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Shell modulation by tailoring substituents in chitosan for LbL-assembled microcapsules

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ABSTRACT

By AFM we report the successful modulation of shell structure (morphology and shell thickness) of microcapsules through tailoring molecular substituents of chitosan. The shell thickness of hollow $(HPCS/SA)_n$ ($n = 5, 7, 9$) capsules is more than 3 times that of the $(QACS/SA)_n$ ($n = 5, 7, 9$) capsules, due to less charges carried by the neutral $-NH_2$ substituent group and the induced coily conformation in HPCS, while more charges carried by the positively charged $-N(CH_3)_3^+$ substituent and the induced extended conformation in QACS (HPCS: hydroxyl propyl chitosan; QACS: quaternary ammonium chitosan; SA: sodium alginate). The ultrathin shells of microcapsules assembled in this work by the layer-by-layer (LbL) self-assembly technique rather than the traditional method of mixing CS, SA and $CaCl_2$ enable the thickness modulation characterization by AFM on the atomic scale. These microcapsules with tunable shell thickness provide important guidance for potential drug delivery and sustained release.

1. Introduction

Modulation of molecular assemblies can provide novel properties [1], and thus can be of paramount importance for microcontainers [2,3], controlled drug release [4,5], and bioreactors [6–8]. Modulation can be achieved by various means including tailoring molecular structures (electron densities at a single ligand atom [9] or crosslinking ions [10]) and changing hydrodynamic conditions in experiments [11].

Modulation of molecular packings and phase behaviors by substituents in compounds are revealed in two-dimensional (2D) Langmuir monolayers at the air–water interface [12,13]. Chemical structure (hydrophilic–hydrophobic balance and bulkiness) [14] and molecular weight [15] have been shown to modulate the thickness of 2D films fabricated by the layer-by-layer (LbL) technique on planar solid substrates. As an important self-assembly technique, the LbL method has been extended from 2D to 3D by replacing the planar solid surfaces with colloidal particles, whose decomposition (core removal) results in intact hollow microcapsules [16–18]. Such microcapsules have many superior properties such as high Young's modulus, perfect stability, and switchable channels in shells [19,20]. An open question is whether the 3D shells of microcapsules can be modulated by tailoring molecular structures compared to that of 2D films, since intermolecular interactions are dependent on the curvature of films [21]. Detailed understanding of the modulation is crucial for tailoring shell morphologies of microcapsules, which might in turn affect physical properties.

Chitosan is naturally biodegradable without accumulation in biological organisms [22], thus microparticles [23] and nanotubes [24] containing chitosan showing no cytotoxicity have been prepared via the LbL assembly for potential drug delivery carriers. It is necessary to note that there are chitosan/alginate microcapsules systems formed not by the LbL technique but by alternatingly mixing alginate, $CaCl_2$, and chitosan, whose thickness could not be modulated on the molecular level, and thus could not be characterized by AFM due to the large diameter of about several hundred micrometers and the big thickness of about tens of nanometers per deposited layer [25,26]. In comparison, the LbL technique has the advantage of fabricating each layer with the thickness of about 1 nm, making the AFM a powerful tool to characterize the shell thickness of microcapsules [27].

In this work, we use the LbL technique to fabricate microcapsules containing chitosan molecules with different substituents. A successful modulation of roughness and thickness of the LbL-fabricated

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microcapsules by tailoring substituents in chitosan molecules is addressed by the AFM characterization. This work helps to understand the surface properties modulated by tailoring the natural polysaccharides in microcapsules, providing guidance for the potential applications in drug delivery and sustained release.

2. Materials and methods

2.1. Materials

$CaCO_3$ microparticles were prepared according to literature methods [28]. Sodium alginate (SA, 100–300 cP) and Rhodamine 6G were from Sigma and Fluka, respectively. All chemicals were used without further treatment. Hydroxyl propyl chitosan (HPCS) and quaternary ammonium chitosan (QACS) were synthesized according to literature methods [29–31]. Fig. 1 shows the schematic of the HPCS and QACS molecules. The viscosity and degree of deacetylation of HPCS and QACS were all 200–800 cP (1% in 1% acetic acid) and 75–85%, respectively. Water used in all experiment had a resistivity higher than 18.2 MΩ cm. All experiments were carried out at room temperature.

2.2. Preparation of microcapsules

Solutions of HPCS, QACS (1 mg/ml in 0.1 M NaCl and 0.02 M acetic acid) and SA (1 mg/ml in 0.1 M NaCl) were used for the assembly of polysaccharide multilayers on $CaCO_3$ microparticles. Before deposition, the polysaccharides were dissolved under stirring at room temperature overnight.

