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Stabilization of layer-by-layer engineered multilayered hollow microspheres

Peng Liu *

State Key Laboratory of Applied Organic Chemistry and Institute of Polymer Science and Engineering, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China

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ABSTRACT

Polymer multilayered hollow microspheres prepared by layer-by-layer (LbL) self-assembly attract more and more interest due to their unique application, especially as drug delivery system (DDS). Unfortunately, the multilayered hollow microspheres assembled via weak linkages could fuse and/or aggregate in high ionic strength media or strong acidic or basic media. This severely restricts the practical applications of the multilayered hollow microspheres as DDS in human physiological medium. In the present work, the progress in stabilization of the multilayered hollow microspheres is reviewed, with emphasis on the assembling process and their crosslinking mechanism.

Contents

1. Introduction

In recent years, polyelectrolyte multilayered hollow microspheres prepared by layer-by-layer (LbL) adsorption of oppositely charged polyelectrolytes onto various colloidal templates have received considerable attention [1], due to their high scientific interest and technological importance in the fields of drug delivery [2], microreactors [3], microcontainers [4] as well as catalysts [5]. Especially for the applications as drug delivery system (DDS), either encapsulation of actives for sustained release [6] or formation of polymeric core–shell particles for controlled release [7], multilayered hollow microspheres assembled with functional materials exhibit the stimuli-responsive characteristics upon the external environmental changes [8], such as pH [9], temperature [10], sugar or carbohydrate [9,11], rodex [12], ultrasound [13], light [14], and magnetic [15]. The triggered release makes it possible to realize the controlled release of drugs by the multilayered hollow microspheres as intelligent DDS [16].

However, the multilayered hollow microspheres assembled via the non-covalent bonds, such as electrostatic interactions or hydrogen bond, could fuse (Fig. 1) [17] and/or aggregate [18] in high ionic strength media or strong acidic or basic media. The average hydrodynamic diameters of the hollow microspheres increased with increasing the NaCl concentration from 0.01 to 0.20 mol/L (see Fig. 2), and the aggregation of the polyelectrolyte microcapsules caused by the changing of the ionic strength was irreversible, revealed by diluting the media

* Tel./fax: +86 931 8912582.
E-mail address: pliu@lzu.edu.cn.

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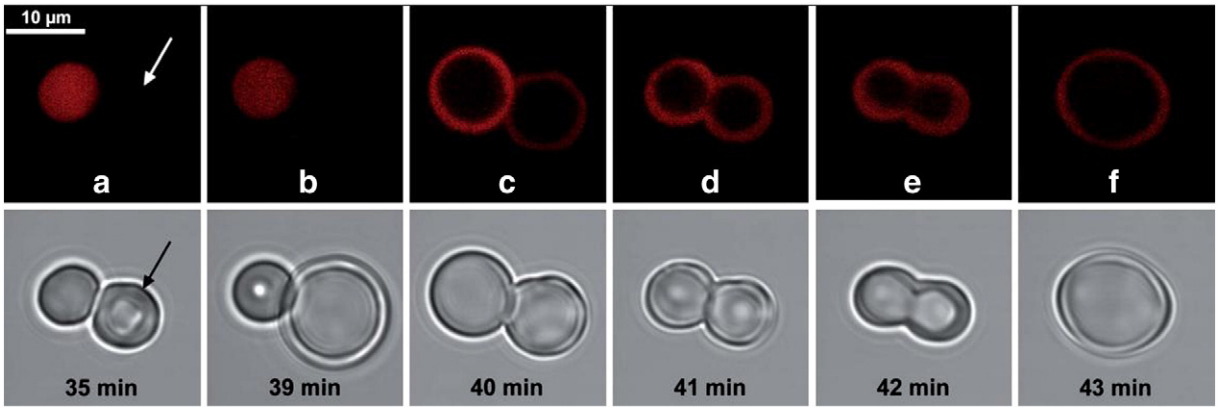

Fig. 1. Fusion of a fluorescently labeled $(RB\text{-}PAH/PSS)_3$ microcapsule in contact with an unlabeled $(PAH/PSS)_2/PAH$ microcapsule in 2.5MHCl. The fluorescence images are contrast-enhanced, the difference in fluorescence between capsules marked with an arrow (unlabelled) and the capsules in contact should be noticed. Fluorescence (a–f) and optical microscopy (underneath) images.
It was taken from reference [17].

NaCl concentration. This severely restricts the practical applications of the multilayered hollow microspheres as DDS in human physiological medium.

