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Voltage-Responsive Vesicles Based on Orthogonal Assembly of Two Homopolymers

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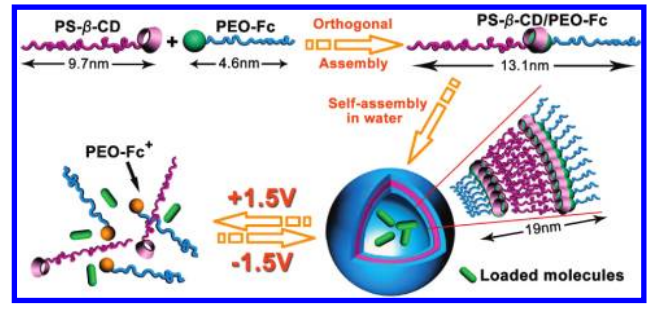
Abstract: Two end-decorated homopolymers, poly(styrene)-β-cyclodextrin (PS-β-CD) and poly(ethylene oxide)-ferrocene (PEO-Fc), can orthogonally self-assemble into a supramolecular diblock copolymer (PS-β-CD/PEO-Fc) in aqueous solutions based on the terminal host−guest interactions. These assemblies can further form supramolecular vesicles, and their assembly and disassembly behaviors can be reversibly switched by voltage through the reversible association and disassociation of the middle supramolecular connection. The vesicles possess an unprecedented property that their assembly or disassembly speed can be controlled by the applied voltage strength. Luminescence spectroscopy demonstrates that the vesicles act as nanocapsules carrying molecules within their hollow cavities and that the external voltage strength accurately regulates the drug release time.

Stimuli-responsive polymeric vesicles have recently attracted significant attention because of their promising applications in the fields of controllable drug transport and gene delivery.[1] As a type of intelligent assembly, they can undergo reversible physical or chemical changes and adjust their aggregated nanostructures in response to external stimuli such as pH,[2] light,[3] temperature,[4] molecules,[5] and redox.[6] In a cell biomembrane system, a typical stimuli-responsive life phenomenon is the triggering of lipid bilayer activities, like membrane fusion and disassembly, by membrane potential. Thus, developing new electrostimuli-responsive assemblies is conducive to elucidating and biomimicing the biological activities of the bilayers. Moreover, artificial voltage-responsive vesicles are well-suited to drug encapsulation and controlled release, and electrical stimulation is easy to realize in cells and the human body.

At present, a general approach to making responsive vesicles is based on the fabrication of a block copolymer. Recently, a "block-copolymer-free" strategy has been pioneered by O'Reilly and Weck's groups. They have synthesized pseudocopolymers based on the orthogonal self-assembly of two or three homopolymers by supramolecular interaction at chain ends, such as H-bonding and a metal−ligand bond.[7] Alternatively, host−guest interaction is also an adaptive noncovalent interplay for fabrication. For example, β-cyclodextrin (β-CD) can exactly form a 1:1 inclusion complex with ferrocene (Fc). Normally, uncharged Fc species or its derivatives are strongly bound in the cavity of β-CD, whereas the charged species (Fc^+) dissociate rapidly from the cavity, and this process can be reversibly switched under external voltage.[8] To realize the polymer vesicles possessing voltage responsiveness, poly(styrene) with β-CD end-decoration (PS-β-CD) and poly(ethylene oxide) containing Fc uncharged end-capping (PEO-Fc) were designed and synthesized, and their self-assembly behavior in water was studied in detail. It is expected that this supramolecular copolymer connected through terminal host−guest inclusion would reversibly undergo an association and dissociation effect, inducing a desirable assembly and disassembly of vesicles upon voltage, as shown in Scheme 1.

Scheme 1. Structure of PS-β-CD and PEO-Fc and Schematic of the Voltage-Responsive Controlled Assembly and Disassembly of PS-β-CD/PEO-Fc Supramolecular Vesicles



To date, several reports have been shown for the fabrication of block-copolymer-free vesicles, but these systems generally involved an inactive connection and irreversible structural transition.[7a,b] In this study, a new type of macromolecular adduct, denoted by PS-β-CD/PEO-Fc, is shown to have an active connection in response to external stimuli and possess desirable solubility in water. (For details of the synthesis and characterization, see the Supporting Information.)

