Materials Science and Engineering C 48 (2015) 384–390

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Controlled release of doxorubicin from electrospun PEO/chitosan/graphene oxide nanocomposite nanofibrous scaffolds

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ARTICLE INFO

Article history:
Received 25 August 2014
Received in revised form 10 November 2014
Accepted 7 December 2014
Available online 10 December 2014

Keywords:
Graphene oxide
Nanofibrous scaffold
Doxorubicin
Controlled drug release
Cell viability

ABSTRACT

Polyethylene oxide (PEO)/chitosan (CS)/graphene oxide (GO) electrospun nanofibrous scaffolds were successfully developed via electrospinning process for controlled release of doxorubicin (DOX). The SEM analysis of nanofibrous scaffolds with different contents of GO (0.1, 0.2, 0.5 and 0.7 wt.%) indicated that the minimum diameter of nanofibers was found to be 85 nm for PEO/CS/GO 0.5% nanofibers. The π–π stacking interaction between DOX and GO with fine pores of nanofibrous scaffolds exhibited higher drug loading (98%) and controlled release of the DOX loaded PEO/CS/GO nanofibers. The results of DOX release from nanofibrous scaffolds at pH 5.3 and 7.4 indicated strong pH dependence. The hydrogen bonding interaction between GO and DOX could be unstable under acidic conditions which resulted in faster drug release rate in pH 5.3. The cell viability results indicated that DOX loaded PEO/CS/GO/DOX nanofibrous scaffold could be used as an alternative source of DOX compared with free DOX to avoid the side effects of free DOX. Thus, the prepared nanofibrous scaffold offers as a novel formulation for treatment of lung cancer.

1. Introduction

Administration of chemotherapeutic drugs is toxic to healthy cells and tissues. Therefore, it is necessary to develop a targeted drug delivery system which could efficiently transport drugs to improve the efficacy of the drug and to reduce the systemic toxicity [1,2]. Various nanocarriers including polymeric micelles, nanofibers, nanoparticles and liposomes have been studied to design an efficient drug delivery system for the delivery of therapeutics to cancerous tissues [3–6]. Among nanocarrier systems, electrospun nanofibers due to the high surface area-to-volume ratio with fine pores have a very strong drug efficacy. The higher surface area and higher porosity of nanofibers provide the higher drug encapsulation efficiency and better stability compared with other drug formulations [7–10].

Natural biodegradable polymers such as cyclodextrin, chitin and chitosan (CS) are polymeric materials to increase the biocompatibility of the matrix for controlled release of therapeutic molecules [11–13]. Among natural polymers, CS due to the unique characteristics such as excellent biocompatibility, biodegradability, and nontoxicity has been widely used for drug delivery systems [14,15]. However, the electrospinning of CS due to the low solubility, low stability and low mechanical properties is extremely difficult [16]. In the past studies, the CS nanofibers were successfully developed by blending of polymers including polyethylene oxide (PEO), poly(vinyl alcohol) (PVA), cellulose, zein, poly(lactic acid), PCL and nylon-6 with CS [16].

Among nanocarriers, graphene oxide (GO) due to excellent biocompatibility and stability as well as large specific surface area is widely used in drug delivery systems [17–20]. Doxorubicin (DOX), an anthracycline antibiotic, has been widely used as an anti-cancer drug in cancer chemotherapy intravenous administration. DOX could make a strong bond with GO surface via π–π interactions [21,22]. This π–π stacking interaction is ascribed as a non-covalent type of functionalization that provides controlled release of drug [23]. Therefore, GO could be used as an ideal nanocarrier for cancer therapy. In addition, GO has epoxy and carboxylic functional groups which can react with amine groups of CS [24]. Considering the above mentioned advantages of GO and CS, the CS/GO nanocomposite is promised as an effective formulation for controlled release of anticancer drug (DOX). In the previous studies, CS/GO nanocomposite carrier is widely used for anticancer delivery systems [25,26]. However, there is no study about controlled release of PEO/CS/GO nanofibrous scaffolds for anticancer drug delivery system.

In the present study, the electrospun PEO/CS/GO nanofibrous scaffolds are developed via electrospinning process. The potential of electrospun

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http://dx.doi.org/10.1016/j.msec.2014.12.039
0928-4931/

