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Reversible thermal-tunable drug delivery across nano-membranes of hollow PUA/PSS multilayer microcapsules

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ABSTRACT

In this paper, hollow aliphatic poly(urethane-amine) (PUA)/sodium poly(styrene sulfonate) (PSS) multilayer microcapsules with smart nano-membranes were prepared for smart drug delivery. Thanks to the variation of the electrostatic interaction between aliphatic PUA and PSS, and the shrinkage of aliphatic PUA above its LCST, the hollow microcapsules displayed the distinguished pH- and thermal-dependent drug release properties. SEM results indicated that the microcapsule membranes had better thermal-responsiveness at pH 4.5 than that at pH 7.4. More importantly, the microcapsule membranes exhibited reversible thermal-tunable drug release property at pH 4.5 with significant response to temperature change for the sake of the regularly shrinkage of aliphatic PUA above its LCST. The results suggest that the prepared hollow microcapsules can be employed as the novel "smart" nano-membranes for the controllable drug delivery.

1. Introduction

Stimuli-responsive microcapsule membranes with precisely controlled size and membrane thickness have attracted considerable attention due to their unique smart properties and potential applications in biomedical area [1,2]. These smart microcapsules are fabricated by layer-by-layer (LbL) technique, which by alternating deposition of oppositely charged polyelectrolyte onto template particles followed by selective removal of the templates [3,4]. Polyelectrolyte multilayer microcapsules prepared by LbL technique have advantages of well-controlled size, finely tunable multilayer thickness, variable compositions and functions, which have been extensively employed in many biomedical areas such as drug delivery and tissue engineering [5–8].

Among the various stimuli-responsive microcapsules, reversible pH- and thermo-responsive microcapsules are attracting an ever-increasing interest in drug delivery area for the sake of their excellent controllable delivery properties [9,10]. So far, pH-responsive microcapsule membranes have been widely studied, which dues to the protonation or deprotonation of the polyelectrolyte groups [9–12]. In generally, the majority of pH-responsive microcapsules are reversible, which can undergo controllable volume changes. For example, Sukhorukov et al. prepared reversible pH-dependent hollow multilayer microcapsules made of poly(allylamine hydrochloride) (PAH) and poly(methacrylic acid sodium salt) (PMA) [9]. On the other hand, poly(N-isopropylacrylamide) (PNIPAAm) is the most popular thermo-responsive polymer for fabricating thermo-responsive microcapsules in biomedical area [13–15]. Poly(diallyldimethylammonium chloride) (PDADMAC) has also been studied as the thermal-responsive component to prepare thermal-dependent polyelectrolyte multilayer microcapsules [16,17]. However, there have been few reports on the reversible thermo-responsive release properties concerning these hollow microcapsule membranes. Moreover, the poor degradability and potential cytotoxicity of PNIPAAm and PDADMAC should not be ignored for their biomedical applications.

In the present work, we intend to prepare thermal-reversible hollow multilayer microcapsules made of aliphatic poly(urethane-amine) (PUA) and sodium poly(styrene sulfonate) (PSS) for controllable drug delivery. Aliphatic PUA has attracted much attention in biological area, because of its thermally induced transition property in aqueous solution at its lower critical solution temperature (LCST) [18,19]. Moreover, the amine group of aliphatic PUA would change to the protonated amino forms with the decreasing of pH value [20,21]. Therefore, aliphatic PUA shows distinct pH- and thermal-dual responsive property, which has attracted a great deal of interest in smart drug delivery area [22,23]. More importantly, aliphatic PUA also represents as a novel self-assembly component of the LbL technique for its positive charge, biodegradability, biocompatibility and noncytotoxicity [24]. In the preliminary work, we had prepared pH- and thermal-dual responsive aliphatic PUA under compressed CO_2 without catalyst, and then hollow PUA/PSS microcapsules were obtained via the self-assembly of aliphatic PUA and PSS [12]. However, the

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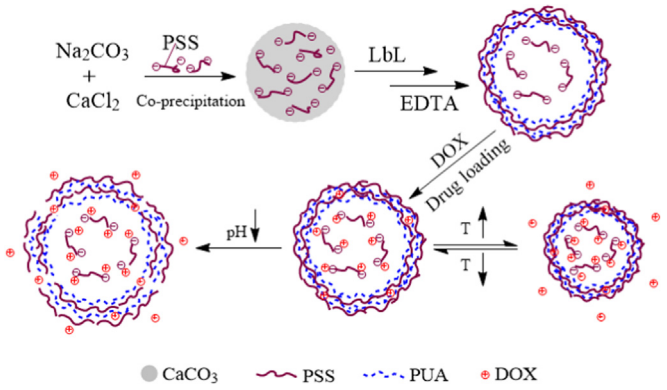

Scheme 1. Schematic illustration of the fabrication of hollow thermal-reversible PUA/PSS multilayer microcapsules.

reversible thermal-tunable properties of the prepared hollow microcapsules were not satisfactory.