Dripping an equal amount of PEO-Fc aqueous solution to PS-β-CD enables self-assembly, which is suggested by the formation of a slightly turbid colloidal mixture. The critical aggregate concentration (CAC) of PS-β-CD/PEO-Fc was ~0.28 mg/mL, monitored by the surface tension measurement. The size of the aggregates was determined by dynamic light scattering (DLS) to be ~102 nm in average radius (Figure S1−S3). To further investigate their nanostructures of the PS-β-CD/PEO-Fc complex, transmission electron microscopy (TEM) was used to visualize the aggregates. The results in Figure 1a clearly show that these supramolecular assemblies have a typical vesicular structure, as evidenced by the distinct contrast between the dark periphery and the lighter central part. The mean wall thickness is ~19 nm, which is in line with the interdigitated molecular length of the PS-β-CD/PEO-Fc pseudocopolymer (13.1 nm by CPK model), indicating the orthogonal assembly in the bilayer membrane (Scheme 1). It is worth noting that these vesicles were quite stable for 3 months without any external stimuli. Surprisingly, upon +1.5 V voltage stimuli, the homopolymer of PEO-Fc was oxidized into charged PEO-Fc^+ species, which could dissociate from PS-β-CD; thus the vesicles partially disassembled and the membrane started to disrupt within 2 h (Figure 1b). Furthermore, the vesicles could completely self-disaggregate into

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small fragments (several nanometers) after 5 h of electrostimulation, indicating the whole disassembly of the vesicular structure (Figure 1c). The disassembly system can be reassembled by exerting a reductive voltage of −1.5 V, and vesicles with similar shapes and sizes can be reformed because the reductive PEO-Fc^+ loses one electron and associates with PS-β-CD again.

To further elucidate the reversibility, cyclic voltammetric (CV) analysis was used. As expected, the redox curve demonstrates that the vesicles underwent an electrochemically controlled assembly−disassembly process (Figure S4a). With no external electric field, the CV profile exhibited a +0.41 V half-wave potential, indicating PS-β-CD/PEO-Fc complex formation. In contrast, upon oxidative voltage, Fc changes to an Fc^+ moiety, which results in a remarkable decrease of half-wave potential to +0.30 V concomitant with a current rise from 1.8 to 4.1 μA, indicating a dissociated process between PS-β-CD and PEO-Fc.[9] In the presence of an opposite voltage for reducing the Fc^+ moiety, the analogous CV profile (+0.40 V) is restored. By applying an oscillating electric field to the supramolecular vesicles, this reversible procedure could be cycled many times (Figure S4b). The average radius of the assemblies jumping repeatedly from 102 to 7 nm upon alternating potential (+1.5 and −1.5 V) by DLS results confirms the voltage-responsive self-assembly and disassembly behavior of the polymer vesicles (Figure S4c). In addition, notably, tuning the external voltage from +0.50 to +5.0 V can accelerate the aggregated disruption from 680 to 12 min. It was therefore proven that the orthogonal assembly of two simple homopolymers endows the formed vesicle with favorable voltage responsiveness.

