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Hierarchically organization of biomineralized alginate beads for dual stimuli-responsive drug delivery

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ABSTRACT

Compartmentalized biomineralized alginate beads ranging from the micro to the visible scales with thermal- and pH-responsive drug delivery properties have been prepared via a one-step method in the present paper. Hollow multilayer microcapsules made of aliphatic poly(urethane-amine) (PUA) and sodium poly(styrenesulfonate) (PSS) serve as drug container to slow down the drug release. The results indicate that internal hollow multilayer microcapsules could hinder the permeation of the encapsulated Vitamin B_2 (VB_2) and retard the initial burst release of VB_2. In addition, the drug release of compartmentalized biomineralized alginate beads exhibit distinguished pH- and thermal-dependent property due to pH-responsive alginate and the thermal-responsive aliphatic PUA. The drug release decreases when decreasing the pH value because the compact construction of alginate and biomineralized layer could prevent VB_2 release from the beads. Moreover, the drug release is higher at 55 °C than that at 37 °C for the sake of the shrinkage of aliphatic PUA above its lower critical solution temperature (LCST). The results demonstrate that the compartmentalized biomineralized alginate beads show great potential as smart materials for controllable drug delivery.

1. Introduction

Alginate is the salt form of alginic acid obtained from brown marine algae, which is a well-known polysaccharide that shows biocompatibility, nontoxicity, as well as bacteriostatic [1,2]. It is known to be a pH sensitive, biodegradation natural hydrogel material with relatively low cost [3]. On the other hand, considerable research efforts have been focused on stimuli-responsive polymeric-hydrogels due to their wealth of potential applications in areas such as drug delivery, microreactors, and tissue engineering [4–8]. Temperature and pH are important signals for phase transitions in hydrogels because they are important environment factors in biomedical and physiological indexes [9]. We have reported in our previous work the temperature/pH-responsive drug-release behavior of calcium alginate/PNIPAAM semi-interpenetrating (semi-IPN) beads [10]. However, these Ca alginate beads have limitations of rapid erosion and initial burst release at neutral pH for dual-stimuli-responsive drug delivery. In the past decade, biomineralization/biomimetic mineralization, as a novel, mild and green platform technology for hybrid materials synthesis [11,12], had been successfully utilized to prepare robust and bioactive organic-inorganic hybrid capsules. Our group [13,14] has also reported the temperature/pH responsive drug release of biomineralized alginate beads. Drug release was found to be retarded under neutral conditions, however, there is no significant effect on rapid erosion and initial burst release.

Over the past few decades, hollow microcapsules are of considerable interest because of their wide range of applications in drug delivery system [15], therapeutics [16–18], micro bioreactors [19], biocatalysts [20,21], and biomedicine [22,23]. Inspired by the cells' structure, compartmentalization capsules with hollow microcapsules were studied, artificial cells have been created with the aim to mimic metabolic processes [24]. Compartmentalization is one of the techniques that cells adopt to enable a high level of control over biochemical process. Jiang et al. [25] have prepared the multicompartment hybrid double membrane microcapsules and constructed a multienzyme system through the synergy of LbL self-assembly and biomineralized. In addition, stimuli-responsive materials were used to widen the usage scope of compartmental systems. Costa et al. [26] have presented compartmentalized alginate beads with temperature and magnetic-based responsiveness. The results showed that compartmentalized structures could tune the permeability of alginate base matrix and control initial burst release effectively.

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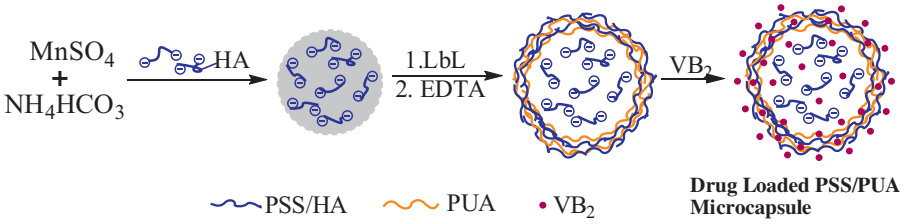


Scheme 1. Schematic illustration of preparation process of drug loaded PSS/PUA microcapsules.

