Photopolymerization of Acrylamide Derivatives in Polyelectrolyte Microcapsules

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Multilayered polyelectrolyte poly(sodium 4-styrenesulfonate)/poly(allylamine hydrochloride) microcapsules prepared using layer-by-layer (LbL) assembly technology were filled by UV-photopolymerization of acrylamide derivatives directly into the capsule interior. Influences of component properties and polymerization conditions on the structure of the obtained composites are discussed. Mixing formed polymer chains with the capsule wall material stabilizes the initial wall conformation and lowers capsule sensitivity to environmental conditions.

Possible application of systems based on acrylamide polymers has been studied intensively due to their biocompatibility, hydrophilicity, and flexible mechanical strength. They stimulate interests to use them as carriers for proteins, drugs, or other materials and as delivery system with variable release mechanisms.[1] Layer-by-layer (LbL) nano-engineered hollow polyelectrolyte microcapsules with wall thickness in the nanometer range have recently drawn great attention.[2] The capsules are permeable for molecules with molecular weight (MW) less than 2000 and not permeable for macromolecules.[3]

Filling hollow microcapsules introduces additional functionality into capsule interiors. In spite the fact that direct polymerization of monomers into the capsule interior can significantly expand the range of loaded materials, it is not often used.[2c] Besides, thermal shrinking of microcapsules was recently reported,[3c] which limits application of thermally induced polymerization. Photopolymerization is an easy-to-control method, which can be conducted safely for biomaterials in mild temperature and neutral pH conditions with good polymerization selectivity.[4] Here, we report UV-initiated polymerization of acrylamide derivatives in multilayered microcapsules concerned with influence of component properties on structure of obtained composites. We also evaluate the possibility of loading the modified capsules with model drugs like FITC and FITC-dextran.

For hollow polyelectrolyte capsule fabrication, four bilayers of poly(sodium 4-styrenesulfonate)/poly(allylamine hydrochloride) (PSS/PAH) microshells were assembled on $MnCO_3$ cores ($5.5 \pm 0.5\,\mu m$ in diameter[5]) by alternate adsorption of polyelectrolytes.[3] Hollow capsules (Figure 1a) were obtained after core dissolution in a 0.1 M HCl solution. The capsules obtained were centrifuged and washed using deionized (DI) water three times and stored in the DI water.

Monomers, uncharged acrylamide (AAm), positively charged (3-acrylamidopropyl)trimethylammonium chloride (AAmPN), negatively charged 2-acrylamido-2-methyl-1-propanesulfonic acid (AAmPS), and photoinitiator [3-(3,4-dimethyl-9-oxo-9*H*–thioxanthen-2-yloxy)-2-hydroxypropyl]trimethylammonium chloride (In) were received from Sigma-Aldrich and used as received.

For polymer synthesis, the stored capsules were centrifuged and the supernatant was discarded. Then the capsules were resuspended in a 0–7.0 M monomer solution containing 0.45–4.5 mM of In and 1.1 mM of fluorescein o-acrylate (FOA) at pH 5 or 8, and the monomers penetrated into the capsules. A broad band BLAK-RAY long wave UV lamp was used as an irradiation source. The emission wavelengths of the lamp are between 320 and 400 nm, with ca. 1950 mean lumen. After 15–60 min of irradiation, the capsules were separated via centrifugation alternated with multiple washings using DI water, with pH adjusted to that used for polymerization. The formed polymers remained inside capsules. The capsules filled with polymers were inspected using confocal laser scanning microscopy (CLSM, Leica DMRE2) with a 60x objective lens and atomic force microscopy (AFM, Quesant Q-ScopeTM 250).

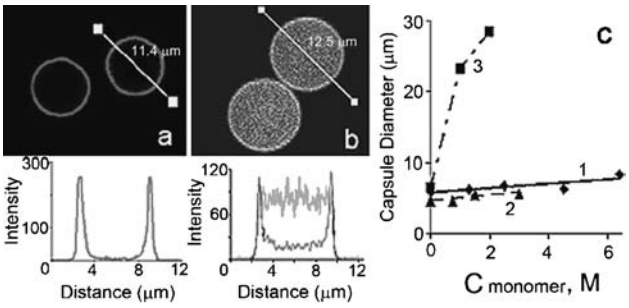

Figure 1. Confocal images of empty capsules labeled with RITC (a), those filled with PAAm-FOA copolymer (b) with corresponding profiles, and swelling characteristics of the capsules filled with polymer vs initial monomer concentration (c). 1-AAm; 2-AAmPN, 3-AAmPS.

Polymerization of AAm is much faster at low pH. It takes ca. 15 min at pH 5 and ca. 60 min at pH 8 to give polymer solutions with capsules of similar viscosity. However, distribution of formed polymer in the capsule interior is affected by pH conditions used during polymerization. The copolymer formed at pH 8 is homogeneously distributed inside the capsules (Figure 1b). Similar images were observed for all monomers. If pH 5 was kept throughout the procedure, the formed polymer was only spread within the capsule walls, but did not fill the capsules. Moreover, very slow diffusion of FITC (at pH 6.5) was observed for capsules filled with PAAm at pH 8 and practically instant diffusion for those obtained at pH 5. The original $(PSS/PAH)_n$ capsules have a loose wall structure at pH lower than 7–7.5, which allows macromolecules to diffuse in and out.[3] Mixing formed polymer chains within wall material seems to stabilize initial wall conformation and lower capsule sensitivity to environment conditions. As a result, pH 8 supporting formation of sealed capsules was used hereafter. The influence of PSS and PAH on polymerization is negligible because the UV absorbance of PSS and PAH is at the wavelength of about 228 nm, which is

far below the emission wavelengths of the UV lamp we used in this work.

