Development of multifunctional cobalt ferrite/graphene oxide nanocomposites for magnetic resonance imaging and controlled drug delivery

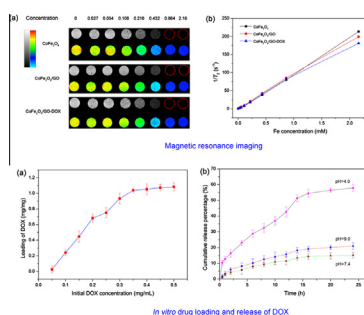Guangshuo Wang [a,*], Yingying Ma [a], Zhiyong Wei [b], Min Qi [b]

[a] Department of Composite Materials and Engineering, College of Equipment Manufacturing, Hebei University of Engineering, Handan 056038, China
[b] School of Material Science and Engineering, Dalian University of Technology, Dalian 116024, China

HIGHLIGHTS

- Cobalt ferrite/graphene oxide ($CoFe_2O_4$/GO) were prepared by a facile sonochemical method.
- GO nanosheets were fully exfoliated and decorated homogeneously with $CoFe_2O_4$ nanoparticles.
- $CoFe_2O_4$/GO showed superparamagnetic behavior, hydrophilic character and negligible cytotoxicity.
- Significant T_2-weighted enhancement effect with relaxivity coefficient of $92.71 \text{ mM}^{-1} \text{ s}^{-1}$.
- Drug loading capacity was as high as 1.08 mg/mg and drug release showed pH-sensitive feature.

GRAPHICAL ABSTRACT

Magnetic resonance imaging

In vitro drug loading and release of DOX

ARTICLE INFO

ABSTRACT

Developing multifunctional theranostic platforms with complementary roles has drawn considerable attention in recent years. In this study, superparamagnetic cobalt ferrite/graphene oxide ($CoFe_2O_4$/GO) nanocomposites with integrated characteristics of magnetic resonance imaging and controlled drug delivery were prepared by sonochemical method. The morphology, microstructure and physical properties of as-prepared $CoFe_2O_4$/GO were investigated in detail by transmission electron microscope (TEM), scanning electron microscope (SEM), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), Raman spectra, N_2 adsorption/desorption isotherm, thermogravimetric analysis (TGA), superconducting quantum interference device (SQUID) and zeta potential measurements. The obtained $CoFe_2O_4$/GO exhibited superparamagnetic property and dose-dependent T_2-weighted enhancement effect with relaxivity coefficient of $92.71 \text{ mM}^{-1} \text{ s}^{-1}$. Furthermore, the $CoFe_2O_4$/GO showed negligible cytotoxicity even at a high concentration after being treated for 96 h. Doxorubicin hydrochloride (DOX) as an anti-tumor model drug was loaded on $CoFe_2O_4$/GO. The nanocomposites were found to be able to efficiently transport DOX into the cancer cells and then cause cell death. The drug loading capacity of this nanocarrier was as high as 1.08 mg/mg and the drug release behavior demonstrated a sustained and pH-responsive way. The results suggested that the as-prepared $CoFe_2O_4$/GO showed great potential as an effective multifunctional nanoplatform for magnetic resonance imaging and controlled drug delivery for simultaneous cancer diagnosis and chemotherapy.

© 2015 Elsevier B.V. All rights reserved.

* Corresponding author.
   E-mail address: wgs8136@163.com (G. Wang).

1. Introduction

Currently, graphene is the carbon allotrope generating the greatest interest, not only from the point of view of academic curiosity, but also considering its potential applications in a wide range of areas owing to its prominent thermal stability, extraordinary mechanical properties, superior electronic conductivity and remarkable structural flexibility [1–3]. Graphene oxide (GO), as the precursor for mass production of graphene-based materials, can be well-dispersed in water and physiological environments due to high density of oxygen-containing groups, such as carboxylic, hydroxyl and epoxide groups on its surfaces and edges. In addition, unique planar structure, high surface area and lack of obvious toxicity make GO a promising candidate for drug carrier substances [4–8]. A number of innovative carrier systems including liposomes, micelles, capsules, dendrimers and polymeric nanoparticles have been developed in the last few decades [9,10]. Although current drug transport vehicles have shown numerous advantages such as drug solubilization and prolonged blood circulation, there are several main obstacles including low drug loading efficiency, nonspecific accumulation and lack of real-time monitoring, which largely hinder the development of modern drug delivery [11,12]. Therefore, it is still a big challenge to develop novel multifunctional theranostic platforms with the abilities of high drug loading efficiency, intelligent controlled release and *in vivo* site targeting delivery and treatment of illnesses [13,14].

