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Regular Article

Facile fabrication of robust polydopamine microcapsules for insulin delivery

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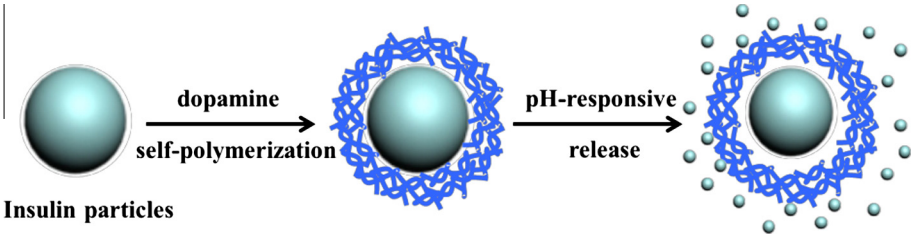
GRAPHICAL ABSTRACT



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ABSTRACT

Inspired by the composition of adhesive proteins in mussel, a facile, low-cost, and green approach to construct robust polydopamine (PDA) microcapsules as carriers for insulin delivery is developed. The morphology and shell thickness of the capsules could be tuned by varying the concentration of dopamine or the pH of Tris-HCl buffer. The PDA capsules are stable enough for long-term storage and transportation in practical application. The fluorescent property of PDA capsules labeled with FITC is beneficial in monitoring the safety and efficacy of drug carriers. Furthermore, the PDA shell coated insulin particles exhibit pH-responsive release behavior, making them promising for the oral administration of insulin in diabetic patients.

1. Introduction

Polymer capsules have attracted considerable attention due to their extensive uses in the fields of drug delivery, catalysis, cosmetic, food, and agriculture [1–5]. Several methods, such as self-assembly, phase separation, polymerization, and template-assisted method, have been developed to prepare a range of polymer capsules. Among them, the layer-by-layer (LbL) assembly technique based on templating synthesis is considered the dominant approach to construct polymer capsules due to its advantages of precise control over the size, composition, wall thickness, and further functions [6–11]. The main principle of LbL assembly is the sequential adsorption of assembly components, followed by removal of the template cores [12,13]. With the increasing diversity of assembly components, a variety of interactions including electrostatic interaction [14], hydrogen bonding [15,16], charge transfer [17], and covalent bonding [18–20] have been used as the driving forces for LbL assembly. Even though, it could not be ignored that the disadvantage of LbL assembly is that multistep procedures make it labor-intensive and time-consuming. Thus, the deposition of polymer films onto template cores through a single-step technique would provide direct benefits for the formation of capsules, minimizing the labor, cost, and assembly complexity.

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Recently, a robust surface-coating strategy based on the oxidative self-polymerization of dopamine has been employed to construct polymer films [21–23]. Dopamine, a simple catecholamine better known as a neurotransmitter, was shown to self-polymerize in a weak alkaline solution inspired by the composition of adhesive proteins in mussels. Polydopamine (PDA) has been demonstrated an effective adhesive that could attach to almost all material surfaces (metals [24], oxides [25], ceramics [26], polymers [23], carbon nanotubes [27], and magnetite nanoparticles [28]). Moreover, active catechol, amine, and imine groups on the surface of PDA films support a variety of reactions with organic species for the creation of functional ad-layers. Since this approach to prepare PDA films is relatively simple, gentle, and controllable, it has been successfully developed to template the formation of hollow PDA capsules [29] with various template particles, such as SiO_2 [30,31], polystyrene (PS) [31], and $CaCO_3$ particles [32–34]. It should be mentioned that the removal of SiO_2 or PS-based sacrificial templates requires harsh chemical reagents, which has limited the application of PDA capsules in biomedical field. An alternative is $CaCO_3$ particles that could be easily dissolved in an aqueous EDTA solution. However, it is still a challenge to obtain PDA capsules with good regularity and dispersion.