Based on the possible fusion mechanism of the multilayered hollow microspheres assembled via electrostatic interactions suggested by Zhang et al. (Fig. 3) [19], there may be two strategies to prevent the multilayered hollow microspheres from fusion or aggregation in high ionic strength media: (i) linking the layers with the strong interactions to form the covalent multilayered hollow microspheres and (ii) concealing the outermost polyelectrolyte layer of the non-covalent multilayered hollow microspheres. In the first strategy, the shell stability is improved by changing the crosslinking nature from ionic to covalent under external stimuli. On the other hand, the polymers could also be covalently assembled onto the templates. The strong intra-layer interactions within these highly stable shells could not be destroyed by the electrostatic shielding of the small electrolytes. So the hollow microspheres are stable in high ionic strength media.

While in the second strategy, the weak non-covalent interactions such as electrostatic interactions or hydrogen bonds remained as the driving forces for the multilayered hollow microspheres without changing to covalent bonds. The electrostatic shielding of the small electrolytes could weaken the intra-layer interactions in the multilayered hollow microspheres, so their ionic strength responsive property might be retained. On the contrary, the polyelectrolyte molecules in different multilayered hollow microspheres could not interact with each other once a concealing layer is modified onto their surfaces, so the fusion or aggregation in high ionic strength media must be prevented consequently.

In the present work, the advances in the stabilization of multilayered (hybrid) hollow microspheres in high ionic strength media or organic solvents via the two strategies mentioned above are reviewed, emphasizing the assembling process and their crosslinking mechanism. And the two strategies are compared correspondingly.

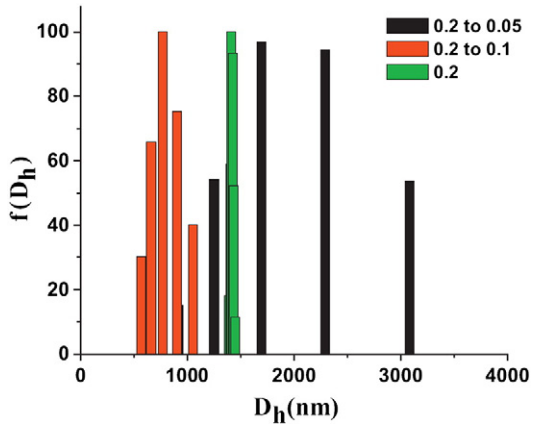

Fig. 2. Typical hydrodynamic diameter distributions (f(Dh)) of the multilayered chitosan hollow microspheres with diluting their media NaCl concentration from 0.20 to 0.10 and 0.05 mol/L.
It was taken from reference [18].

2. Covalent multilayer hollow microspheres

2.1. Covalently crosslinking

The shell stability of the non-covalent multilayered hollow microspheres could be improved by changing their crosslinking nature from ionic or hydrogen bond to covalent under external stimuli (photo, heat, or oxidation), or based on carbodiimide chemistry or click-chemistry reaction, in which the covalently crosslinking bonds are formed between the inherent functional groups of the two assembled polymers (Fig. 4). In another process, the foreign crosslinkers are used to link the intralayers covalently.

2.1.1. Inherent functional groups

2.1.1.1. Photo-crosslinking. Caruso et al. fabricated the hollow polyelectrolyte microcapsules with diazo-resins (DAR) as polycation. The photosensitive nature of the DAR layers was exploited to construct highly stable, covalently attached films by exposure of the ionic self-assembled DAR/PSS multilayered films to UV-irradiation (Fig. 5) [20]. The mechanically robust polymerized multilayered films on the colloids and as free-

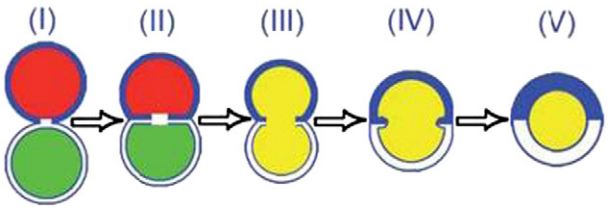

Fig. 3. Fusion mechanism of microcapsules: (I) Salt creates defects and pores in the contacting membranes; (II) pores enlarge by lateral tension; (III) the inner contents of neutral polymers mix, and (IV–V) the polyelectrolyte molecules in the membranes do not mix. The magnified areas show the changes in the membranes, including the decrease of charges and water content, the conformational change of the polyelectrolyte molecules from extended to coiled ones. Only 2 bilayers in each microcapsule are illustrated.
It was taken from reference [19].