Positively charged HPCS (or QACS) was first absorbed on $CaCO_3$ by immersing the microparticles into a solution of HPCS (or QACS) for 30 min. Gentle sonication for 15 s was applied at the beginning of deposition to separate aggregated particles and to promote infiltration of the polysaccharides into the microparticle pores. Three times of rinsing (10 min each) were followed. Positively charged HPCS (or QACS) and negatively charged SA were alternatingly deposited for 30 min on $CaCO_3$ and then rinsed three times with water until the desired number of layers. The $CaCO_3$ microparticles were decomposed by disodium ethylenediaminetetraacetic acid salt (EDTA), followed by three times of rinsing with water.

2.3. Characterizations of the microcapsules

Confocal laser scanning microscopy (CLSM) images were taken on a Leica TCS SP IRE2. Scanning electron microscopy (SEM) was performed by Gemini Leo 1550. Transmission electron microscopy (TEM) measurements were carried out on Zeiss EM 912 Omega. Atomic force microscopy (AFM) images were taken on Digital Instrument Nanoscope IIIa with the tapping mode.

3. Results

First we fabricated the $(HPCS/SA)_5$ microcapsules. Fig. 2 shows the CLSM images of microcapsules with the $CaCO_3$ core (Fig. 2A and B) and hollow microcapsules (Fig. 2C and D) obtained via

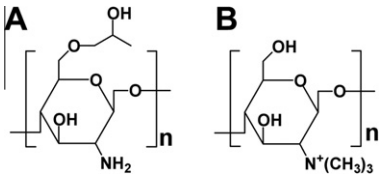

Fig. 1. Schematic of the (A) HPCS and (B) QACS molecules.

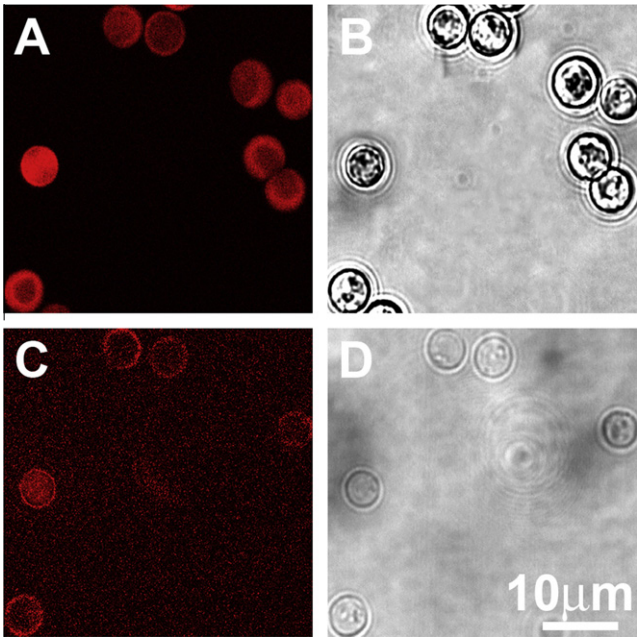

Fig. 2. CLSM images of $(HPCS/SA)_5$ microcapsules (A and B) with the $CaCO_3$ core and (C and D) hollow microcapsules via *in situ* decomposition of the $CaCO_3$. (A and C) the fluorescence mode and (B and D) the transmission mode were used, respectively.

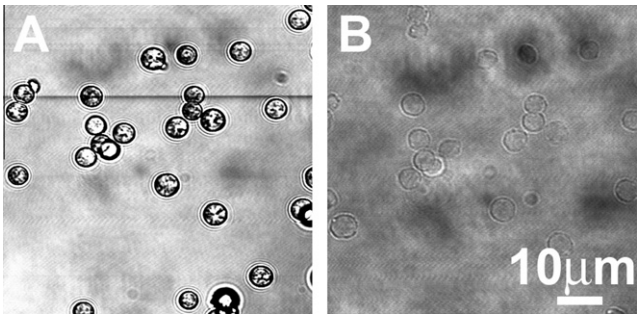

Fig. 3. CLSM images of $(HPCS/SA)_5$ capsules (A) before and (B) after *in situ* core decomposition. No dyes were added and only the transmission mode was used.

in situ decomposition of the core. Bright emission from both interior and the shell for the microcapsules with the $CaCO_3$ core can be observed in the fluorescence mode, indicating the infiltration of dye molecules in the pores of $CaCO_3$ particles. After the core removal, hollow microcapsules are stable and intact.

The diameter of the hollow capsules with five bilayers is the same as that of the template $CaCO_3$ core, indicating a molecular packing of polysaccharides in the shell mechanically stable against osmotic pressure shock during core decomposition. So neither swelling (increase of capsule diameter) nor burst of capsules is observed.

The hollow capsules show strong adhesion on solid slides. Most of them stayed where they were, even if rinsed thoroughly by water. After five times of rinsing with water, most of the hollow capsules were not washed off or moved (Fig. 3).

To tailor the molecular structure we replaced the HPCS with QACS and fabricated $(QACS/SA)_5$ microcapsules. Due to resolution limitation, observed under CLSM the modulation effect was not resolved. Similar diameter and adhesive property was for $(QACS/SA)_5$ microcapsules before and after *in situ* decomposition of the $CaCO_3$ core, as shown in Fig. 4.