Reductively and hydrolytically dual degradable nanoparticles by "click" crosslinking of a multifunctional diblock copolymer

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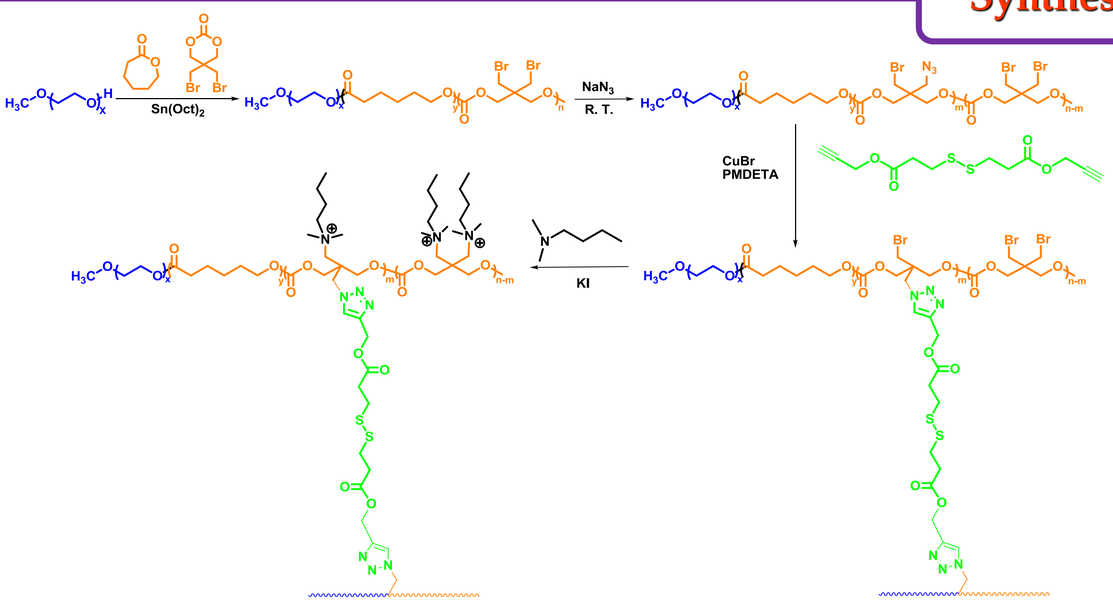
Introduction

The synthesis and subsequent self-assembly of amphiphilic block copolymers into micelles have emerged as an interesting class of biomaterials for their versatile applications in pharmaceutical science and drug delivery[1-2]. And these micelles should posses not only high stability *in vivo* but also great biocompatibility and biodegradability[3-4]. To achieve it, we synthesized dual degradable core crosslinked nanoparticles based on a amphiphilic block copolymer, employing poly(ethylene glycol) as corona and partially azidated poly((ε-caprolactone)-*co*-(5,5-dibromomethyl trimethylene carbonate)) as core matrix, which was crosslinked by a disulfide crosslinker in nonselective solvent via "click" chemistry. The morphology and the reversible redox crosslinking are characterized by DLS and TEM. Moreover, the remaining bromomethyl groups in the core could undergo quaternization with *N*,*N*-dimethylbutylamine to give cationic nanoparticles, which makes it as a potential smart nanocarrier for drug and gene delivery.

Synthesis and characterization



Scheme 1 Synthetic routes of dual degradable core crosslinked nanoparticles.

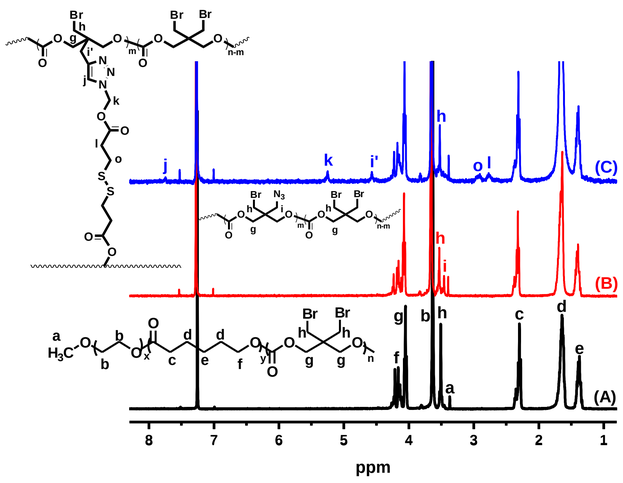


Fig. 1 ^{1}H NMR spectra of: (A) mPEG-*b*-PDBTCL, (B) mPEG-*b*-PDBTCL-N_3 and (C) core-crosslinked nanoparticles.

