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Layer-by-layer assembled biopolymer microcapsule with separate layer cavities generated by gas-liquid microfluidic approach

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ABSTRACT

In this work, a layer-by-layer (LbL) assembled biopolymer microcapsule with separate layer cavities is generated by a novel and convenient gas-liquid microfluidic approach. This approach exhibits combined advantages of microfluidic approach and LbL assembly method, and it can straightforwardly build LbL-assembled capsules in mild aqueous environments at room temperature. In particular, using this approach we can build the polyelectrolyte multilayer capsule with favorable cavities in each layer, and without the need for organic solvent, emulsifying agent, or sacrificial template. Various components (e.g., drugs, proteins, fluorescent dyes, and nanoparticles) can be respectively encapsulated in the separate layer cavities of the LbL-assembled capsules. Moreover, the encapsulated capsules present the ability as colorimetric sensors, and they also exhibit the interesting release behavior. Therefore, the LbL-assembled biopolymer capsule is a promising candidate for biomedical applications in targeted delivery, controlled release, and bio-detection.

1. Introduction

Microcapsules have been extensively studied in recent years due to their attractive applications in the biomedical field including controlled release [1–3], targeted delivery [4–6], enzyme immobilization [7], cell implantation [8], and bioreactors [9,10]. In particular, the biopolymer microcapsules are more suitable for biomedical applications because of their appealing properties such as biocompatibility, biodegradability, and non-toxicity [11–13]. For instance, Cook et al. studied the alginate-chitosan microcapsules as an enteric delivery vehicle for probiotic bacteria [14]. Shi and Tan reported that a chitosan/ethylcellulose complex microcapsule can be applied in controlled release of Vitamin D_2 [15].

At present, several methods have been developed for preparing capsules, including double emulsions method [16], complex coacervation [17,18], microfluidic approach [19,20], and layer-by-layer (LbL) assembly [21]. Among these methods, the microfluidic approach has received considerable attention because it can generate capsules with controlled shapes and monodisperse sizes, which would benefit subsequent applications of the resulting capsules [22,23]. It is noteworthy that a gas-liquid microfluidic approach has been employed to produce uniform-sized chitosan microcapsules containing quantum dots, which offers advantages such as the simple operation, no need for organic solvents, and the simplified post-treatment compared with typical liquid-liquid microfluidic approaches [24]. In addition to the above-mentioned research, little attention has been paid to the gas-liquid microfluidic approach on fabricating capsules.

Layer-by-layer assembly method has emerged as a simple and highly versatile method for surface modification, and now it is attracting considerable attention for biomedical applications [25–27]. It should be noted that layer-by-layer assembly is another important method for constructing microcapsules. In this method, capsules are usually produced by assembling oppositely charged polyelectrolytes onto sacrificial templates, then removing the templates [28–31]. For example, De Temmerman et al. used $CaCO_3$ particles as sacrificial templates to prepare dextran sulfate/poly-L-arginine-based polyelectrolyte microcapsules containing proteins via LbL assembly [32]. To date the LbL assembly method has been received much attention because it allows capsules to be generated in mild aqueous conditions [33]. Furthermore, the LbL assembly method can be employed to build polyelectrolyte capsules with multilayer structures that possess the capability to incorporate different types of biomolecules [34]. It should be noted that the above LbL assembly method required sacrificial templates in the preparation of capsules, which introduced complicated procedures including adding and removing the templates. However, little attention has been paid to fabricating capsules through a layer-by-layer assembly method without sacrificial templates. On the other hand, each layer of the above-mentioned polyelectrolyte multilayer capsules assembled

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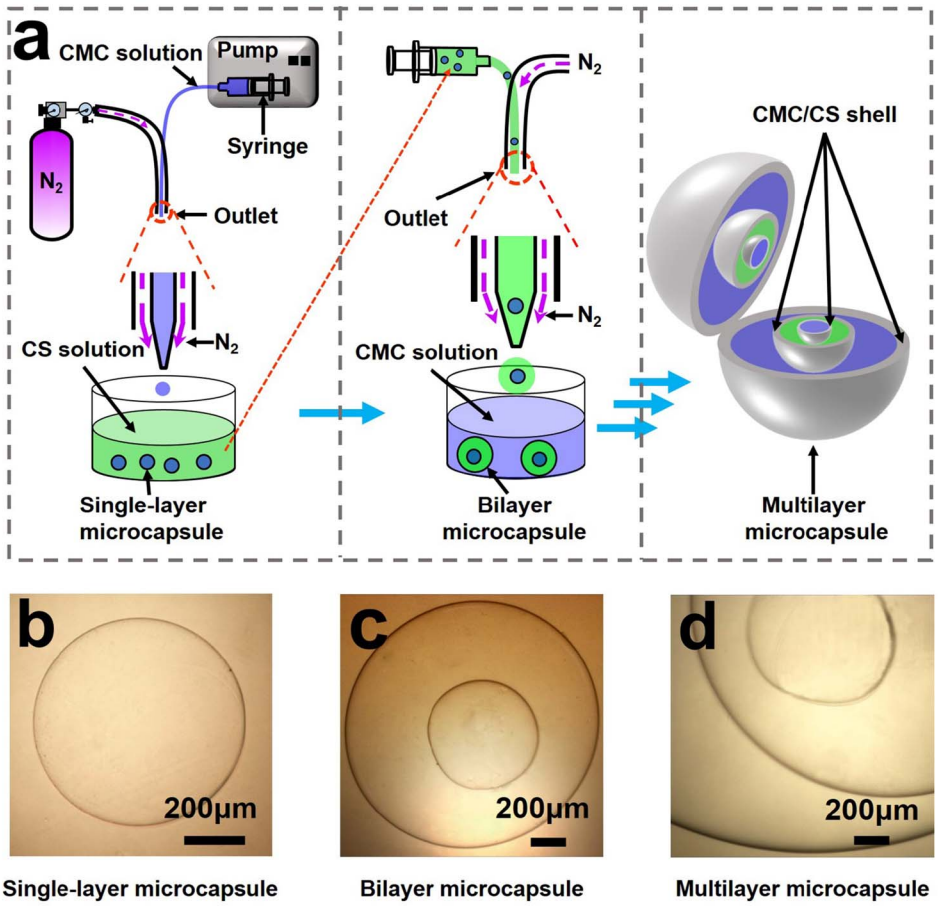