Cobalt ferrite ($CoFe_2O_4$) nanoparticles have attracted great attention in the past two decades and are being explored in a variety of biomedical applications especially for magnetic resonance imaging (MRI) owing to high magnetic anisotropy and moderate magnetization [15–18]. MRI is a well-known noninvasive imaging tool to visualize internal structure of the body in detail, which is considered as one of the most powerful clinical diagnostic techniques for the evaluation of various diseases [19,20]. The immobilization of $CoFe_2O_4$ nanoparticles on GO nanosheets will develop a novel nanoplatform having dual-functional characteristics with synergistic effects of MRI and drug delivery for a more efficient cancer therapy. On one hand, the novel nanoplatform acts as drug delivery system with efficient drug loading, targeted drug delivery and controlled release due to its large specific surface, magnetic targeting ability and unique electrochemical properties. This intelligent drug system can improve the delivery effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site. On the other hand, MRI imaging technology allows real-time assessment of drug distribution to visualize tumor coverage and maximize therapeutic effect to the target tissue by driving the drug carriers effectively into tumor tissues under a guided magnetic field, as well as to follow the therapeutics effect on the progression of disease.

Recently, the incorporation of superparamagnetic nanoparticles with GO nanosheets to prepare magnetic nanocomposites has attracted considerable interest [11,21–23]. Such nanocomposites are gaining ground in biomedical applications due to their favorable biocompatibility and good colloidal stability. Despite much efforts paid to prepare various GO-based magnetic nanocomposites, there are several challenges need to be addressed. For instance, the synthetic methods for superparamagnetic nanoparticles such as co-precipitation, solvothermal synthesis and thermal decomposition would lead to low-quality and polydisperse magnetic nanoparticles. Meanwhile the covalent integration of magnetic nanoparticles onto GO nanosheets would require a well-established functionalized surface of the nanoparticles, which is very sensitive to the nanoparticles type. In addition, so far there has been no perfect control over the GO-based nanocomposites in

terms of particle size, size distribution and the loading amount of the magnetic nanoparticles. All these challenges need to be overcome in order to enable the obtained nanocomposites to be useful in biomedical applications.

Herein, a facile sonochemical method was utilized to prepare $CoFe_2O_4$/GO nanocomposites in this study, which held dual-functional characteristics with complementary roles of MRI feature and pH-sensitive controlled drug delivery. The reaction was efficient and controllable, in which $CoFe_2O_4$ nanoparticles were homogeneously decorated on the surface of GO nanosheets. MRI contrast ability and cytotoxic effect were evaluated in vitro to investigate bio-imaging potential of the obtained $CoFe_2O_4$/GO. Moreover, an anti-tumor model drug of doxorubicin hydrochloride (DOX) was loaded on $CoFe_2O_4$/GO and the loading capacity and release behavior of DOX from $CoFe_2O_4$/GO-DOX were also examined. The obtained $CoFe_2O_4$/GO nanocomposites is expected to be an effective multifunctional nanoplatform for diagnostic and therapic applications by combining magnetic resonance imaging and controlled drug delivery.

2. Experimental

2.1. Materials

Natural flake graphite with an average particle size of 40 mesh (NFG, 99%) was obtained from Qingdao Tianhe Graphite Co., Ltd. Potassium permanganate ($KMnO_4$, AR), sulfuric acid (H_2SO_4, AR), sodium nitrate ($NaNO_3$, AR), hydrogen peroxide (H_2O_2, 30% aq.), sodium hydroxide (NaOH, AR), polyvinylpyrrolidone (PVP K30, M_n = 30,000), ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, 98%) and cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_2O$, 98%) were purchased from Sinopharm Chemical Reagent Co., Ltd. Doxorubicin hydrochloride (DOX, >99%) was supplied by J&K Chemical Co., Ltd. All the other chemicals were used as received, without further purification.

2.2. Preparation of GO nanosheets

GO nanosheets were prepared by a modified Hummers' method. In a typical experiment, a four-necked flask containing 250 mL of H_2SO_4 was placed in an ice bath, and followed by the addition of 2.5 g $NaNO_3$ and 5 g NFG. The mixture was stirred for 15 min below 5 °C, and then 35 g $KMnO_4$ was slowly added into the mixture. The rate of addition was controlled carefully, avoiding a sudden increase of temperature. After 30 min of mechanical stirring below 10 °C, the temperature was raised to 35 °C and maintained for 60 min. Then 240 mL deionized water was added dropwise into the mixture under strong mechanical stirring and the temperature was controlled below 98 °C via a water bath. After 30 min mechanical stirring, the viscous mud was diluted by 1000 mL deionized water. A certain amount of 30% H_2O_2 was dripped into the diluted mud to reduce the unreacted $KMnO_4$ until the pH of supernatant became neutral. Finally, the resulting solid was filtered and dried at 60 °C for 24 h in vacuum, where a brown film was obtained.

2.3. Preparation $CoFe_2O_4$/GO nanocomposites

The $CoFe_2O_4$/GO nanocomposites were synthesized by sonochemical method with the assistance of ultrasonic vibrations. In a typical experiment, 100 mg GO were dispersed in 150 mL deionized water by ultrasonic treatment for 30 min, and followed by the addition of 0.67 g PVP, 1.6 g $FeCl_3 \cdot 6H_2O$ and 0.81 g $CoCl_2 \cdot 6H_2O$. The mixture solution was added dropwise into 250 mL three-necked