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Preparation and characterization of DOX loaded keratin nanoparticles for pH/GSH dual responsive release

Yanmei Li [a,1], Xuelian Zhi [a,1], Jiantao Lin [b], Xin You [a], Jiang Yuan [a,*]

[a] Jiangsu Key Laboratory of Biofunctional Materials, College of Chemistry and Materials Science, Nanjing Normal University, Nanjing 210023, China
[b] Guangdong Medical University, Dongguan 523808, China

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ABSTRACT

Smart drug carriers are the current need of the hour in controlled drug delivery applications. In this work, pH and redox dual responsive keratin based drug-loaded nanoparticles (KDNPs) were fabricated through two-step strategies. Keratin nanoparticles were first prepared by desolvation method and chemical crosslinking, followed by electrostatic adsorbing doxorubicin (DOX) to afford drug loaded keratin nanoparticles (KDNPs). The size, size distribution, and morphology of the KDNPs were characterized with dynamic light scattering (DLS) and Scan electronic microscope (SEM). Drug delivery profiles showed that KDNPs exhibited pH and glutathione (GSH) dual-responsive characters. Under tumor tissue/cell microenvironments (more acidic and high GSH level), KDNPs tended to accumulate at the tumor region through a potential enhanced permeability and retention (EPR) effect and perform surface negative-to-positive charge conversion. Hemolysis assay indicated that KDNPs had good blood compatibility. Cellular uptake assay demonstrated that KDNPs could be internalized by A 549 cells through endocytosis. Intriguingly, KDNPs were capable of promoting nitric oxide (NO) release from endogenous donor of S-nitrosoglutathione in the presence of GSH. All of these results demonstrated that keratin based drug carriers had potential for drug/NO delivery and cancer therapy in clinical medicine.

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1. Introduction

Cancer is a leading cause of death with an estimated rising trend of deaths worldwide [1]. Cancer patients are treated by conventional modalities including surgical resection, radiation, and chemotherapy to prolong their lives [2]. Although various therapies have been developed for cancer treatment, chemotherapy remains as the most common approach [3]. However, severe cytotoxicity, side effects, drug resistance, and ineffective access to cancer local limit the application of chemotherapy [4]. For instance, doxorubicin (DOX) is a well-known hydrophobic drug that exhibits therapeutic activity against several solid tumors, including brain, ovarian, cervix, breast, and others. Nevertheless its high antitumor activity is frequently hampered by relevant side effects. When DOX is administered directly, it lacks tumor-targeting ability, kills normal cells, and harm to the human body [5]. Therefore, great efforts have been made to reduce these poor treatment response and serious adverse effects for clinical practice by means of biological and pharmacological strategies. Recently, various anticancer drug delivery systems with extraordinary pH-responsiveness have been devolved, such as liposomes [6,7], micelles [8,9], nanoparticles [10,11], and nanogels [12–14]. In particular, nanoparticle drug carriers (nanocarriers) have aroused great interest due to their distinct advantages [15,16]. Nanocarriers have smaller size, narrow particle size distribution, and high drug loading capacity, which can be incorporated with hydrophilic or hydrophobic drug. Nanocarriers with an ability to recognize the location of a tumor and conveniently functionalized with stimuli-responsive groups.

With respect to materials options for nanocarriers, many researchers have explored the use of natural macromolecules due to their excellent biocompatibility, biodegradability, and abundant renewable source [17]. In the past few decades, protein-based nanocarriers have attracted great attention due to their intrinsic ability to function as a synthetic extracellular matrix that facilitates cell-cell and cell-matrix interactions [18–20]. There are many kinds of naturally-derived biomaterials, including albumin, collagen, fibroin, gelatin and keratin. Among them, keratin has emerged as potential candidates for revolutionizing the biomaterial world. As a kind of fibrous proteins, keratin is a chief component found in hairs. The high content of cysteine residues within hairs would form tougher and more durable structures via intermolecular disulfide bond formation [21–23]. There are also some active groups such as carboxyl, carbonyl, and amine groups on the keratin chains, which can interact with DOX molecule via hydrogen bonds. However, little work has been done on keratin-based drug carrier. Van Dyke group have described the delivery and activity of the antibiotic ciprofloxacin

* Corresponding author.
E-mail address: jyuan@njnu.edu.cn (J. Yuan).
[1] These authors contributed equally to this work.

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delivered from keratin hydrogel [24]. Wang group have prepared keratin based hydrogel and film for controlling drug release [25,26]. Liu group have synthesized poly(ethylene glycol) and poly(*N*-(2-hydroxypropyl)methacrylamide) conjugated keratin and used as micelles for dual reduction and enzyme responsive drug carriers [27,28].

