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Synthesis of nanogels of poly(ε-caprolactone)-b-poly (glycidyl methacrylate) by click chemistry in direct preparation

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ABSTRACT

The controlled synthesis of nanogels was carried out in a single step using "click" chemistry. Poly(ε-caprolactone)-*b*-poly(glycidyl methacrylate) (PCL-*b*-PGMA) block copolymers were prepared by the combination of ring-opening polymerization and the reversible addition fragmentation chain transfer polymerization, and subsequently functionalized with azido groups. The direct formation of nanogels of the azide-functionalized PCL-*b*-PGMA-N_3 was controlled using dipropargyl adipate (DPA) as a cross-linking agent from the homogeneous solution in a nonselective solvent. The results revealed that the formation of macrogels or nanogels with core cross-linked block copolymers depends on the concentration of the block copolymer and the cross-linker and the chain length of the PGMA-N_3 block, so that the preparation of nanogels was manipulated simply with adjusting the molar ratio of alkyne to azide groups. The nanogels were confirmed by nuclear magnetic resonance, X-ray photoelectron spectroscopy, transmission electron microscopy, dynamic light scattering analyses and gel permeation chromatography. DPA was found to cross-link the block copolymer effectively and afford robust nanostructures, while leaving click-readied azide functionalities throughout the core domain, which are proposed to be readily available for further chemical modification.

1. Introduction

The preparation of well-defined cross-linked polymeric micelles by a novel route has been attracted much interest in recent years. The advantage of polymeric micelles has been intensely studied due to the potential applications such as drug delivery and biomedical devices [1,2]. During the past decades, many studies have focused on the development and the feasibility of polymeric micelles for therapeutic and diagnostics medicine applications [3,4]. However, the micelle stabilization is the biggest obstacle for these applications. The stability of micelles is influenced by various factors such as low concentration, high temperature and different environmental conditions. Under these conditions, the polymer micelles dissociate into unimers, which cause non-targeted drug release and toxicity [1]. Therefore, the cross-linking of micelles is one of the most powerful tools to stabilize the self-assembled structure.

Cross-linking of block polymeric micelles can be carried out at the end of core chains, within the core, at the core–shell interface, or at the shell of micelles. In the last decade, there have been numerous articles reported for the crosslinking reaction of block copolymer micelles [5]. Wooley et al. reported shell cross-linked (SCL) polymeric nanoparticles having a glutathione-responsive disulfide cross-linked corona, which is potential for paclitaxel delivery [6]. Core cross-linked (CCL)

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micelles of block polymers were reported using degradable cross-linkers by reversible addition fragmentation transfer (RAFT) polymerization [7,8]. We have reported core-surface cross-linked nanoparticles by interblock RAFT polymerization of poly(ethylene oxide)-*b*-polystyrene block copolymer using divinyl benzene as a cross-linker [9].

On the other hand, Yoshida et al. have reported cross-linked micelles prepared directly in a nonselective solvent by hydrogen bond cross-linking of nonamphiphilic poly(vinylphenol)-*b*-polystyrene using 1,4-butanediamine as a cross-linker [10]. The size and aggregation number of the micelles which depended on the copolymer concentration were investigated. In other examples, the protonation of poly[(4-pyridinemethoxymethyl)styrene]-*b*-polystyrene by perfluoroalkyl dicarboxylic acid led to CCL micelles in a nonselective solvent [11]. In this case, the micellar size and aggregation number were dependent on the chain length of the cross-linker. Amamoto et al. presented the cross-linking of diblock copolymers consists of poly(methyl methacrylate) and poly(methacrylic esters) with alkoxyamine moieties to form CCL star-like nanogels. The structural transformation from star-like nanogels to diblock copolymers was performed by dynamic covalent exchange among alkoxyamine units in the star-like nanogels and excess added alkoxyamine compounds [12,13]. Jackson et al. prepared CCL star polymers which constructed from two types of polymer chains possessing aldehyde and amino functions. These functional groups facilitated cross-linking of polymer chains through the reversible imine bond formation that can be responded to pH and temperature [14,15]. So far, the one-step direct micellization was mostly induced by physical crosslinking or reaction between different types of polymer chains.