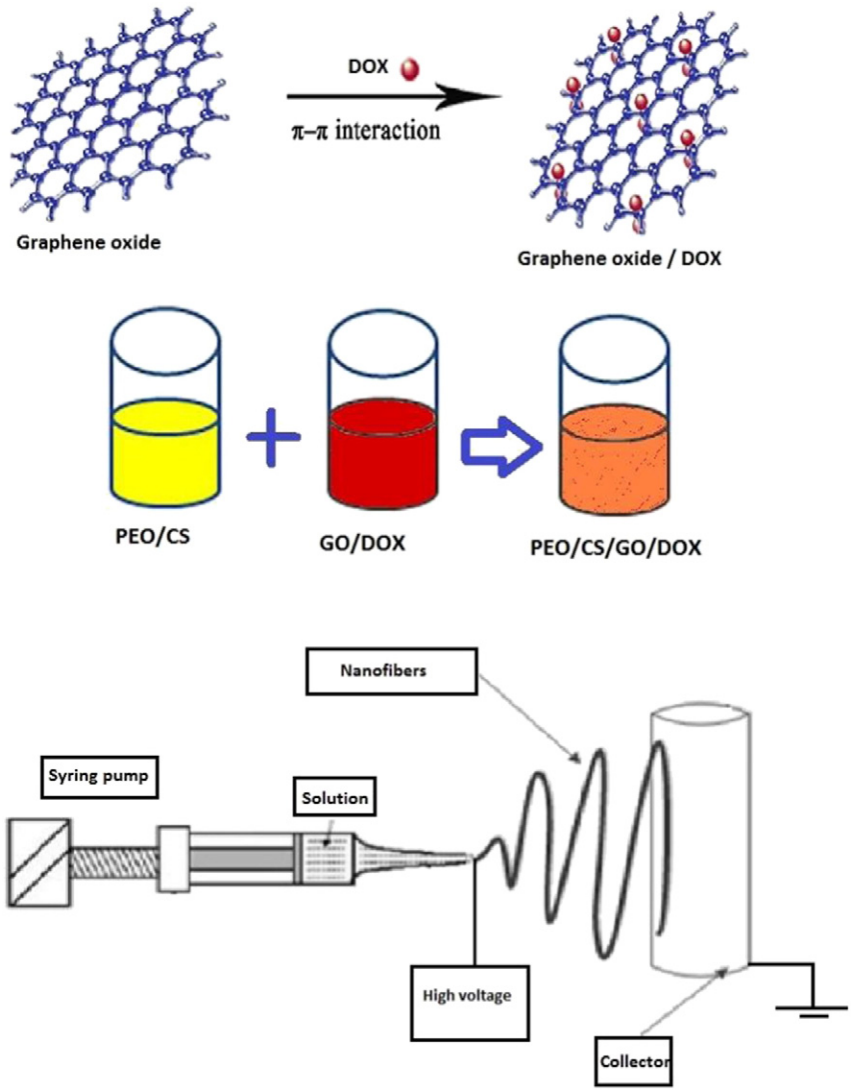

Fig. 1. The schematic of the process for preparation of PEO/CS/GO nanofibers.

nanofibers is investigated for DOX loading as an anticancer drug delivery. The Fourier transform infrared (FTIR) analysis is used to investigate the interaction between constituents. In order to clarify the acid responsiveness in vitro drug release from PEO/CS/GO/DOX nanofibrous scaffold is investigated in buffer solutions of pH 7.4 and 5.3, antitumor activity of the DOX-containing PEO/CS/GO nanofibers is investigated.

2. Experimental

2.1. Materials

CS (MW of 200 kDa and deacetylation degree of 75–85%) and PEO (MW of 900 kDa) were purchased from Sigma-Aldrich (Sigma-Germany). Sulfuric acid (H_2SO_4, 97%), hydrogen peroxide (H_2O_2, 30 wt.%), acetic acid and phosphoric acid were obtained from Fluka (Fluka—Switzerland). Doxorubicin hydrochloride was provided from Sobhan Pharmaceuticals, Iran (Sobhan-Iran).

2.2. Synthesis of GO

Graphite oxide was synthesized from pure graphite powder via modified Brodie method [27]. Briefly, raw graphite (1.0 g) and potassium chloride (8.0 g) were mixed in a flask containing 20 mL nitric acid with stirring for 24 h. The following processes such as washing, filtration and cleaning were carried out as in Brodie method. The synthesized graphite oxide (10 mg) was dispersed into the 30 mL of NaOH solution at pH 10 and was sonicated for 1 h to make a homogeneous solution. After ultrasonication, samples were immediately precipitated by a centrifuge at 15,000 rpm for 10 min and washed with HCl (5%) and deionized water several times until the pH of the supernatant was neutral. Finally the material was dried and then sonicated to obtain brown GO.

2.3. Loading of drug into the GO

The GO aqueous suspensions were sonicated in different concentrations (0.1, 0.2, 0.3, 0.5, 0.6 and 0.7% wt%) for 1 h to obtain homogenous solutions. Then, 50 mg/g of DOX was added into the GO solutions and were stirred for 24 h. Then, the prepared solutions were centrifuged at 9000 rpm for 1 h. Finally, the solutions were washed in dionized water for 1 h.

2.4. Preparation of PEO/CS/GO/DOX solutions

The CS (8% w/v) and PEO (10% w/v) powder were initially added to a solution of 2 wt.% acetic acid in distilled water and stirred for 24 h to obtain the homogenous solutions of PEO and CS. Then, the PEO/CS solution was obtained by blending of CS and PEO with a ratio of 9:1 and stirring them for 24 h. Then, glyoxal as a crosslink agent was added to the