Journal of Drug Delivery Science and Technology 43 (2018) 103–106

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Planar polymer-graphene oxide nanohybrid as a 5-fluorouacil carrier in pH-responsive controlled release

Majid Aliabadi[a,*], Arash Yunessnia lehi[b], Hamidreza Shagholani[b], Ali Gerayeli[b]

[a] Department of Chemical Engineering, Islamic Azad University, Birjand, Iran
[b] Institute of Nanoscience and Nanotechnology, University of Kashan, Kashan, Iran

ARTICLE INFO

Keywords:
Controlled release
5-fluorouracil
Graphene oxide
Nanohybrid
Tannic acid

ABSTRACT

The aim of current study was to develop a pH-responsive controlled release system of a cancer drug (5-fluorouracil) by the use of a planar nanohybrid to reduce the dosing frequency and consequently improve the patient compliance. This nanohybrid was developed by taking advantage of graphene oxide sheets as a support and poly (ethyleneimine) and tannic acid as materials to encapsulate the drug molecules. The release rates of this cancer drug molecule from the nanohybrid were significantly sensitive to the existence of H^+ ions in the environmental solution (74% in pH = 5.8 and 59% in pH = 7.4). In phosphate buffered saline solution, the release of 5-fluorouracil from the nanohybrid was fast in the earliest time but stayed steady after few hours. The degradation experiments revealed that the collapse of this nanohybrid is drastic in pH = 5.8 during 10 days.

1. Introduction

Modern medicine needs to promote discovery of new and effective drug delivery systems for intensifying the therapeutic profile and efficacy of therapeutic agents. Advances in nanoscience and nanotechnology enabling the syntheses of creative nanomaterials with specific functional groups have led to the development of a number of futuristic drug delivery systems [1]. The carbon materials are the most common elements in our ecosystem and therefore, they are expected to be more environmentally and biologically compatible and convenient than inorganic materials [2]. Among these kinds of materials, graphene as a modern substance has attracted an increasing research attention to be utilized in biological applications. Due to unique structure and geometry, it possesses remarkable physical and chemical properties. The properties cause graphene to be considered as a promising material. In the area of biological applications, graphene and its composites have been emerged as new biomaterials [1].

Graphene oxide (GO) is an oxidized derivative of graphene which has been studied in nanomedicine and biological applications for few years. Because of the presence of abundant hydrophilic groups on its surface, GO is well dispersed in water and physiological mediums. Also, GO can be more easily functionalized covalently or non-covalently with other molecules and drugs. Large surface area (> 500 m^2/g) of GO exposes a potential for the immobilization or loading of various chemicals and biomolecules such as drugs, genes, proteins, etc. In addition, GO can enhance the cellular uptake of small molecules and macromolecules because of its capability for traversing the plasma membrane [3]. Potentiality of GO as an effective nanocarrier have been demonstrated for delivery of multiple anticancer drugs. Combination of GO and cationic polymers could help to load siRNA and aromatic anticancer drugs onto GO sheets [4].

Apart from that, poly(ethyleneimine) (PEI) has been put into practical uses as a result of its inherent and natural properties as a water soluble cationic polymer in both forms of linear or branched. PEI-based polymers could form a complex with DNA or siRNA for gene delivery, assist the endosomal release and escort their cargo into the nucleus in the intracellular trafficking [5]. On the other hand, tannic acid (TA) is a tannin which can be hydrolyzed under mild acidic or alkaline conditions to yield glucose and phenolic acids such as gallic acid. Hot water or enzymes can also lead to hydrolysis of tannic acid [6]. In this study, we tried to hybridize these polymers with graphene oxide sheets to form a planar TA-PEI-GO nanocomposite. This nanohybrid was applied as a novel drug delivery system for 5-Fluorouracil (5-Fu). This new nanocarrier could be destroyed in acidic medium of cancerous cells and therefore, drug molecules could be released in targeted tissue because of hydrolysis of tannic acid.