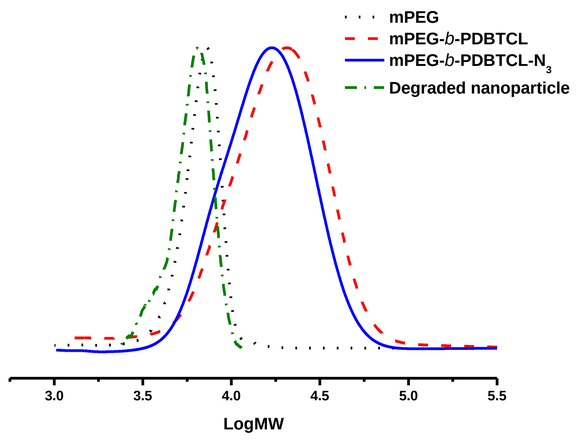


Fig. 2 GPC traces of mPEG, mPEG-*b*-PDBTCL, mPEG-*b*-PDBTCL-N_3 and degraded nanoparticle (treating with PBS, 0.02 M, pH 9.1).

Characterization of nanoparticles

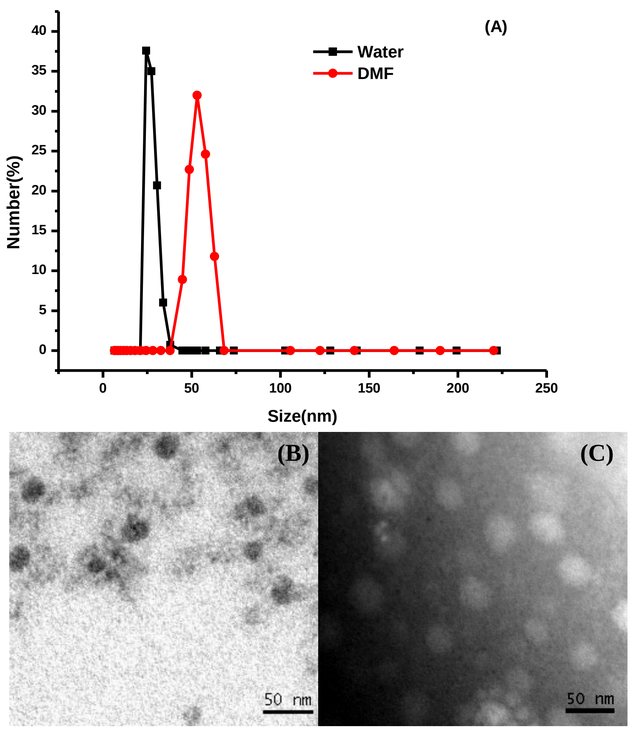
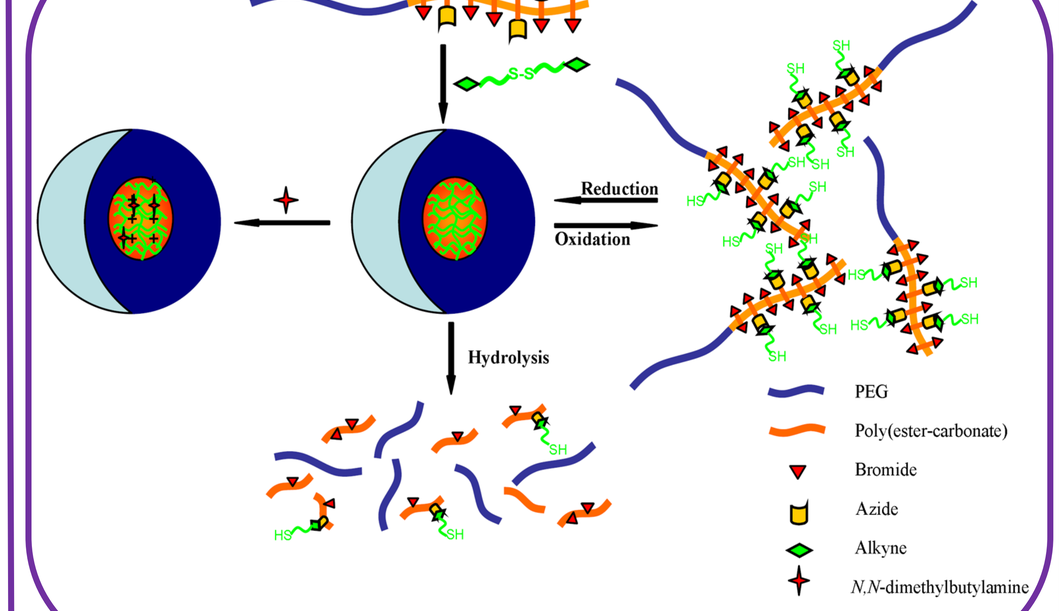


