



## The tumor accumulation and therapeutic efficacy of doxorubicin carried in calcium phosphate-reinforced polymer nanoparticles

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### ABSTRACT

A mineral (calcium phosphate, CaP)-reinforced core-shell-corona micelle was evaluated as a nanocarrier of doxorubicin (DOX) for cancer therapy. The polymer micelles of poly(ethylene glycol)-*b*-poly(L-aspartic acid)-*b*-poly(L-phenylalanine) (PEG-PAsp-PPhe) in the aqueous phase provided the three distinct functional domains: the hydrated PEG outer corona for prolonged circulation, the anionic PAsp middle shell for CaP mineralization, and the hydrophobic PPhe inner core for DOX loading. CaP mineralization was performed by initial electrostatic localization of calcium ions at anionic PAsp shells, and the consequent addition of phosphate anions to trigger the growth of CaP. The mineralization did not affect the micelle size or the spherical morphology. The CaP-mineralized micelles exhibited enhanced serum stability. The DOX release from the DOX-loaded mineralized micelles (DOX-CaP-PM) at physiological pH was efficiently inhibited, whereas at an endosomal pH (pH 4.5), DOX release was facilitated due to the rapid dissolution of the CaP mineral layers in the middle shell domains. The *in vivo* tissue distribution and tumor accumulation of the DOX-CaP-PM that were labeled with a near-infrared fluorescent (NIRF) dye, Cy5.5, were monitored in MDA-MB231 tumor-bearing mice. Non-invasive real-time optical imaging results indicated that the DOX-CaP-PM exhibited enhanced tumor specificity due to the prolonged stable circulation in the blood and an enhanced permeation and retention (EPR) effect compared with the DOX-loaded non-mineralized polymer micelles (DOX-NPM). The DOX-CaP-PM exhibited enhanced therapeutic efficacy in tumor-bearing mice compared with free DOX and DOX-NPM. The CaP mineralization on assembled nanoparticles may serve as a useful guide for enhancing the antitumor therapeutic efficacy of various polymer micelles and nano-aggregates.

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### 1. Introduction

Smart nanocarriers with high therapeutic efficacy have played a central role in successful cancer chemotherapy [1–4]. Currently, one of major research trends has focused on the enhancement of the delivery efficiency of major nanocarriers such as polymer micelles and polymer nano-aggregates with a core-shell structure [5–7]. In this area, one of the most desirable approaches for the successful delivery of anti-cancer drugs is the development of nanocarriers that can meet the following requirements: i) maintenance of a robust structure after *i.v.* administration, ii) effective protection of drug leakage in the bloodstream, iii) enhanced

targeting ability by the enhanced permeation and retention (EPR) effect, and iv) facilitated drug release within the target tissues [8,9].

Since the pioneering work reported by Wooley et al. in 1996, shell cross-linking techniques have been introduced for many polymer micelle nanocarriers [10–12]. At present, this approach has shown great progress in the field of nanomedicine, and the employment of stimuli-labile cross-links that are intact at extracellular conditions and can be cleaved within target cells have enabled polymer micelles to satisfy the above-mentioned prerequisites. To date, stimuli-sensitive cross-links, such as pH-labile ketal or acetal, redox-responsive disulfide bonds have been utilized and have contributed to enhanced antitumor efficacy [8,9,13–15]. However, the organic cross-linking may have the following drawbacks: First, the cross-linking reaction with organic compounds has always accompanied the variation of polymer structures, which inevitably produce undefined species after degradation *in vivo*. This

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