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The use of pH-sensitive positively charged polymeric micelles for protein delivery

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ABSTRACT

In this investigation, a nano-sized protein-encapsulated polymeric micelle was prepared by self-assembling human serum albumin (HSA) as a model protein and degradable block copolymer methoxy poly(ethylene glycol)-poly(β-amino ester) (PEG-PAE) with piperidine and imidazole rings. From the zeta potential measurement, the protein-encapsulated polymeric micelle showed a pH-tuning charge conversion from neutral to positive when pH decreases from 7.8 to 6.2. It was envisioned that the pH-tunable positively charged polymeric micelle could enhance the protein delivery efficiency and, simultaneously, target to the pH-stimuli tissue, such as cancerous tissue or ischemia. The pH-dependent particle size and scattering intensity were also measured and showed 50–70 nm particle size. Consequently, the circular dichroism (CD) spectroscopy confirmed that the secondary structure of albumin was unaffected during the pH changing process. The *in vitro* cytotoxicity for the polymeric micelle was evaluated on MDA-MB-435 cell lines and no obvious toxicity could be observed when the polymer concentration was below 200 μg/mL. To assess the ability of this pH-tunable positively charged polymeric micelle as a vehicle for protein delivery to *in vivo* acidic tissues, we utilized a disease rat model of cerebral ischemia that produced an acidic tissue due to its pathologic condition. The rat was intravenously injected with the Cy5.5-labled albumin-encapsulated polymeric micelle. We found a gradual increase in fluorescence signals of the brain ischemic area, indicating that the pH-tuning positively charged protein-encapsulated polymeric micelle could be effective for targeting the acidic environment and diagnostic imaging.

1. Introduction

Polymeric carriers can be employed as promising nonviral vectors for delivering drugs and diagnostic agents in biomedical applications [1,2]. In particular, the polymeric complex has been proved as an effective strategy for gene and protein delivery efficiently [3,4] due to its safety, well biocompatibility and available function [5]. Moreover, the complexes from cationic polymer and anionic DNA/protein can maintain a stable state through electrostatic interactions in an aqueous medium [6,7].

Therapies for common diseases tend to predominantly utilize protein-based drugs, such as insulin (for diabetes) and erythropoietin (for renal anemia), because protein has high specificity and activity at a relative low concentration [8]. However, it could cause particle aggregation easily for encapsulating protein directly into polymeric vehicles, significantly limiting protein delivery via the non-invasive administration [9]. Moreover, the microspheric vehicle has a relatively large particle size so that it is difficult to deliver proteins to the specific site of pathological tissues through the blood circulation system [10]. Therefore, the protein-encapsulated nanocomplex is considered to be potential and promising for protein delivery. Some polymeric nanocomplexes have been reported to deliver and release proteins in response to environmental stimuli, such as pH [11], enzymes exposure [12], and redox environment [13]. In recent years, Kataoka *et al.* developed

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