Fig. 3 Particle size and distribution of core crosslinked nanoparticles measured by DLS (A) and morphology of nanoparticles observed by TEM in DMF (B) and water (C).



Scheme 2 Preparation and dissociation of the cationic nanoparticles

Reversible dissociation and irreversible degradation of nanoparticles

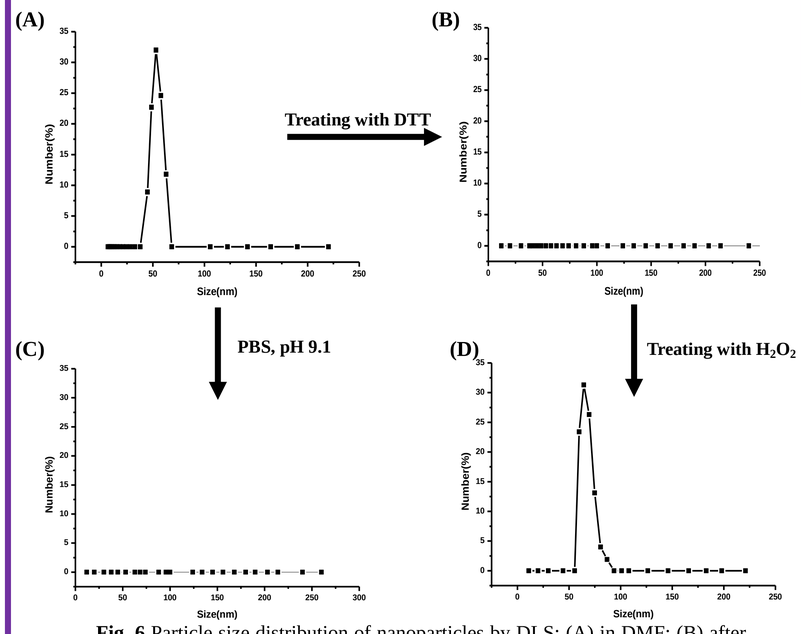


Fig. 6 Particle size distribution of nanoparticles by DLS: (A) in DMF; (B) after treating A with DTT; (C) after treating with phosphate buffered saline (PBS, pH 9.1); (D) after treating B with H_2O_2.

The stability of the core-crosslinking nanoparticles can be proved by the nanoparticles still maintained their nanostructures in DMF just as in water, as shown in Fig. 6. The reversible core-crosslinking of the nanoparticles which have great influence on its stability was detected by DLS via reducing by DTT and oxidizing by H_2O_2, implied that the core-crosslinked nanoparticles will be stable under physiological conditions in the circulation as well as in extracellular tissues because of a low concentration of GSH, while will quickly dissociated in a highly reductive environment in cells. Fig. 6C also exhibited that the nanoparticle which composed of poly(ester-carbonate), could undergo hydrolysis to degraded.