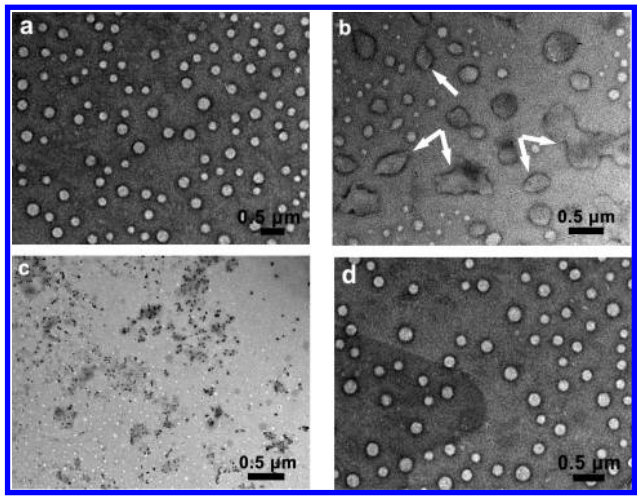

Figure 1. TEM images of the reversible assembly and disassembly of the voltage-responsive PS-β-CD/PEO-Fc vesicles upon electric stimuli: (a) no external voltage, (b) +1.5 V (after 2 h), (c) +1.5 V (after 5 h), and (d) −1.5 V (after 5 h). All vesicle solutions were at 0.30 mg/mL in water.

As demonstrated, this kind of voltage-responsive vesicles can be employed to encapsulate and release small molecules. Using fluorescent Rhodamine B (RB) as a model, RB-loaded PS-β-CD/PEO-Fc vesicles were prepared to perform controlled release experiments. The assemblies solution was dialyzed against the deionized water until the water outside the dialysis tube exhibited negligible RB fluorescence. To understand the release behavior of the RB molecules upon various voltages, a solution of RB-loaded vesicles was kept in a dialysis tube and then exposed to an external potential. Thus, the release of RB was monitored by the increasing fluorescence of the solution outside the tube. From the curve in Figure 2, an abrupt release (~32 min) was observed upon application of high voltage (+4.0 V). More importantly,

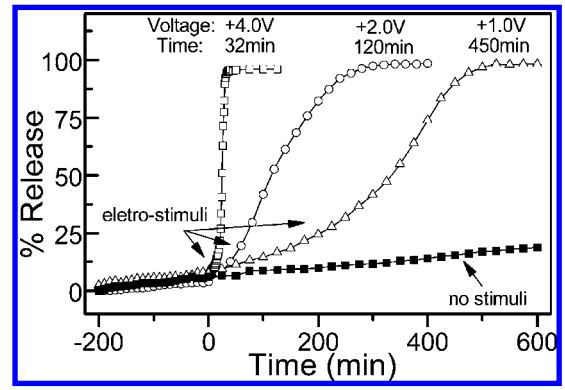

Figure 2. Controlled release of RB from the supramolecular vesicles upon various voltage stimuli as a drug nanocapsule and in comparison with the free release of RB from the vesicles without stimuli.

the RB release time could be precisely tuned through variation of the external potential strength. Encapsulated molecules showed a slower release (~120 min) upon lower voltage stimuli (+2.0 V) and the slowest rate (~450 min) at the lowest voltage (+1.0 V). Moreover, triggered by different voltages, the release quantities of RB could all reach ~100%, comparing favorably with other polymer nanocapsulated systems. It should be pointed out that, even by exerting a voltage of +0.4 V (slightly greater than the standard electrode potential: $Fc^+ + e^- \leftrightarrow Fc$, $E^\circ = 0.32$ V), the vesicles were still able to undergo a distinct self-disruption, indicating good sensitivity to stimuli and mild operation conditions. In contrast, in the absence of external potential, the capsules only showed a low-level free release that is less than 25% within 10 h. Thus, the conclusion can be drawn that PS-β-CD/PEO-Fc supramolecular vesicles can serve as nanocapsules that will release functional molecules or drugs over a tunable time and quantity through artificial voltage control.

In summary, the orthogonal self-assembly of two end-decorated homopolymers and their voltage-responsive reversible assembly and disassembly were investigated. The new supramolecular vesicular system is highly sensitive to the electric response mode, and various voltage strengths can manipulate the self-disaggregation speed of these vesicles. Considering the active nature of the host−guest linker existing in the PS-β-CD/PEO-Fc pseudocopolymer and the stimulus conditions readily realized, it is anticipated that this kind of voltage-responsive supramolecular assembly has potential to function as drug-loaded nanocapsules, enabling a new type of electrochemical therapeutics.

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Supporting Information Available: Synthesis, characterization, and other experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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