In the present work, we explored robust PDA microcapsules as carriers for the delivery of insulin. PDA coated insulin delivery system was constructed through the spontaneous oxidative polymerization of dopamine onto insulin particles, and its insulin release behavior with response to pH was studied in detail (Scheme 1). To investigate the physicochemical properties of PDA microcapsules, monodisperse $MnCO_3$ microparticles were employed. The PDA microcapsules were prepared by the self-polymerization of dopamine onto $MnCO_3$ particles, followed by removal of the template core. This approach to fabricate polymer capsules offers a number of distinct advantages. Firstly, as-prepared PDA capsules are shown to be quite regular, monodisperse, and robust. The shell thickness of the capsules can be tuned by changing the concentration of dopamine or the pH of Tris-HCl buffer. Secondly, the $MnCO_3$ templates can be dissolved under mild EDTA solution, avoiding the use of any harsh chemical reagent during the core removal step. Thirdly, PDA capsules can be obtained using a single-step polymerization process, eliminating the sequential deposition process typically required in conventional LbL assembly. Finally, PDA capsules can be easily modified with FITC molecules to show fluorescence property, which is beneficial in monitoring the safety and efficacy of drug carriers. Overall, this work provides a new approach for the preparation of PDA capsules with controlled shell thickness and defined physicochemical properties. Moreover, these capsules are promising for oral insulin delivery.

2. Experimental section

2.1. Materials

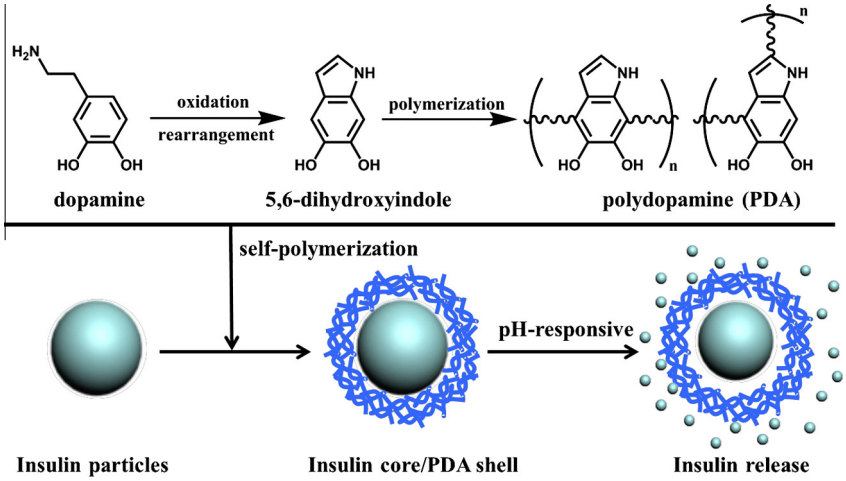
Dopamine hydrochloride, tris(hydroxymethyl)aminomethane (Tris), and fluorescein isothiocyanate (FITC) were purchased from Sigma Aldrich. Insulin from bovine pancreas, Coomassie brilliant blue G250, disodium hydrogen phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2PO_4), and sodium chloride (NaCl) were obtained from Solarbio Corporation. Sodium hydroxide (NaOH), hydrochloric acid (HCl), manganese sulfate ($MnSO_4$), ammonium hydrogen carbonate (NH_4HCO_3), ethanol, potassium bromide (KBr), and ethylenediaminetetraacetic acid (EDTA) were purchased from Sinopharm Chemical Reagent Co., Ltd. Ultrapure water used in all experiments was prepared in a Milli-Q apparatus (Millipore) and had a resistivity higher than 18.2 MΩ cm.

2.2. Synthesis of $MnCO_3$ microparticles

$MnCO_3$ microparticles with narrow size distribution were synthesized according to the co-precipitation method described in the literature [35,36]. Briefly, 100 mL of $MnSO_4$ in ultrapure water (0.016 M) was mixed thoroughly with 10 mL of ethanol under ultrasound treatment for 10 s. The resulting solution was mixed with 100 mL of NH_4HCO_3 in ultrapure water (0.16 M) under ultrasound treatment for 30 s. Then, as-prepared solution was quiescent at ambient condition for 30 min. The $MnCO_3$ particles with spherical shape about 4.5 μm in size were obtained followed by triple rinsing with water.

2.3. Preparation of polydopamine (PDA) microcapsules with $MnCO_3$ templates

$MnCO_3$ microparticles were used as sacrificial templates to prepare PDA capsules. In a typical procedure, $MnCO_3$ particles were prewashed with Tris-HCl buffer (10 mM, pH 8.5) via several centrifugation and dispersion cycles. The resulting $MnCO_3$ particles were resuspended in Tris-HCl buffer (10 mM, pH 8.5) of dopamine hydrochloride (1 mg mL^{-1}), followed by shaking (900 rpm) at ambient condition for 12 h. Then, the dark brown colored particles were centrifuged (3000 rpm, 5 min) and washed with fresh Tris-HCl buffer for 3 times. Finally, the PDA capsules were obtained



Scheme 1. Schematic illustration for the formation of PDA coated insulin delivery system and the pH-responsive insulin release.