In this paper, pH- and thermal-dual responsive aliphatic PUA with reversible thermal-tunable properties had been prepared under compressed CO_2 using salen–Mn complex as the catalyst. Then, hollow PUA/PSS multilayer microcapsules with reversible thermal-tunable nano-membranes were prepared via LbL method, as illustrated in Scheme 1. Salen–Mn complex (the structure is illustrated in Fig. 1) has high catalytic activity for the copolymerization of 2-methylaziridine and CO_2. Compared with the copolymerization of 2-methylaziridine and CO_2 without catalyst [12], salen–Mn complex could ensure the high center electron cloud density for the insertion of CO_2 into the copolymer, which gives the resulting aliphatic PUA with a high content of urethane units (49.57%, however, the value for PUA prepared without catalyst is only 41.86%). The increase in urethane content could lead to a relatively lower LCST for the aliphatic PUA synthesis [22,23], which is significant in obtaining the PUA with LCST closing to human body temperature. More importantly, the relatively high center electron cloud density derived from salen–Mn complex has a great effect on decreasing the stereoregularity of the resulting PUA, and then obtaining aliphatic PUA with a clearly sharp hysteresis and the excellent reversible thermal-tunable properties. The formation of microcapsules was based on consecutive coating of two oppositely charged polyelectrolytes (aliphatic PUA and PSS) on PSS-doped $CaCO_3$ microparticles, followed by $CaCO_3$ core dissolution. Thanks to the electrostatic interaction and hydrogen bonding under weak-acid condition between aliphatic PUA and PSS, hollow microcapsule membranes were obtained successfully. The pH- and

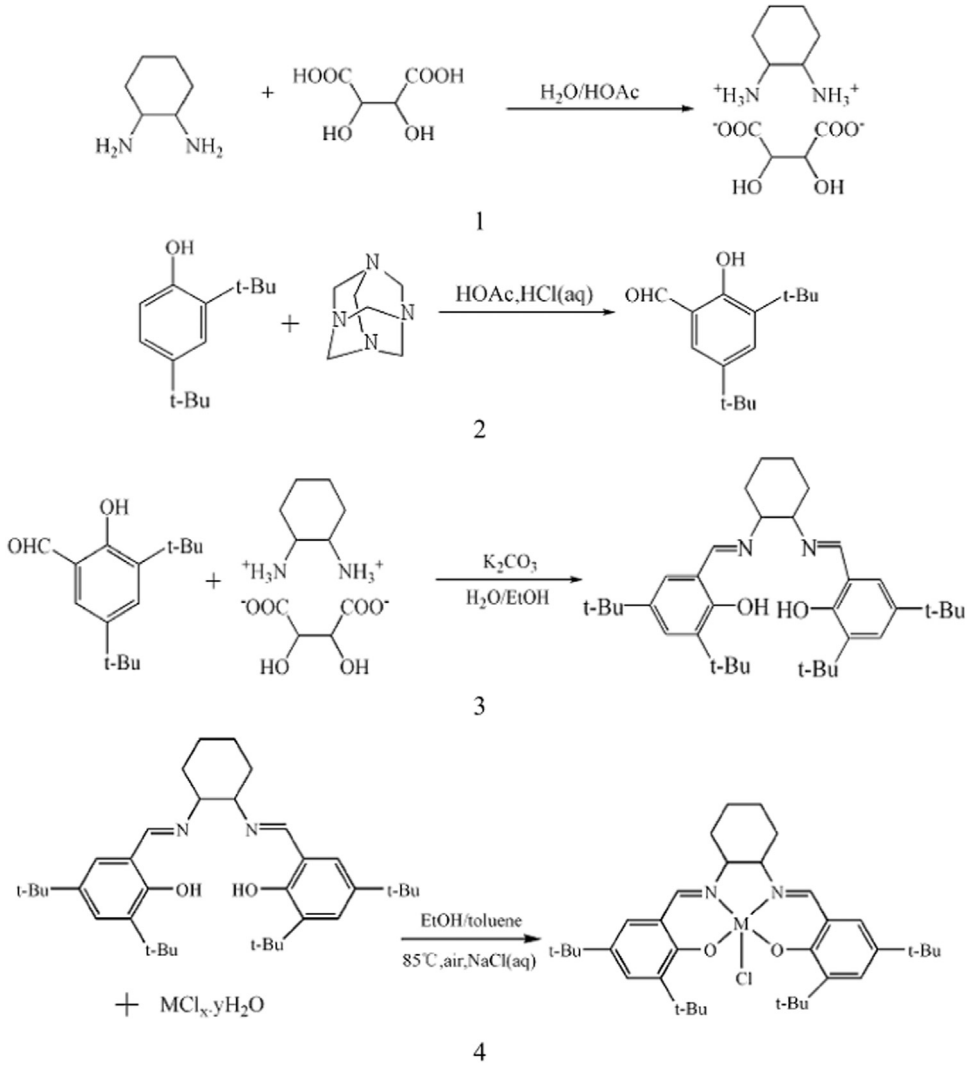

Fig. 1. Synthetic illustration of salen–Mn catalyst. 1, 2, 3 and 4 refer to the preparation of 3,5-di-tert-butylsalicylaldehyde, (R,R)-1,2-diammoniumcyclohexanemono-(+)-tartrate, (R,R)-N,N′-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine and (R,R)-N,N′-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino manganese (III) chloride, respectively.