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Novel Gelatin-based Nano-gels with Coordination-induced Drug Loading for Intracellular Delivery

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In this study, we develop the gelatin-dopamine (Gel-Dopa) nano-gels (GDNGs) and explore their potential as drug delivery vehicles. The Gel-Dopa precursor is synthesized using EDC/NHS coupling reaction, in which the catechols can coordinate with transition metal ions such as Fe^{3+}. These novel GDNGs exhibit excellent cytocompatibility. The model drug, doxorubicin (Dox), is readily conjugated into catechol of GDNGs by the coordination cross-link of Fe^{3+} ion. The morphology and size distribution of the nano-gels are characterized via field emission scanning electron microscopy and particle size analyzer, respectively. The GDNGs loaded with Dox (GDNGs-Dox) is capable of efficiently penetrating cell membrane and enter the HeLa cells. The endocytosed GDNGs-Dox release Dox molecules and subsequently kill the tumor cells.
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1. Introduction

Various nano-particles have been prepared from numerous natural or synthetic materials and widely employed as drug delivery vehicles, aiming to enhance therapeutic effects and minimize side effects of drug formulation[1–3]. Gelatin is derived from animal collagen through acid or alkaline hydrolysis; it is biocompatible, and relatively cheap as well as readily available[4–6]. Like collagen, gelatin bears some cell recognized moieties (such as RGD sequence); the multiple functional groups (e.g. -COOH, $-NH_2$) endow gelatin with the opportunity to be modified using various targeting ligands[5]. Besides, gelatin exhibits low anti-genicity and good solubility due to its denatured property[6]. Gelatin has been considered "generally safe" material by the United States FDA[7].

Gelatin nano-gels have been extensively used for the delivery of anticancer drugs, such as doxorubicin (Dox)[8]. Gelatin nano-gels can be easily prepared by many methods (such as desolvation, emulsification, coacervation, and nanoprecipitation); they are generally cross-linked with glutaraldehyde(GA)[9], genipin[10], or carbodiimide/N-hydroxysuccinimide[11]. The special characterizations of gelatin (e.g. low cost, cytotoxocity and anti-genicity, good solubility) offer many advantages for the applications of gelatin nano-gels in drug delivery. Gelatin nano-gels can be effectively internalized and localized into cells, indicating gelatin nano-gels have the ability to overcome cellular barriers and serve as efficient intracellular drug delivery vehicles[8,12,13]. More importantly, gelatin nano-gels possess passive targeting capability via the enhanced permeability and retention (EPR) effect and then accumulate in tumors for plenty of time, which ensures the release, concentration, and work of the loaded drugs in situ[8,14].

Various strategies have been explored to load drugs into gelatin nano-gels, such as physical interactions (e.g. hydrogen bonds, hydrophobic interactions)[15,16], electrostatic interactions[17], and covalent conjugation[9]. Recently, coordination bond has emerged as an intriguing method to prepare nano-complexes for biomedical applications[18–21], and which may propose a new avenue to assemble drug into polymer nano-particles. Compared with the common methods for drugs' loading, complexation-driven drug installing exhibits intrinsic stability and pH-responsiveness based on the selection of different transition metals[18,22]. Besides, the complexation-based drug loading is facile and versatile[18].

In this study, we develop novel gelatin-dopamine (Gel-Dopa) nano-gels (GDNGs) as drug delivery vehicles. The design rationale of GDNGs is to achieve coordination complexation based drug loading into gelatin-based nano-gels and drug release after internalization into tumor cells (Fig. 1). Gel-Dopa conjugate is prepared by

