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A smart micellar system with an amine-containing polycarbonate shell

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ABSTRACT

The present paper reports the design and preparation of an amphiphilic triblock co-polymer poly(ε-caprolactone) (PCL)–poly(6,14-dimethyl-1,3,9,11-tetraoxa-6,14-diaza-cyclohexadecane-2,10-dione) (PADMC)–PCL and the use of micelles composed of them as carriers for pH-sensitive drug release. The triblock co-polymers were synthesized via two-step ring-opening polymerization with catalysis by Novozym-435 lipase. By adjusting the feed ratio, three co-polymers with different PCL lengths and the same PADMC length were produced. The block structure of the co-polymers obtained was confirmed by comparative studies on PCL–PADMC–PCLs and the corresponding random poly(ε-caprolactone-random-6,14-dimethyl-1,3,9,11-tetraoxa-6,14-diaza-cyclohexadecane-2,10-dione) (poly(CL-*r*-ADMC)) by means of nuclear magnetic resonance and differential scanning calorimetry. Cell cytotoxicity tests showed that the co-polymer displayed no apparent cytotoxicity to 293T and HeLa cells. Transmissions electron microscopy indicates that the self-assembled micelles exhibited a well-defined spherical shape with a diameter between ~30 and 50 nm. The critical aggregation concentration was dependent on the block composition. Due to the presence of ionizable tertiary amine groups in the PADMC block, acid-induced variation in the micellar morphology was evident with respect to micelle size and size distribution. The size–pH curve was characterized by a smooth sigmoid form, and had a dramatic upward shift with decreasing pH from 6.5 to 4.5, which correlated well with the buffer range of hydrophilic PADMC. As a demonstration of the potential of PCL–PADMC–PCL micelles to control drug delivery, acid induced drug release for prednisone acetate-loaded micelles was explored. PCL–PADMC–PCL micelles show good promise as smart drug carriers, sensing the local specific pH decrease around lesion sites.

1. Introduction

Well-defined amphiphilic block co-polymers represent a major advance in the development of soft materials [1,2]. Those co-polymers consisting of hydrophilic and hydrophobic building blocks readily undergo microphase separation in aqueous media and self-assemble into versatile structures. As one typical example, nano-sized micelles have attracted significant attention for the formulation of continuous delivery systems for poorly water soluble drugs as well as therapeutic genes and proteins, leading to substantially improved drug bioavailability and stability [3–5]. The nanoscale dimension of the micelles is well documented to contribute to passive tumor targeting, enhanced efficiency in crossing biological barriers, and a prolonged lifetime in the blood circulation [6–9]. The gradual understanding of the virtues of micelle-based delivery systems has further stimulated the development of so-called "smart" micelles for stimulus-responsive drug release, in order to reduce drug-associated toxicity and promote therapeutic efficacy [10–13].

To date most amphiphilic block co-polymers have been based on the hydrophilic poly(ethylene glycol) (PEG), which is thermosensitive and has "stealth" properties, and structural optimization has mainly been directed towards the hydrophobic blocks [14–16]. Several other hydrophilic polymers, such as poly(N-isopropylacrylamide) (PNIPAAm), poly(acrylic acid) (PAA), poly(N,N-dimethylaminoethyl acrylate) (PDMAEA), poly(2-N-(morpholino)ethyl methacrylate) (PMEMA) have also been extensively explored and utilized for the construction of pH- or temperature-responsive micelles [10–13,17]. Although advantages and encouraging results have been shown when using those micelles for various drug delivery applications in vitro and in vivo, safety concerns remain regarding their non-degradable nature, latent immunogenicity and antigenicity, significant toxicity of residual monomers, and/or difficulties with renal excretion from the body [18–21]. On the other hand, several biodegradable, hydrophilic polymers have been utilized to develop amphiphilic block co-polymers, however, most of them lack stimulus-responsive function [22–25]. In this regard, the search for biodegradable and biocompatible polymers to act as the hydrophilic building block of "smart" micelles is appealing but still challenging at present.

Given the electrolyte enriched environment in the human body, specifically designed nanostructures surrounded by a polycationic

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