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One-pot syntheses of dual-responsive core cross-linked polymeric micelles and covalently entrapped drug by click chemistry

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ABSTRACT

A facile drug delivery system for prednisolone 21-acetate (PA) based on dual-responsive core cross-linked (CCL) micelles was prepared efficiently by alkyne-azide click chemistry. Poly(ethylene oxide)-*b*-poly(glycidyl methacrylate), PEO-*b*-PGMA, was firstly synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization, and the PGMA parts were subsequently functionalized with azido groups. The CCL micelles of the PEO-*b*-PGMA-N_3 and covalently entrapped PA were prepared simultaneously using the alkyne-functionalized hydrazone-containing PA and disulfide-containing cross-linking agent in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate. The CCL micelles showed a much improved PA loading efficiency (83%) compared to physically loaded micellar system. The CCL micelles illustrated the structural stability of the micelles under physiological condition, while decross-linking through the cleavage of disulfide groups took place rapidly in dithiothreitol reduction circumstance. In addition, the pH-sensitive hydrolysis of the hydrazone groups in PA derivative in the micellar core presented a burst release of the drug at pH 5 and 37 °C in marked contrast to little release at pH 7.4.

1. Introduction

In recent years, the advantages of polymeric micelles based on core–shell structure have been extensively studied due to the hydrophobic drug solubility, prolonged circulation time, and specific tissue targeting [1–3]. Core–shell type assemblies of amphiphilic block copolymers consist of insoluble core and soluble corona in water, which are frequently built from hydrophobic and hydrophilic polymers [4,5]. However, the inherent instability of micelles is a significant obstacle for many applications. Under certain conditions, the polymeric micelles dissociate into unimers which can be eliminated from blood circulation [6]. This causes non-targeted drug release and toxicity [7–11]. Therefore, stabilization of polymeric micelles is an urgent problem which has recently attracted numerous studies [12–15]. The cross-linking of micelles is one of the most powerful tools to stabilize the self-assembled structure [16–19]. Significant advances in cross-linking micelles do not only enhance the stability of the nanocarriers but also enable controllable tuning of drug release in micelles. Cross-linked

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hydrophilic shells may affect the stealthiness of the drug delivery systems and the mobility of the hydrophilic moiety [20,21], and they are unable to avoid undesired inter-micellar cross-linking [22,23]. Core cross-linked (CCL) micelles become more favorite strategy and cross-linking could be reversed or degraded in a redox circumstance to improve the release of active agents [24–27]. Core cross-linked micelles were prepared by various methods including UV irradiation of photo-sensitive block copolymers [28,29] and metal–ligand coordination [30]. They could release the drug under UV/NIR light [31,32] or pH changes [16,33,34].

In conventional core cross-linking, a hydrophobic drug is physically loaded onto the micellar core and then the core is subsequently cross-linked. Consequently, the entrapped drug may be pushed out during the process of the core condensing leading to the declined drug loading efficiency [8,30,35,36]. In addition, some anticancer drugs cause severe side effects due to the prominent drug concentration at healthy tissues while drug dosage is significantly reduced at tumor tissues [37]. It is desirable that the drug should be covalently attached to the micellar core not only to ensure its retention within the micelles during the circulation time but also to be released by the bond cleavage process after reaching the target site. To this purpose, a drug conjugated polymer has been proposed to increase drug loading efficiency of polymeric micelles, which shows great promise *in vivo* therapeutic application. The lipophilic drug could be released from polymer by enzymatic release [17], passive hydrolysis [38–41], or redox-responsive release [42]. Among these, the drug conjugated polymer based on hydrazone bonds has gained much interest. The hydrazone linkage is acid-sensitive, which is relative stable at pH 7.4 of blood but do release the active drug in the acidic tumor microenvironment (pH 5) [38,43]. Polymer drug conjugates via hydrazone linker include polymers which contain a drug incorporated as a part of the polymer backbone [44] or drug attached as cross-linking agent groups of the micellar core [45]. These methods could obtain high drug uploading capacity. However, the polymer-drug conjugate and drug-free polymers were difficult to isolate and needed a little complicated procedure. Furthermore, these polymerization reactions were obviously uncontrollable and they were carried out with a low concentration of drug bearing monomers leading to less payload [46,47]. Therefore, it is desirable to load a high concentration of drug with a stimuli responsive linkage by using facile click chemistry. We have also reported CCL micelles for synthesis of nanogels by using azide-alkyne cycloaddition click reaction [48].

