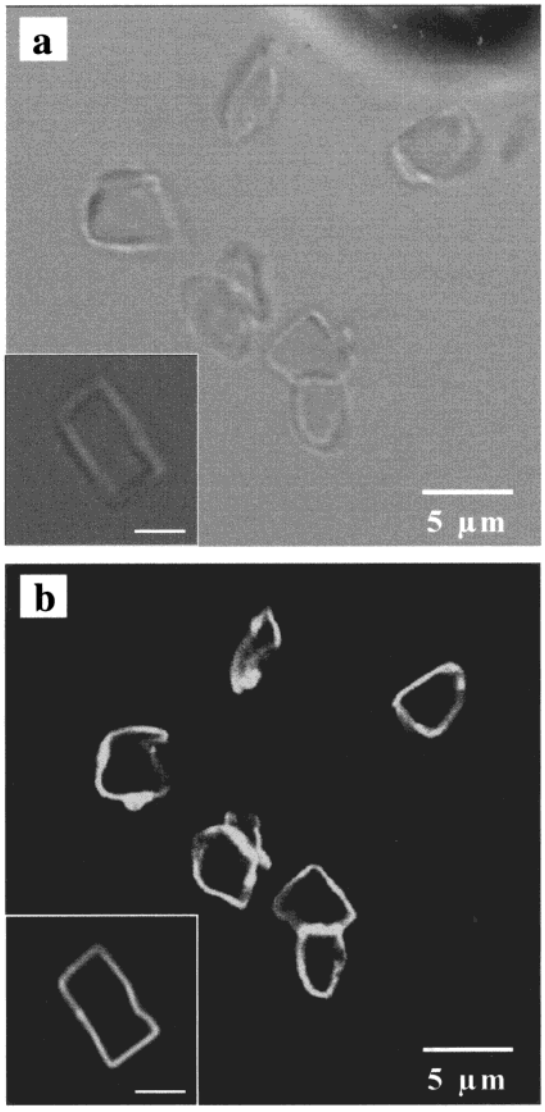

Figure 3. CLSM transmission (a) and fluorescence (b) micrographs of hollow polymer capsules derived from polymer-coated FDA microcrystals. The polymer capsules were obtained by removal of the crystal core upon exposure to ethanol. The FDA microcrystals were dispersed by adsorption of PSS and additionally coated with nine polyelectrolyte layers with the outermost layer being PAH−FITC, $[(PAH/PSS)_4/PAH-FITC]$. The insets show an individual hollow polymer capsule, obtained after dissolution of the core from FDA dispersed with SDS and coated with eleven polyelectrolyte layers $[(PAH/PSS)_3/PAH/(PSS/PAH-FITC)_2]$. The scale bars in the insets correspond to 2 μm.

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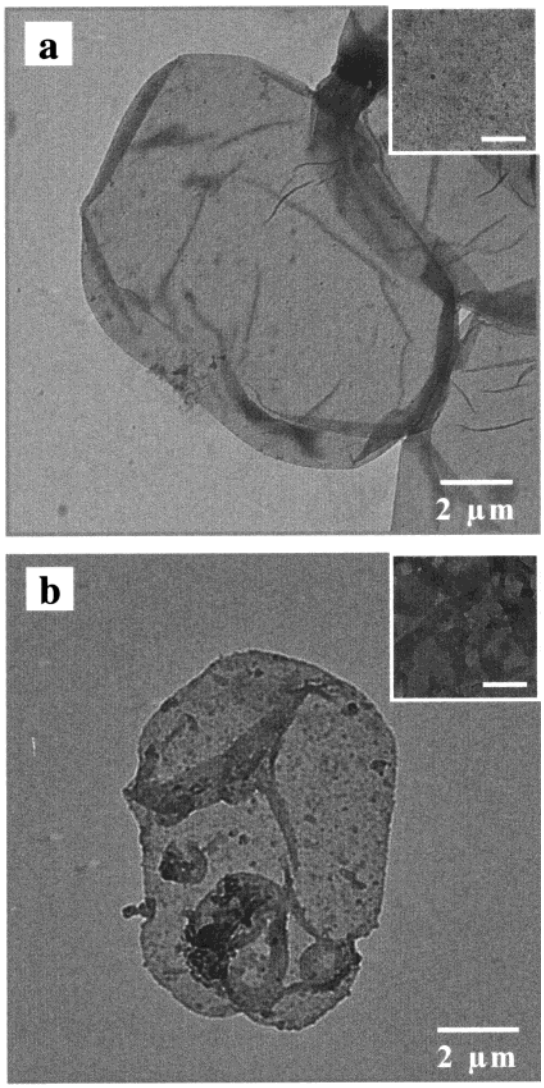

