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Controllable exploding microcapsules as drug carriers†

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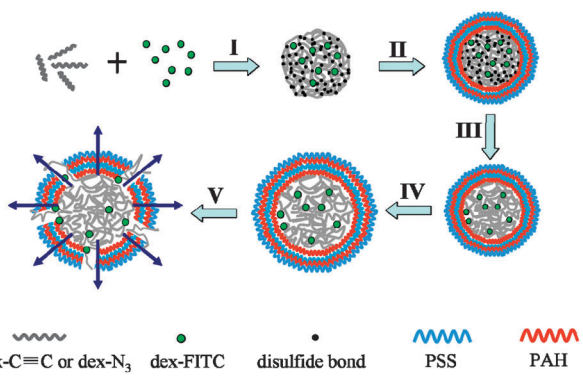
Controllable exploding polyelectrolyte microcapsules were developed by layer-by-layer assembly of poly(allylamine hydrochloride) (PAH) and poly(sodium 4-styrenesulfonate) (PSS) on a dextran microgel core containing a cleavable disulfide bond fabricated *via* click chemistry. The microcapsules can explode upon the injection of DTT with an explosive release of the drug.

Drug delivery methods can have a significant effect on the therapeutic efficacy of the drug.[1] Conventional methods for drug delivery, such as oral and injecting delivery systems always produce a rapid initial increase of drug concentration to a peak above the therapeutic range, followed by a fast decrease in concentration to a level below the range of effective therapy. The initial high concentration can cause a serious risk of toxicity and related complications for potent drugs.[2] Controlled drug release therefore focused on achieving a constant release of drug over a long period. However, under some conditions, sustained or continuous release is not optimal. Recently, cancer therapy has focused on modifying the drug carriers with targeting moieties.[3–5] Typically, these devices are capable of targeting a certain tissue and releasing the drug over a period ranging from minutes to months or years. But these devices also have disadvantages, in that the loaded drug suffered sustained release in the circulation of blood before reaching the target tissue. It is desirable for therapies that the drug can be suddenly released from the drug carrier at a certain location after being hosted for a while during the process of blood circulation. Thus, to develop drug carriers that can reach an appointed target before explosive drug release is critically important.

Recently, De Geest *et al.* proposed a self-exploding microcapsule, which consists of a degradable dextran-hydroxyethyl methacrylate microgel core loaded with a macromolecular drug and a surrounding semipermeable membrane.[6–8] The explosion-like release of the drug was realized by adjusting the pH to 13–14 *via* the addition of 1 M NaOH solution. When the microgel core degrades by hydrolysis of carbonate esters, a solution of free polymers is formed in the microcapsule, leading to a high osmotic pressure, which forces the surrounding membrane to explode. However, for biomedical applications, the core destruction has to take place under physiological conditions. Whether a similar explosion can occur at physiological pH (7.4) remains a big challenge.[9]

Here, we aimed to design controllable exploding microcapsules, which are able to achieve sudden drug release under physiological conditions. First, through "click chemistry", biodegradable dextran microgels containing disulfide bonds were prepared. The obtained microgel is called a dextran click microgel. Secondly, a layer-by-layer (LbL) membrane was applied to coat the prepared microgels. As shown in Scheme 1, the so-called "controllable exploding" microcapsule consists of a biodegradable microgel and a surrounding LbL membrane. The synthesis route of dextran click microgels based on alkyne-modified dextran (dex-C≡C) and azide modified dextran (dex-N_3) is represented in Scheme 2. Dextran click microgels are biodegradable due to the reduction of disulfide bonds by dithiothreitol (DTT).[10,11] Upon the addition of DTT, the crosslinkages containing disulfide bonds are cleaved, leading to increased swelling pressure of the dextran core. When the swelling pressure is higher than the membrane can resist, the surrounding LbL membrane will rupture followed by an exploding release of the entrapped drug. Using this controllable exploding microcapsule, the



Scheme 1 Schematic representations of the exploding microcapsules: (I) Fabrication of the dextran microgel *via* click chemistry. (II) LbL assembly of the $(PAH/PSS)_3$ membrane on the surface of the microgel. (III) The microgel degrades by adding DTT to cleave the disulfide bond in the crosslinkages of the dextran chains. As degradation proceeds, the three-dimensional network of the microgel changes to free dextran chains. After degradation, the core of the microcapsule has become a dextran solution and the corresponding swelling pressure causes the microcapsule to swell (IV) and finally explode (V).