2. Experimental

2.1. Synthesis of planar TA-PEI-GO nanohybrid

First of all, graphene oxide (GO) sheets were synthesized as a

* Corresponding author. Department of Chemical Engineering, Islamic Azad University, Birjand Branch, P.O. Box: 97177-11111, Birjand, Iran.
E-mail addresses: aliabadi@iaubir.ac.ir (M. Aliabadi), arash_yunessnia_lehi@yahoo.com (A. Yunessnia lehi), shagholani@grad.kashanu.ac.ir (H. Shagholani).

http://dx.doi.org/10.1016/j.jddst.2017.09.020
Received 21 July 2017; Received in revised form 27 August 2017; Accepted 26 September 2017
Available online 28 September 2017
1773-2247/

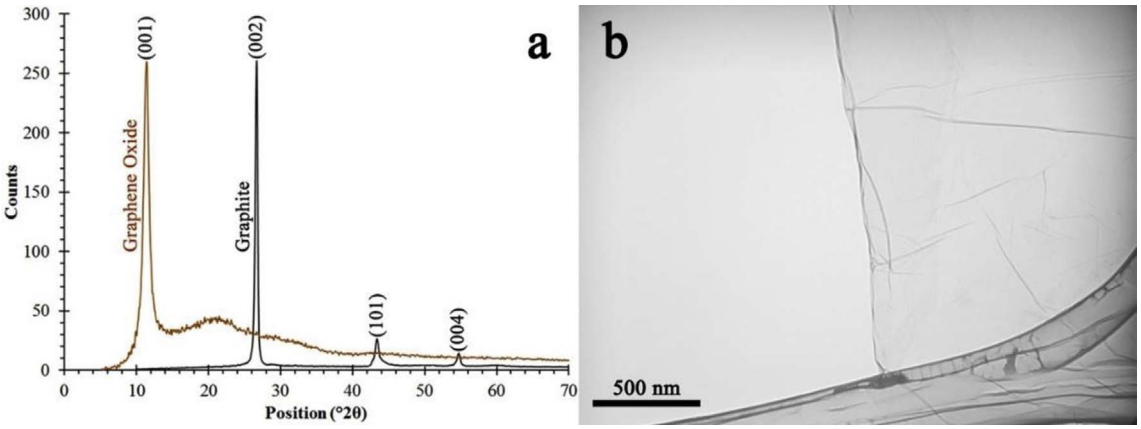

Fig. 1. XRD patterns of graphite and GO (a) and TEM image of GO (b).

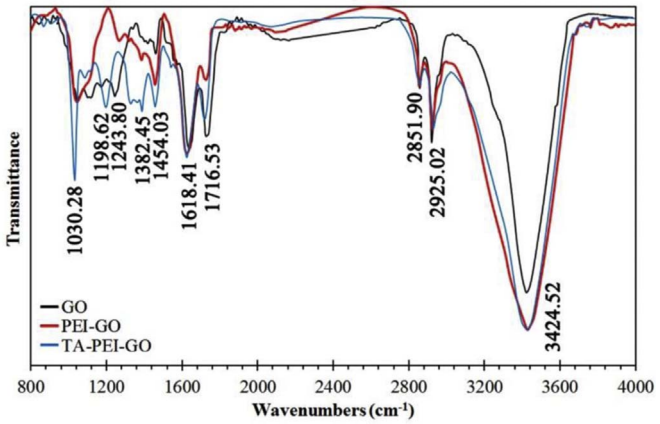

Fig. 2. FTIR spectra of GO, PEI-GO and planar TA-PEI-GO nanohybrid.

procedure published previously [7]. Briefly, a mixture of graphite, $NaNO_3$ and concentrated H_2SO_4 was continuously stirred at 0 °C. Then, $KMnO_4$ was gradually added to the mixture. The mixture was stirred for 90 min at 0 °C and after that, the temperature was reached to 35 °C and stirred for 2 h. Distilled water was used to dilute the resulting suspension. H_2O_2 solution was poured into the suspension to obtain graphite oxide. The graphite oxide was separated from that by a centrifuge at 16,000 rpm for 10 min and washed with distilled water repeatedly until pH reached to 7. Graphite oxide powder was dispersed by sonication bath to obtain a GO suspension. It should be stated that thick multilayer flakes of GO were removed by centrifuging at low speeds (2000 and 4000 rpm). Eventually, thin graphene oxide powder was dried in the oven at 60 °C for 24 h.