Figure 4. TEM images of air-dried hollow polymer capsules, obtained after removal of the templated microcrystal core with ethanol. (a) The PYR core was dispersed by SDS and coated with 11 polyelectrolyte layers. (b) FDA was dispersed by PSS and coated with 9 polyelectrolyte layers. The polymer capsules flattened as a result of drying and folds and creases are seen. A significant difference in porosity was observed for the polymer capsules, depending on whether surfactant (a, less porous) or PSS (b, more porous) was used to disperse the microcrystals. Similar differences were observed for both the PYR and FDA systems. The scale bars in the insets correspond to 200 nm.

may be ascribed to the initial conformation of the first adsorbed layer (in terms of homogeneity) used to disperse the crystals and the effect it has on the structure and density of subsequently deposited polyelectrolyte layers. In addition, the presence of surfactant in the capsule wall cannot be excluded. Surfactant bound to the polyelectrolyte (i.e., complexed) may have the effect of reducing the porosity of the capsules. Nevertheless, the above illustrates the importance of the first adsorbed layer in determining the porosity of the resulting thin-walled hollow polymer capsules. Control over the pore size in such hollow microcapsules is expected to have important implications in technology as it may allow regulation of the release rate of encapsulated materials. To this end, systematic studies are underway to investigate the effect of the first adsorbed layer on microcapsule porosity.

Examination of the apparent heights of air-dried polymer capsules by using tapping mode AFM yielded values of approximately 25−30 nm for capsules comprised of 10 polyelectrolyte layers. This dimension is equivalent to twice the polymer capsule wall thickness; hence, the average thickness per polyelectrolyte layer is between 1 and 1.5 nm, a value that is close to those obtained for polymer multilayers on other colloidal templates.[10]

An attractive feature of the process employed for the formation of hollow polymer capsules is the facile removal of the templated microcrystal core. Previous methods have involved extremely acidic (pH = 1)[10,15] or basic (pH > 12)[10,17] solutions. Clearly the use of such conditions is limited, particularly when biological compounds are present during the core removal process. In addition, the undesirable changes in the composition and properties of the hollow polymer capsules that occur with such harsh conditions[25] can be avoided.

The systems examined provide excellent model drug release systems to study various parameters on the release rate of encapsulated low molecular weight compounds. An interesting strategy would be to control the release rate by varying the thickness and composition of the polymer capsule walls, as well as the nature of the first adsorbed layer. We are currently pursuing such experiments with the aim of optimizing and understanding the release characteristics of such stable, multilayered colloidal systems.

Conclusions

We have demonstrated the successful templating and encapsulation of poorly water-soluble, low molecular weight organic compounds through a multistep process that entails pre-charging microcrystals with an amphiphilic substance, followed by coating with layers of oppositely charged polyelectrolytes. In a further step, the microcrystal template was released by exposure to a mild solvent, leaving behind hollow polymer capsules. The type of amphiphile used to charge the microcrystals determined the porosity of the resulting capsules. The strategy presented can potentially be applied to encapsulate a host of significant uncharged compounds, both crystalline and amorphous. Optimization of the capsule wall thickness and composition is expected to yield unique, highly flexible systems with tailored release properties for drug delivery applications.

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