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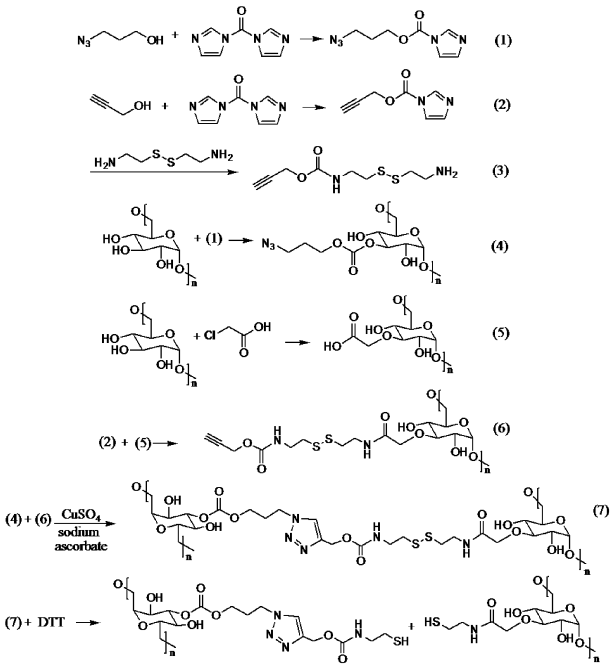

Scheme 2 The synthesis route to azide-modified dextran (**4**) and alkyne-modified dextran (**6**). A click reaction between (**4**) and (**6**) crosslinks the dextran chains (**7**). Cleavage of the disulfide bond by DTT degrades the dextran network and produces free dextran chains.

controlled sudden release of a drug can be achieved under physiological conditions by injecting DTT at the exact location.

Dextran click microgels were fabricated by the rapid vortexing of an aqueous dex-C≡C/dex-N_3 phase and an aqueous poly(ethylene glycol) (PEG) phase.[12] Due to the immiscibility of the two phases, a water-in-water emulsion was obtained. Subsequently, a click reaction between the dex-C≡C's pendent alkyne moieties and dex-N_3's pendent azide moieties was initiated. Dextran click microgels with an average diameter of 7 μm were obtained after several washes with de-ionized (DI) water. The conversion of the alkyne and azide moieties to a triazole ring was confirmed by Fourier Transform-Infrared Spectroscopy (FTIR). The FTIR spectra of lyophilized dex-C≡C, dex-N_3 and dextran click microgels are displayed in Fig. 1. The typical peaks of the azide in azide-modified dextran and the alkyne in alkyne-modified dextran are clearly visible at 2108 cm^{-1} and 2124 cm^{-1}, respectively. In the spectrum of dextran click microgels, the two typical peaks are significantly reduced or have even disappeared, indicating the consumption of the azide and alkyne functional groups.

Fig. 2A shows the confocal laser scanning microscopy (CLSM) image of dextran click microgels loaded with fluorescein isothiocyanate modified dextran (dex-FITC), which was used as a model drug. It was found that dex-FITC stays inside the microgels. To obtain microgels with anionic surface charge, to enable sequential LbL assembly, only some of the carboxyl groups of carboxymethyl dextran (CMD, **5** in Scheme 2) were reacted with propargyl cystamine (**3** in Scheme 2) during the synthesis of dex-C≡C. The remaining carboxyl groups of the dextran chains enable the resulting

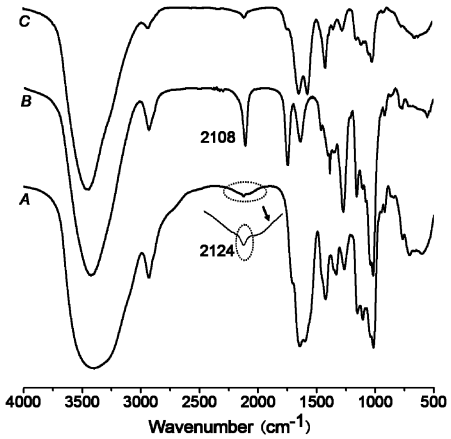

Fig. 1 FTIR spectra of alkyne-modified dextran (A), azide-modified dextran (B) and a dextran click microgel (C). The extra curve is an expansion of the alkyne stretch shown in curve A.

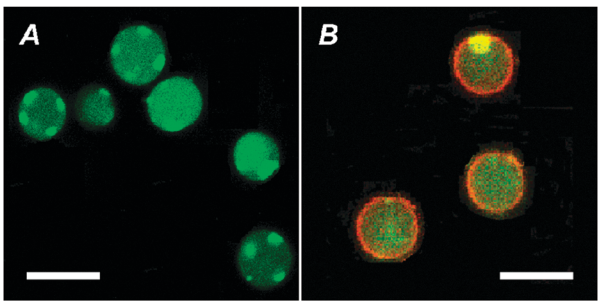

Fig. 2 CLSM images of dextran click microgels (A) and $(PAH/PSS)_3$-coated dextran click microgels. (The scale bar is 10 μm).

microgels to hold a ζ-potential of −19 mV. Because propargyl cystamine (**3**) connected to the dextran backbone contains a cleavable disulfide bond, the degradation of the dextran click microgels will occur by the addition of DTT, yielding dextran chains.