This study is aiming to prepare a dual responsive biomineralization alginate bead with hierarchical construction. At the same time, the introduction of inorganic minerals and hollow microcapsules could retard the erosion and initial burst release of alginate. In this work, compartmentalized biomineralized alginate beads with thermal- and pH-responsive drug delivery properties and hierarchical organization ranging from the micro to the visible scales were prepared via a one-step method (as illustrated in Schemes 1 and 2). Hollow multilayer microcapsules made of aliphatic PUA and PSS served as drug container to slow down the drug release. Aliphatic PUA shows a thermally induced reversible transition property in aqueous solution at the lower critical solution temperature (LCST) [27–30]. The final bead is an external biomineralized bead containing internal hollow microcapsules. Without any poisonous organic solvent, this method is facile and environmentally friendly [31,32]. More importantly, compartmentalized biomineralized alginate beads also have the key advantage that such beads display smart tunable permeability and hinder the initial burst release of VB_2 effectively. In addition, the hierarchically beads shows pH- and thermal-responsive drug delivery property because of the introduction of thermal-responsive aliphatic PUA and pH-responsive alginate.

2. Materials and methods

2.1. Materials

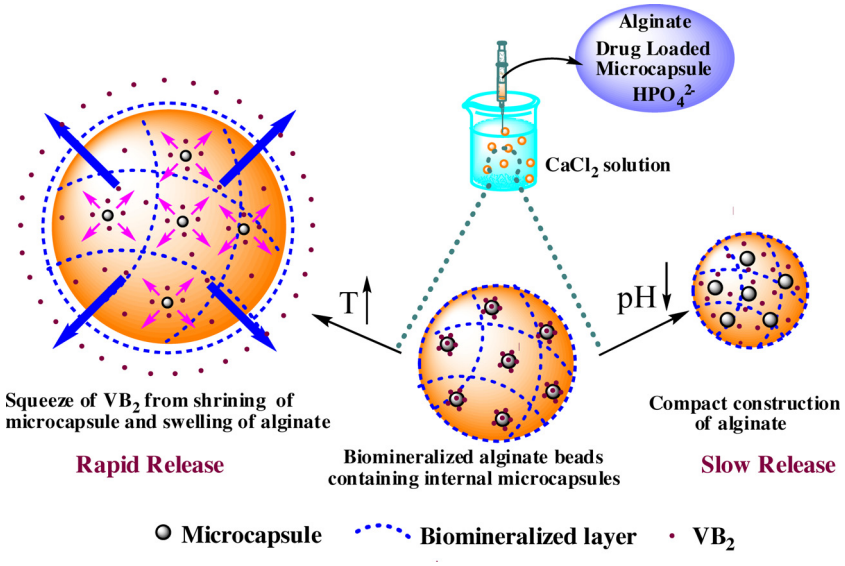
Sodium alginate (viscosity of 1% solution at 20 °C, Shanghai Chemical Reagent Co. Ltd, China), sodium poly(styrene sulfonate) (PSS, M_w = 70,000, Sigma–Aldrich Co.), vitamin B_2 (VB_2, Tianjin Damao Chemical Reagent Factory, China), sodium hyaluronate, $CaCl_2$, NH_4HCO_3 and $MnSO_4$ were used as received. The synthesized of aliphatic PUA was according to literature [12]. The LCST of aliphatic PUA is 50 °C as measured by a temperature-variable UV–vis spectrometer. The urethane content is 41.86%. M_w and PDI of the aliphatic PUA are 1.2×10^4 and 1.67, respectively.

2.2. Preparation of drug loaded hollow microcapsules

To prepare the $MnCO_3$ particles, sodium hyaluronate (100 mg) was completely dissolved in $MnSO_4$ (0.016 M) under magnetic agitating, into which isopropanol (1 mL) and NH_4HCO_3 aqueous solution (0.16 M) were rapidly poured at 50 °C and stirred for 15 min. The precipitated $MnCO_3$ were washed and collected by centrifugation. The $MnCO_3$ particles were immersed alternately in aliphatic PUA and PSS solutions (2 mg mL^{-1}) for 15 min, then washed and centrifugated. This process was repeated until four bilayers had been assembled. After the $MnCO_3$ cores were chelated by incubating in ethylene diaminetetraacetic acid disodium salt (EDTA) solution (0.1 M, pH 7.2) for twice, each for 30 min, hollow microcapsules were obtained. Then, the hollow microcapsules were transferred into 4 mL of VB_2 solution (0.25 mg mL^{-1}) for 12 h at 30 °C.

2.3. Preparation of compartmentalized biomineralized alginate beads

Solution composed of sodium alginate (1.5%, w/v) containing drug loaded hollow microcapsules, NaCl (0.15 M), and Na_2HPO_4 (0.1 M) were prepared. The mixed solution was transferred



Scheme 2. Schematic illustration of preparation and drug release mechanism of biomineralized alginate beads containing internal microcapsules.