Stimuli-responsive drug carriers have gained widespread interest as they enable triggered delivery of therapeutics under a specific physiochemical environment [29–32]. The pH and GSH responsiveness are of particular interest for tumor-specific targeted drug delivery because of more acidic and high reducing tumor microenvironments. As known, the GSH concentration in cancer tissues (0.5– 10 mM) is about 7– 10 fold higher than that in normal tissues (2– 20 μM), while the extracellular environment of tumor tissues is notably more acidic (pH 6.2– 6.9) than normal tissues and systemic blood pH (pH 7.4). The enriched cysteine and carboxyl would endow keratin based nanocarriers with the potential of dual pH and GSH responsiveness.

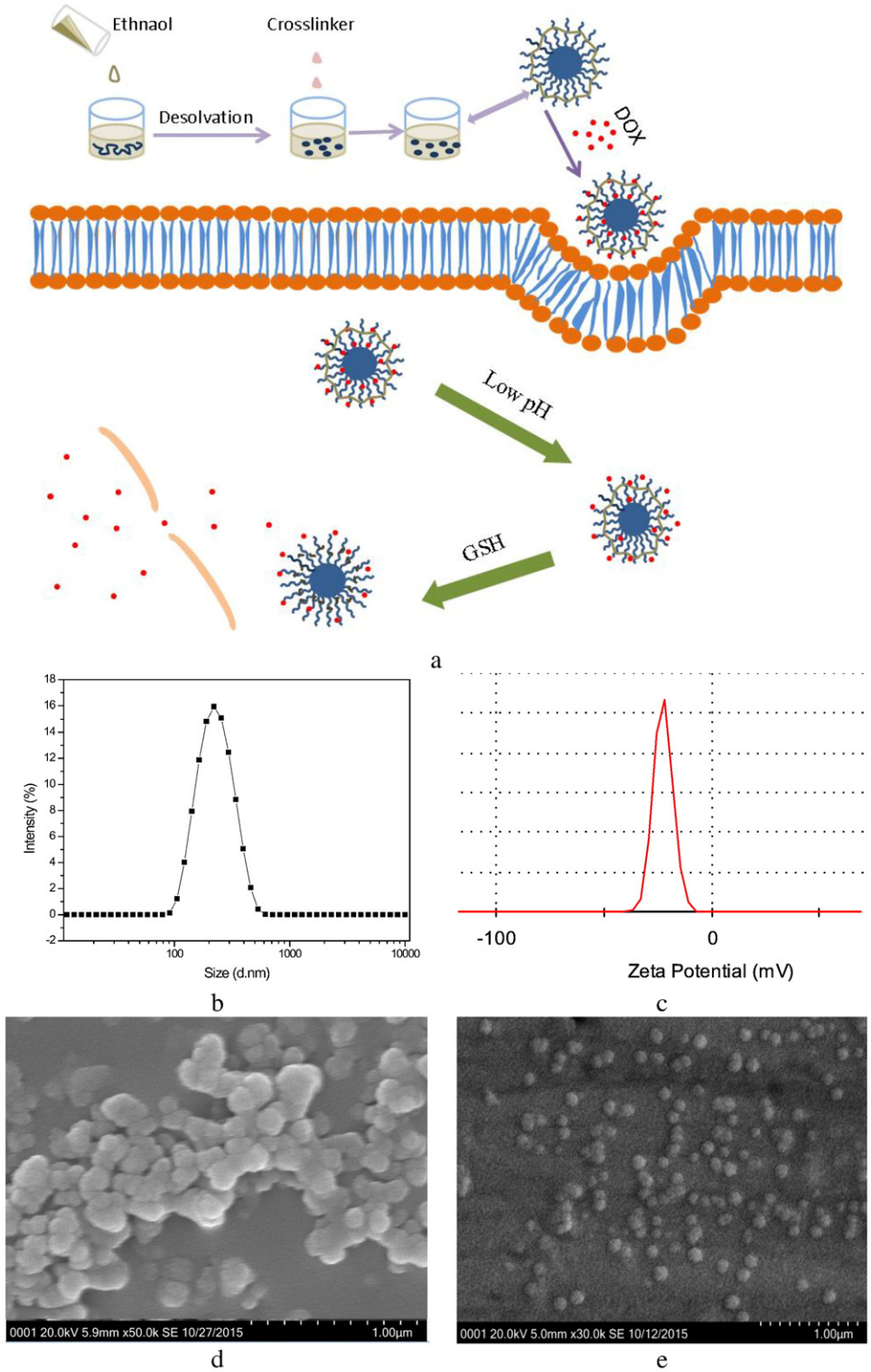

Fig. 1. (a) Schematic illustration of Keratin/DOX NPs preparation and dual pH/GSH responsive release, (b) size distribution of KNPs by DLS test; (c) zeta potential of KNPs by DLS test; (d) SEM image of KDNPs (×50 K); and (e) SEM image of KDNPs (×30 K).

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