We then tried to coat the dextran click microgels with polyelectrolytes using LbL deposition.[13–15] Here, poly(allylamine hydrochloride) (PAH) served as polycations and poly(sodium 4-styrenesulfonate) (PSS) served as polyanions. In order to visualize the coating membrane, PAH was modified with rhodamine B. Fig. 2B shows the CLSM image of $(PAH/PSS)_3$-coated dextran click microgels. The $(PAH/PSS)_3$-coated dextran click microgel is designated as a microcapsule. It can be seen that the microcapsule has a regular red ring, which indicates a polyelectrolyte membrane is successfully formed to surround the microgel.

To investigate how the degradation of the dextran click microgel core influences the LbL coating, the microcapsules were incubated in both DI water (pH 7.4) and 1 M DTT solution at 37 °C, respectively. After one day, the microcapsules were observed under CLSM. Fig. 3A represents microcapsules incubated in DI water (pH 7.4). One can see that all the microcapsules remained intact and filled with dex-FITC. This demonstrates that a drug can be hosted by the microcapsules at pH 7.4. In contrast, Fig. 3B shows the ones incubated in 1 M DTT solution. It was found that most of the microcapsules were ruptured and the model drug dex-FITC got released,

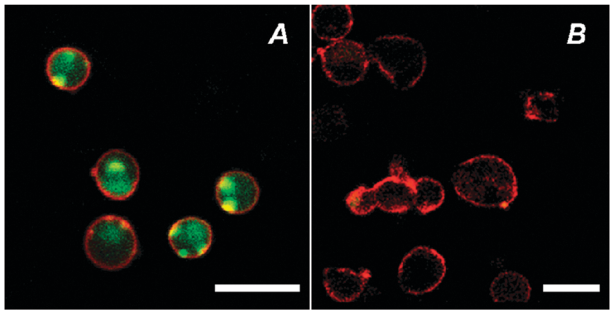

Fig. 3 CLSM images of $(PAH/PSS)_3$-coated dextran click microgels after one day of incubation in DI water (pH 7.4) (A) and 1 M DTT solution (B) at 37 °C. (The scale bar is 10 μm).

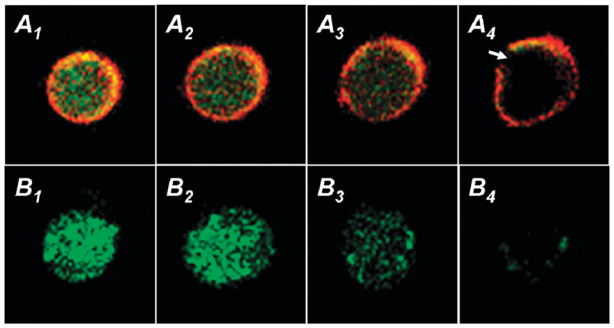

Fig. 4 Snapshots of the exploding process of the microcapsule (A_1–A_4) and the degradation of the uncoated dextran click microgel (B_1–B_4). The time interval between the snapshots is 6 min. (The arrow in Fig. $4A_4$ indicates the gap through which the drug is released).

indicating that DTT was the trigger for the exploding release of drugs in microcapsules. Thus the controllable exploding capsules were successfully obtained.

As shown in Fig. 3B, only the debris of broken polyelectrolyte shells was observed after the degradation of the dextran click microgel core. To prove the explosion of the microcapsules after the addition of DTT, we tried to witness the explosive behavior of the microcapsules. Both dextran click microgels and the microcapsules were incubated in 1 M DTT aqueous solution (pH 7.4) at room tempertature. The particles were subsequently examined by CLSM and followed over time. Fig. $4A_1$–A_4 shows four snapshots of the microcapsules taken at 6, 12, 18 and 24 min respectively. In the first 6 min, the small molecule DTT penetrated into the microgel core and the disulfide bonds began to cleave. In the next 6 min, more and more disulfide bonds got cleaved to produce free polymer chains, and osmotic pressure started to accumulate. At the 18th min, it was found that the microcapsules had swelled up due to the increasing osmotic pressure inside. At the 24th min, explosion of the coating membrane occurred and the encapsulated dex-FITC was suddenly released from the carriers. As a control we also followed the behavior of uncoated dextran microgels. As shown in Fig. $4B_1$–B_4, the microgels degraded gradually in the DTT solution and the encapsulated dex-FITC was released gradually.

In conclusion, we demonstrate the explosive release of a loaded drug from a novel controllable exploding microcapsule under physiological conditions (pH 7.4). This device shows the appealing ability to achieve sudden drug release upon addition of DTT. In this way, normal tissue can avoid being damaged by the potent drug, and these controllable exploding microcapsules will have great potential in cancer therapy.

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