In the next step, epichlorohydrine was used as a coupling agent for mounting poly(ethyleneimine) (PEI, MW = 60,000 g/mol) onto GO sheets [8]. 30 mg of GO was dispersed in 60 ml of deionized water by sonication bath for 1 h. 0.1 g of NaOH was added to the suspension followed by adding 5 ml of epichlorohydrin and stirred vigorously. Then, 50 ml of PEI solution (2 mg/ml) was added to the GO mixture. The reaction was continued for 4 h with continuous circular stirring at 40 °C and then, formed PEI-GO was centrifuged at 4000 rpm for 1 h and the supernatant was removed. In the last step, 30 mg of PEI-GO was dispersed in deionized water by sonication bath for 2 h. Then, 150 mg of tannic acid was dissolved in deionized water and mixed to last suspension. The mixture was stirred for 15 min to allow tannic acid to interact with amine groups on the PEI-GO surface. After that, 1 ml of glutaraldehyde (GA) and 1 ml of HCl 1 N was added to the mixture. The reaction was carried for 15 min and then, final planar TA-PEI-GO nanohybrid was centrifuged at 4000 rpm for 20 min.

Morphology of graphene oxide sheets and nanohybrids was examined by transmission electron microscopy (TEM, Zeiss) and filed emission scanning electron microscopy (FE-SEM, Hitachi S-4160, Japan). FT-IR spectroscopy (Nicolet Magna IR 550) and XRD patterns (Cu K_α radiation, Bruker d8 advance) were accomplished for qualitative analysis of graphene oxides.

2.2. Degradation, drug loading and release study of planar TA-PEI-GO nanohybrid

The degradation behavior of planar TA-PEI-GO nanohybrid was studied by immersing the samples in phosphate buffered saline (PBS) solution (pH = 7.4 and 5.8) at 37 °C for 2 and 10 days. After given time intervals, the samples were separated from the solution, washed two times with deionized water and then, dried at room temperature. Scanning electron microscopy was used to study changes of the surface morphology of TA-PEI-GO nanohybrid.

Drug loading and release behavior of planar TA-PEI-GO nanohybrid was observed by using 5-fluorouracil (5-Fu) as a model drug. A mixture of 5-Fu solution and TA-PEI-GO nanohybrid (50% wt.) was sonicated and kept for 24 h at room temperature. Then, TA-PEI-GO nanohybrid was separated from the solution by centrifuging. The quantity of unabsorbed 5-Fu molecules in the solution was determined by a UV-Vis

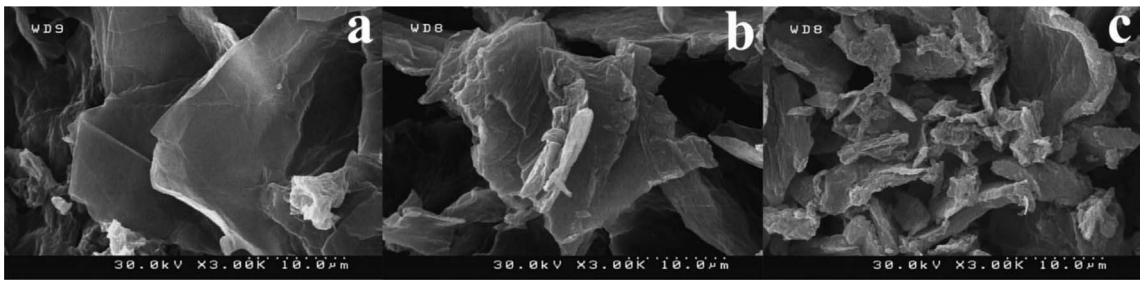

Fig. 3. FE-SEM images of GO (a), PEI-GO (b) and planar TA-PEI-GO nanohybrid (c).