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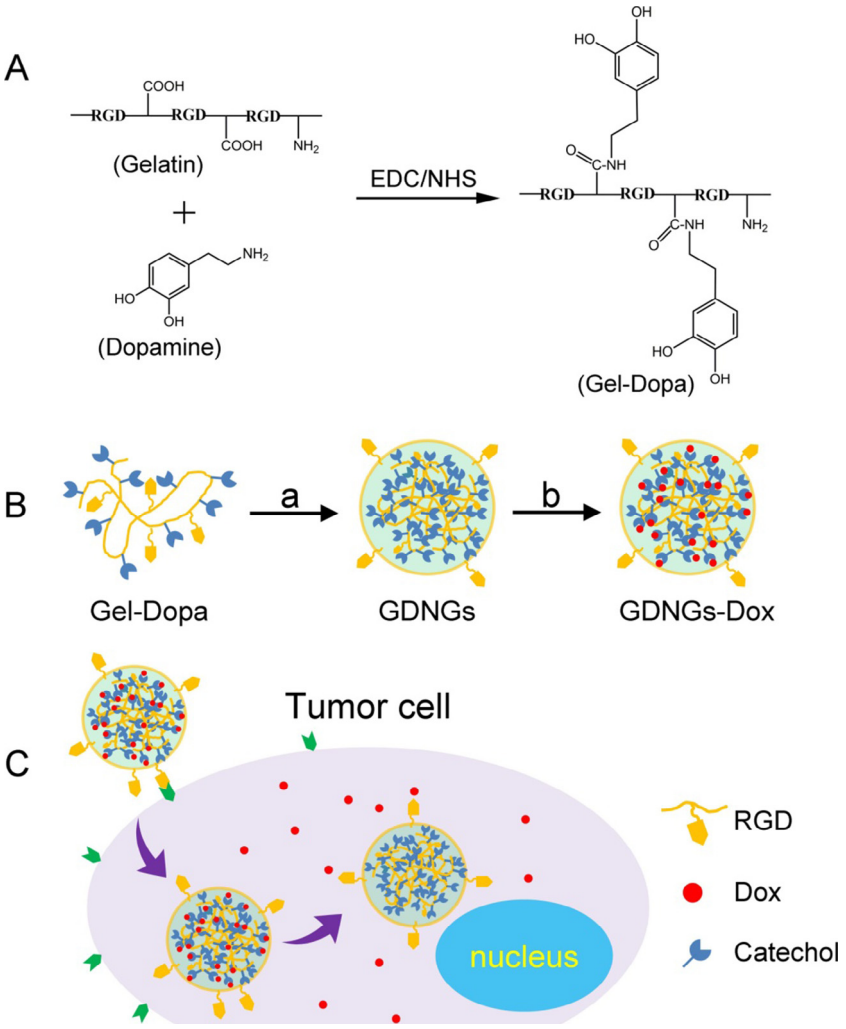

Fig. 1. (A) Synthesis scheme of Gel-Dopa precursor via EDC/NHS chemistry. (B) Schematic fabrication process of GDNGs-Dox from Gel-Dopa precursor: (a) GDNGs are first synthesized via a desolvation method; subsequently, (b) the GDNGs suspension is stirred with Dox in the presence of $FeCl_3$, achieving GDNGs-Dox. (C) Schematic illustration of targeting and endocytic process of GDNGs-Dox by a tumor cell.

grafting dopamine onto gelatin backbone, and acts as the precursor to fabricate GDNGs. The GDNGs are formed by an established desolvation process and accompanying GA cross-link (Fig. 1(B)-a). The model drug Dox is simply loaded into GDNGs through the coordination interactions between Fe^{3+} ions and ligands (including catechols in GDNGs and phenolic groups in Dox) (Fig. 1(B)-b). The morphology and size distribution are studied by FESEM and a particle size analyzer, respectively. Cellular uptake of Dox-loaden GDNGs (GDNGs-Dox) is observed under a fluorescence microscope. The in vitro cytotoxicities of GDNGs and GDNGs-Dox are evaluated in detail.

2. Materials and Methods

2.1. Synthesis of gel-dopa

The dopamine is grafted onto gelatin by ethyl-dimethyl-aminopropylcarbodiimide (EDC) and N-hydroxy-succinimide (NHS) coupling chemistry[23]. Typically, 1.0 g of gelatin (Type A from porcine skin, Sigma-Aldrich, G2500) is added into 50 mL of phosphate buffered saline (PBS, pH 7.4) solution in a 250 mL round-bottom flask and dissolved under microwave irradiation. The flask is immersed in an oil bath at 37 °C for 1 h, and the pH value of gelatin solution is adjusted to 5.0–6.0. Subsequently, 0.25 g of EDC (Sigma-Aldrich, E6383) and 0.15 g of NHS (Sigma-Aldrich, 56480), dissolved in 2 mL of deionized (DI) water, are added into the solution, respectively, followed by stirring for 30 min. Dopamine hydrochloride of 1.0 g (Sigma-Aldrich, H8502) dissolved in 2 mL of DI water is added dropwise, and pH value of the reaction solution is maintained at 5.0–6.0. After stirring for 12 h at 37 °C, small amount of precipitation is filtered off, and the filtrate is dialyzed against DI water for two days. The solution is filtered through a 0.45 μm membrane filter, and then freeze-dried for four days to obtain Gel-Dopa conjugate foam.

2.2. Proton nuclear (^1H NMR)

The ^1H NMR spectra of the resultant gelatin-dopa conjugate is recorded on a Bruker Avance-300 NMR spectrometer by transferring Gel-Dopa solution (1.5%, w/v) in deuterium oxide(D_2O) into a 5 mm NMR tube. In addition, the ^1H NMR spectra of gelatin and dopamine hydrochloride are determined as control.

2.3. UV-visible (UV-Vis) spectroscopy

The grafting content of dopamine in Gel-Dopa conjugate is determined by the UV absorbance at 280 nm[24]. Briefly, the

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