Capsules filled with PAAm or PAAmPN are slightly swollen after polymerization (Figure 1c), the size increases from the initial 5.0 μm to 6–8 μm. However, for capsules with PAAmPS polymer inside, unexpectedly big swelling is observed. The capsule diameter increases more than 5 times. This expansion seems to be critical for the capsules. If high monomer concentrations are used, swelling probably caused by osmotic pressure enhanced with repulsion of negatively charged PAAmPS completely destroys the capsules as soon as a washing is applied.

The wall thickness of an empty dried $(PSS/PAH)_4$ capsule is about 25 nm as derived from AFM images (Figure 2a). Increasing height and size indicates on newly formed polymer in the capsule interior (Figure 2b). Considering the shape and size of the capsules obtained from AFM and taking the density of solid residua as 1.1 g/cm^3, the mass of capsules was calculated (Figure 2c). An estimated conversion of initial monomer into the polymer remaining in the capsules is $16.4 \pm 0.4\%$ for AAm, $3.2 \pm 1.6\%$ for AAmPN, and $68.0 \pm 3.0\%$ for AAmPS. The percentage of converted monomer apparently does not depend on initial monomer concentration and is a function of exposure time and monomer type. Besides, the capsules retain some permeability for low molecular weight substances after filling with polymer and oligomeric products could be removed by multiple washings.

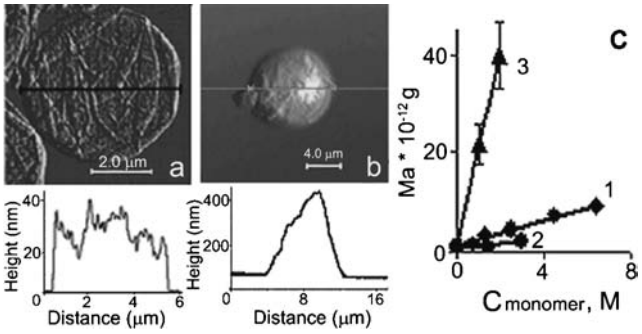

Figure 2. AFM images of a dried empty $(PSS/PAH)_4$ microcapsule before (a) and after (b) polymerization of 6.5 M AAm (60 min, pH 8) with corresponding height profiles. Calculated capsule mass as function of initial monomer concentration (c): 1. AAm, 0.45 mM In, 60 min, 2. AAmPN, 4.5 mM In, 15 min, 3. AAmPS, 0.45 mM In, 60 min.

Calculated on the basis of dry capsule masses (using AFM data) and their actual sizes, the concentration of polymer in the capsule interior in solution is less than 10% w/w (mass ratio of polymer/water) and depends on initial monomer concentration. The mass of polymers in a single capsule is ca. $0.8–1.5 \times 10^{-12}$ g. The ability of capsules filled with polymer to swell strongly influences the apparent concentration of encapsulated polymer. For example, for capsules with PAAmPS polymer, the swelling results in a significant increase of their volume and brings the polymer concentration down to ca. 0.3% w/w instead of 13–25% w/w as calculated without swelling.

Used as model drugs, FITC and FITC-dextrans were tested to be adsorbed into the polymer loaded capsules. Adsorption of FITC and FITC-dextran (MW 4400 and 77,000) in capsules filled with polymers was evaluated by CLSM. The capsules were kept in a 0.1 mg/mL FITC or 1.0 mg/mL FITC-dextran solution for 12 h, washed with DI water, and fluorescence distribution across the capsules was obtained. Distribution of dye adsorbed in the capsule interior depends on the type of the monomer used for polymerization. At pH 6.5, FITC is slightly negative ($pK_a \approx 6.4$[6]) and its adsorption is much higher on positively charged material (PAAmPN) than on PAAm (Figure 3).

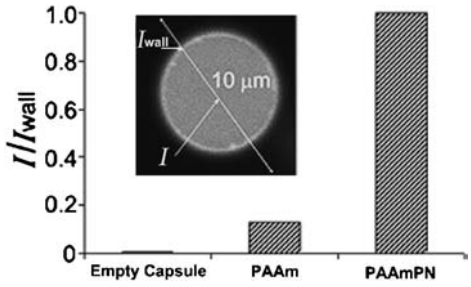

Figure 3. Normalized FITC distribution in capsules filled with different polymers at pH 6.5. The insert explains the choice of data for the diagram. (The higher charge density of the capsule walls resulted in the adsorption of more FITC, thus higher fluorescence intensity (I_{wall})).

Macromolecular FITC-dextrans were also evaluated using capsules filled with cationic polymers; the fluorescence was detected to be distributed uniformly on the interior of the capsules after adsorption and washing. We expect that the capsules filled with charged polymers can serve as promising vehicles in the field of controlled drug delivery.

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