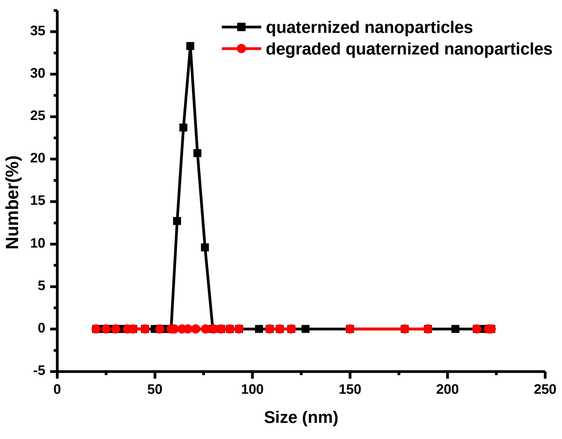


Fig. 4 Particle size distribution of quaternized nanoparticles in DMF and after treating with PBS (0.02 M, pH 9.1) in water by DLS.

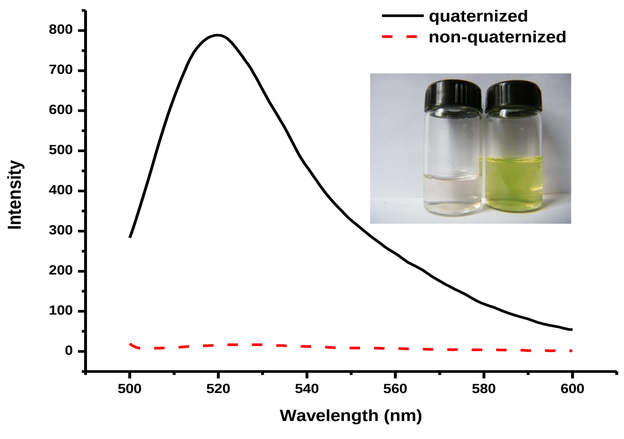


Fig. 5 Fluorescence spectra and photograph of quaternized and non-quaternized nanoparticles with fluorescein disodium in aqueous solution.

The cationic particles with zeta potential of +22.6 mV were further measured by adding fluorescein disodium into the quaternized nanoparticles solution and stirred for a while at room temperature. The free fluorescein disodium was removed by dialysis against water. A control group was set up by adding fluorescein disodium into the DMF solution of non-quaternized nanoparticles and *N*,*N*-dimethylbutylamine, then dialysis against water. Fig. 5 exhibits the fluorescence spectrum of quaternized nanoparticles stained with fluorescein disodium via strong ionic interaction with ammonium groups, which displays a strong emission peak at 521 nm when excited at 490 nm while the unquaternized nanoparticle solution doesn't show any emission under the same conditions.

Conclusions

- Reductive and hydrolytic dual degradable nanoparticles were synthesized by crosslinking the reactive mPEG-*b*-PDBTCL-N_3 diblock copolymer in nonselective solvent using a disulfide crosslinker via "click" chemistry.
- The remaining bromomethyl groups in the core could undergo quaternization with tertiary amine to give cationic nanoparticles for gene delivery.
- The reversible crosslinking have great influence on stability of the nanoparticles, which can be achieved via reducing in the treatment of DTT and oxidizing by H_2O_2, will making the nanoparticles have potential applications in drug delivery and realize controlled release and targeted delivery.
- The matrix of nanoparticle core is composed of poly(ester-carbonate), which could undergo hydrolysis to degraded, implied the biocompatibility and biodegradability of the nanoparticles.

References & Acknowledgments

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The authors are grateful to the financial supports from the National Natural Science Foundation of China (21274121 and 51173163), the Major State Basic Research Project (2011CB606001), Scientific Research Fund of Zhejiang Provincial Education Department (Y201121828) and A Project Supported by Open Foundation of Zhejiang Provincial Top Key Academic Discipline of Applied Chemistry and Eco-Dyeing & Finishing Engineering (YR2012006).