Fig. 1. (a) Schematic illustration of the fabrication of LbL-assembled CMC/CS capsules by the gas-liquid microfluidic approach. Optical micrographs of CMC/CS single-layer capsule (b), CMC/CS bilayer capsule (c), and CMC/CS multilayer capsule (d).

tightly, therefore it lacks sufficient layer cavity to accommodate different components (e.g., drugs or biomolecules). To our knowledge, no work has been done on constructing LbL-assembled capsules with separate layer cavities that could encapsulate different materials in different layers.

In this study we develop a novel and convenient gas-liquid microfluidic approach to fabricate the LbL-assembled biopolymer microcapsule with separate layer cavities. Particularly, this approach has combined advantages of the microfluidic approach and the LbL assembly method, and it can straightforwardly and conveniently build LbL-assembled capsules in mild aqueous environments at room temperature. In comparison with the liquid-liquid microfluidic approach, this approach has special benefits such as no need for organic solvents and emulsifying agents, and the simplified post-treatment. In contrast to the LbL assembly method, this approach can build the polyelectrolyte multilayer capsule with favorable cavities in each layer, and without the need for sacrificial templates. More importantly, the approach in this work can be used to respectively encapsulate diverse components (e.g., drugs, proteins, fluorescent dyes and nanoparticles) in different layer cavities of the LbL-assembled capsules, which is promising for application in drug carriers, targeted delivery, controlled release, biodetection, and bio-imaging.

2. Materials and methods

2.1. Materials

Chitosan (CS, 90% deacetylation degree), sodium carboxymethyl cellulose (CMC), sodium alginate (ALG), rhodamine B, fluorescein sodium, sodium salicylate, bovine hemoglobin, and sodium dodecyl sulfate (SDS) were purchased from Sinopharm Chemical Reagent Co., Ltd., China. Other chemicals were of analytical grade and were obtained from the commercial sources in China.

2.2. Preparation of LbL-assembled biopolymer microcapsules

Chitosan solution (0.5% *w/v*) was prepared by dispersing chitosan powder in distilled water, and adding 1.0 M HCl dropwsie with stirring to dissolve the chitosan, then adjusting pH to 5.0 with 1.0 M NaOH, finally filtering the solution to remove undissolved particles. Carboxymethyl cellulose solution (0.5% *w/v* and 1% *w/v*) was prepared by dissolving carboxymethyl cellulose powder in distilled water, and then adjusting pH to 5.0 with 1.0 M HCl.

We prepared layer-by-layer assembled CMC/CS capsules by a gas-liquid microfluidic approach. To begin with, we built the first gas-liquid microfluidic device using dual-coaxial quartz glass capillaries. The outlet of this gas-liquid microfluidic device was produced by inserting a cylindrical quartz glass capillary (600 μm in inner diameter, 800 μm in outer diameter) with a cone opening (200 μm in diameter) in a square quartz glass capillary (1.0 mm in inner dimension). The other end of the cylindrical quartz glass capillary was connected to a syringe pump (LP215, Xin He Feng Medical Technology Co., China), while the other end of the square quartz glass capillary was connected to a N_2 tank. Then, the CMC solution (1% *w/v*) was injected in the microfluidic device through the syringe pump at flow rate of 4.0 mL/h, and the solution was sheared into little droplets by N_2 with a specific flow rate (e.g., 0.7 L/min) when it flowed through the outlet of the microfluidic device. Subsequently, the little droplets fell in the CS solution (0.5% *w/v*) to generate CMC/CS single-layer capsules.

Next, the above CS solution containing the single-layer capsules was injected in the second gas-liquid microfluidic device, which possessed a bigger size compare to the first device, by the syringe pump at flow rate