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Hybrid nanoparticles based on ortho ester-modified pluronic L61 and chitosan for efficient doxorubicin delivery

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ABSTRACT

Tumor intrinsic or acquired multidrug resistance (MDR) is still one of the major obstacles to the success of nanomedicine. To address this, the pH-sensitive nanoparticles (L61-OE-CS) with MDR-reversal ability were prepared by the crosslinking between acid-labile ortho-ester-modified pluronic (L61-OE) and chitosan (CS) for efficient doxorubicin (DOX) delivery. The size and micromorphology of the prepared nanoparticles were observed by dynamic light scanning and scanning electron microscopy and the nanoparticles displayed a uniform spherical shape with a diameter around 200 nm. The pH-triggered morphology change of the nanoparticles was also observed by scanning electron microscope. Drug release profiles under different pH values showed that DOX release amount within 72 h reached 16% (pH 7.4) and 76.5% (pH 5.0), respectively. In vitro cellular uptake and MTT assay demonstrated that the ortho ester and pluronic-based nanoparticles had higher cytotoxicity than non-sensitive nanoparticles. In vivo antitumor experiments also proved the superiority of the dual-functional nanoparticles, and the tumor growth inhibition rate (TGI) on day 14 was higher than 80%. Therefore, L61-OE-CS nanoparticles have great potential to be used as drug carriers in anticancer therapy.

1. Introduction

Over the past few decades, a variety of nano-drug delivery systems (NDDS) have emerged as innovative and potential strategies for cancer imaging and treatment, thanks to their ability to load various compounds and the tunable and controllable physicochemical properties [1–3]. Many efforts have demonstrated that these NDDS, such as nanoparticles, liposomes, micelles and nanoparticles, can significantly improve the solubility, stability and circulation time of chemotherapeutics agents and simultaneously reduce toxicity [4–6]. Based on the enhanced penetration and retention (EPR) effect, these NDDS can effectively accumulate at tumor tissues and increase the drug concentration [7].

Among these NDDS, nanoparticles with inherent crosslinked three-dimensional networks possess appropriate serum stability and excellent biocompatibility [8,9]. The size, drug loading efficiency and releasing rate of the nanoparticles can be easily adjusted by changing the composition and structure during the preparation [10,11]. Choosing an appropriate chemical bond to crosslink the network structure of nanoparticles can endow them with stimulus responsiveness and achieve controlled drug release at the target site based on the difference between the physiological environment of normal and pathological tissues [11,12]. Especially due to the special pH difference of tumor microenvironment, pH-sensitive bonds such as acid-labile acetals, ketals and ortho ester bonds have been widely used in drug delivery system [13]. In our previous works, a crosslinking agent based on ortho ester was synthesized, and several pH-sensitive nanoparticles were obtained by free radical polymerization with natural macromolecules in aqueous solution [14]. These nanoparticles have good stability in blood circulation, and gradually are degraded and release the loaded drugs in the mildly acidic environment of tumors, showing excellent antitumor effects.

Unfortunately, tumor intrinsic or acquired multidrug resistance (MDR) is still one of the main obstacles to the success of nanomedicine [15]. P-glycoprotein (P-gp) and multidrug resistance proteins (MRPs) overexpressed on tumor cells could dramatically reduce drug accumulation in tumor cells. It has been reported that drug-loaded nanoparticles could bypass the efflux pump to a certain extent and accumulate in cells by passive or active targeting. However, the efficacy of these nanoparticles were still severely limited by MDR during treatment [13,16,17]. Therefore, in order to deliver sufficient anticancer drugs to tumor cells, there is an urgent demand to design and develop novel pH-sensitive nanoparticles with MDR-reversed ability. Pluronic is an amphiphilic triblock copolymer, which is composed of hydrophilic poly (ethylene oxide) (PEO) blocks and hydrophobic poly (propylene oxide) (PPO) blocks (PEO-PPO-PEO) [18]. Pluronic could suppress the ability of P-gp and MRPs by inhibiting mitochondrial respiration and

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