In the present work, one-pot syntheses of a covalently linked drug and CCL polymeric micelles were proposed with click chemistry (Fig. 1). The block copolymer of poly(ethylene oxide)-*b*-poly(glycidyl methacrylate) (PEO-*b*-PGMA) was synthesized by the reversible addition-fragmentation chain transfer (RAFT) polymerization using a PEO-based macroinitiator followed by the azidation process (Fig. 2). The Huisgens cycloaddition was then allowed to take place between azide groups

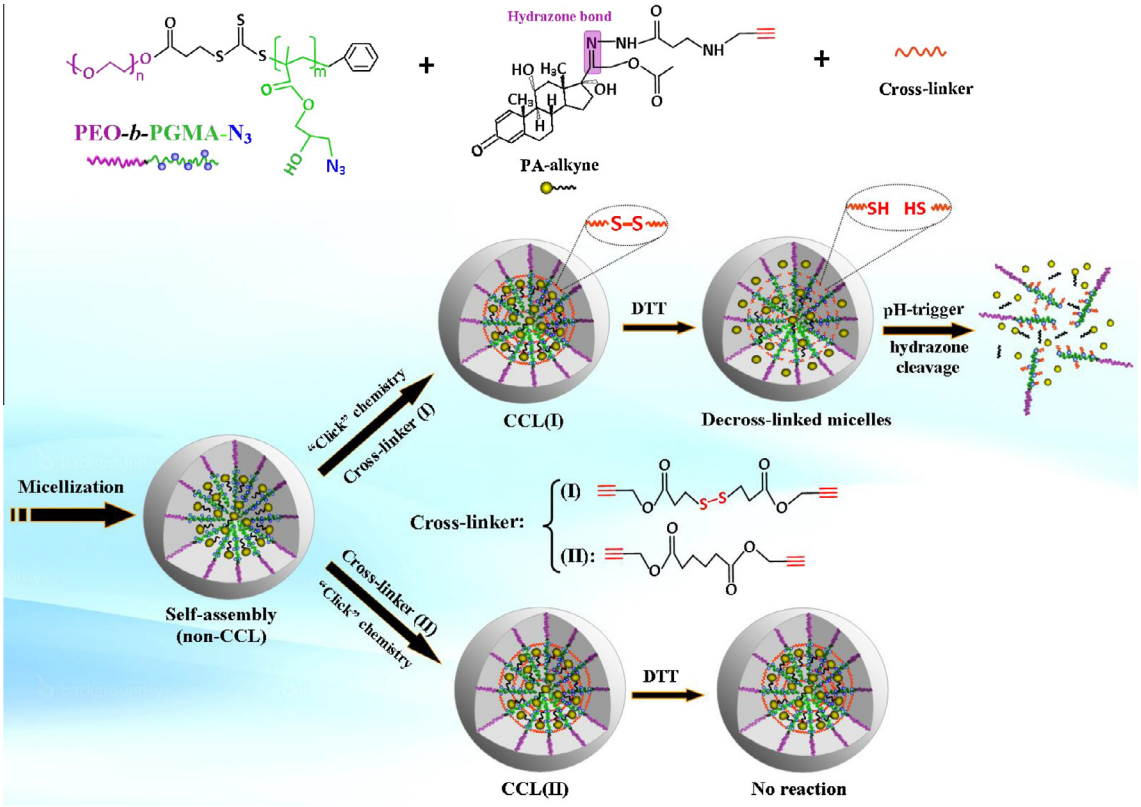

Fig. 1. CCL micelles of PEO-*b*-PGMA-N_3 block copolymers, followed by degradation and drug release in the presence of DTT.