The click reaction was utilized to the formation of cross-linked micelles by the reaction between alkynyl-functionalized core/shell micelles of block copolymers and azide-terminated cross-linkers [16–18]. Similarly, CCL micelles were prepared from micelles of amphiphilic block copolymers by click chemistry using degradable cross-linkers which responsed to the reducing reagent [19]. The above studies are related to a two-step procedure, where micelles are formed first in a selective solvent and then the cross-linking of micelles occurs subsequently by click chemistry. The prior formation of well-defined micelles, however, need a little complicated procedure of the dialysis method and is also dependent on block copolymer composition, copolymer concentration, type and concentration of added ions and the nature of the common solvent used in micelle preparation [20], which limits its application in a wide range of block copolymers.

In this study, a facile one-step preparation method was reported with the click reaction induced micellization of unimers in a nonselective solvent to produce nanogels. The block copolymer of poly(ε-caprolactone)-*b*-poly(glycidyl methacrylate) (PCL-*b*-PGMA) was prepared by the combination of ring-opening polymerization (ROP) and RAFT polymerization followed by the azidation process. Click reaction, a high yield and sensitive reaction, took place between azide-functionalized PCL-*b*-PGMA-N_3 and a dialkyne cross-linker to form CCL micelles from the homogeneous solution. The size and aggregation phenomena of CCL micelles of the block copolymer were investigated in detail. The formation of nanogels could be controlled simply by adjusting the molar ratio of alkyne to azide groups. To the best of our knowledge, it is the first attempt that nanogels of block copolymers are prepared directly by click reaction in a nonselective solvent.

2. Experimental details

2.1. Materials

ε-Caprolactone (97%), 2-mercaptoethanol, carbon disulfide (99%), benzyl bromide (98%), tin(II) 2-ethylhexanoate (95%), sodium azide (NaN_3, 99.99%), ammonium chloride (NH_4Cl, 99.5%), propargyl alcohol (99%), adipic acid (99.5%), p-toluenesulfonic acid monohydrate (98.5%), ethylenediamine tetraacetic acid (EDTA, 99%), copper (I) bromide (CuBr, 99,99%), and N,N,N′,N″-pentamethyldiethylenetriamine (PMDETA, 99%) were purchased from Sigma–Aldrich (Korea). Tetrahydrofuran (THF) and acetonitrile were dried over CaH_2 and distilled prior to use. Glycidyl methacrylate (97%, Sigma–Aldrich) was passed through a neutral alumina column and 2,2′-azobis(isobutyronitrile) (AIBN) (98%, Sigma–Aldrich) was recrystallized in methanol prior to use. 2-Benzylsulfanylthiocarbonylsulfanyl ethanol (RAFT agent) was synthesized as reported previously [21]. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.62 (t, 2H, CH_2—O), 3.88 (t, 2H, CH_2—S), 4.60 (s, 2H, CH_2-Ph), 7.31 (m, 5H, Ph). Dipropargyl adipate (DPA) was synthesized according to the previous literature [22]. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.63 (s, 4H, CH_2—OCO), 2.43 (s, 2H, CH), 2.32–2.34 (t, 4H, OCO—CH_2—CH_2), 1.64–1.66 (m, 4H, CH_2—CH_2—CH_2—OCO). Other solvents and chemicals of analytical grade were used as received.

2.2. Synthesis of poly(ε-caprolactone)-based RAFT agent (PCL-RAFT)

The RAFT agent with hydroxyl end-group was used as an initiator for ROP. A solution of ε-caprolactone (4.56 g) and RAFT agent (0.24 g) was stirred at 90 °C for 1 h under nitrogen. Afterward, tin(II) 2-ethylhexanoate (0.041 g) was added to the yellow mixture, and the solution was purged with nitrogen and stirred at 140 °C for 12 h. At the end point, the viscosity of the mixture increased dramatically. The product was dissolved in THF, precipitated in methanol, filtered. This procedure was repeated three times. The final product was dried under vacuum for 24 h.

2.3. Synthesis of PCL-b-PGMA block copolymer

The block copolymer of PCL-*b*-PGMA was synthesized by the RAFT method using the PCL-RAFT macroinitiator. In a typical procedure, PCL-RAFT (0.64 g, 0.044 mmol), glycidyl methacrylate (1.137 g, 8 mmol), AIBN (0.008 g, 0.05 mmol), and THF