



Construction of a novel fluorinated graphene-based magnetic nanocomposite and its application in cancer photo-chemotherapy



Jiuyao Du¹, Jinfeng Liu¹, Peiwei Gong^{*}, Meng Tian, Lu Sun, Shuaijie Ji, Lei Zhang, Zhe Liu^{*}

The Key Laboratory of Life–Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, Institute of Anticancer Agents Development and Theranostic Application, Qufu Normal University, Qufu 273165, PR China

ARTICLE INFO

Article history:

Received 18 January 2017

Received in revised form 21 February 2017

Accepted 23 February 2017

Available online 27 February 2017

Keywords:

Carbon materials

Microstructure

Fluorinated graphene

Photothermal performance

ABSTRACT

Fluorinated graphene (FG) inherits the excellent performance of graphene and fluorinated carbon, and has many outstanding properties in biological fields. However, the hydrophobic nature and harsh preparation conditions greatly limit its further functionalization and practical applications. Herein, a novel strategy is reported to prepare water-soluble fluorinated graphene oxide (FGO), and this method also facilitates us for the first time to decorate FGO with magnetic Fe₃O₄ nanoparticles. The constructed novel (FGO/Fe₃O₄) nanocomposite not only shows good biocompatibility even at high concentration, but exhibits excellent photothermal efficiency in near infrared region. Moreover, the improved dispersibility and high surface area also enable the nanocomposite to have drug loading capacity, and cell experiment study indicates the nanocomposite is a valuable candidate for cancer photo-chemotherapy.

© 2017 Published by Elsevier B.V.

1. Introduction

Fluorinated graphene (FG), a new derivative of graphene, has many excellent properties such as high surface area, good photothermal response, and benign biocompatibility [1,2]. Especially, due to fluorine, FG also possess magnetic resonance imaging (MRI) property based on ¹⁹F. Accordingly, FG has been drawing enormously increasing research interest in many applications [3–6]. However, conventional production methods still have various limitations, and the hydrophobic and inert C–F bonds severely affect its large-scale applications, further functionalization. Therefore, it is necessary to develop a facile and efficient preparation method to prepare water-dispersible FG sheets and then realize the functionalization of FG for further applications.

On the other hand, Fe₃O₄ nanoparticles have great potentials in many applications [7,8] because of their unique magnetic property, which can be employed as magnetic target and MRI in cancer therapy. However, Fe₃O₄ nanoparticles have high surface area and easily agglomerate in solutions. An effective way to avoid this is to decorate Fe₃O₄ onto graphene, therefore it is reasonably speculated that a novel nanocomposite based on FG and Fe₃O₄ can not only realize magnetic target and dual mode MRI, but accomplish

drug loading and phototherapy. Moreover, it is also eagerly expected what other novel properties can be brought if this nanocomposite is constructed and studied.

In this work, we report a novel and simple strategy to import oxygen functional groups into FG and water-soluble fluorinated graphene oxide (FGO) is readily obtained, and this then makes it possible for Fe₃O₄ functionalization and drug loading. As far as we know, this is the first work that realizes modification of FG with Fe₃O₄ nanoparticles. Moreover, the oxygen groups on FGO can greatly enhance the affinity of Fe₃O₄ nanoparticles in hydrothermal method and make the composite stable in solutions. As supposed, the FGO/Fe₃O₄ nanocomposites are obtained by the efficient and low cost method, and exhibit excellent biocompatibility, high photo-thermal performance and drug loading capacity, showing great potential in cancer photo-chemotherapy.

2. Experimental details

2.1. Synthesis of FGO

Fluorinated graphite (FGi) was activated and exfoliated according to our previous work with some modifications [9]. Then 3 g product was added in a mixed solution of concentrated H₂SO₄ (24 mL), P₂O₅ (5 g) and K₂S₂O₈ (5 g) and stirred for 6 h at 80 °C. Further oxidation was accomplished by adding 12 mL H₂SO₄ and 2 g KMnO₄ at 30 °C for 4 h. The formed FGO was obtained by filtration and purified by dialysis.

* Corresponding authors.

E-mail addresses: gongpeiwei10@mails.ucas.ac.cn (P. Gong), liuzheqd@163.com (Z. Liu).

¹ The first two authors are equal first authors.

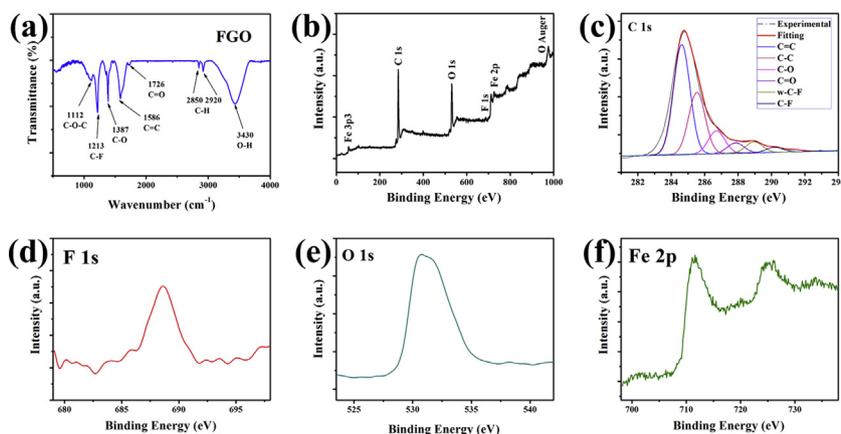


Fig. 1. (a) FTIR spectrum of FGO. (b) Full XPS spectrum of FGO/Fe₃O₄. The chemical components of the sample are labeled. High resolution XPS spectra of C1s and corresponding Gaussian fitting results (c), and F1s, O1s and Fe 2p (d–f).

2.2. Synthesis of FGO/Fe₃O₄

Nanocomposites with different ratios and reaction conditions were prepared and tested, and the optimal ratio is as follows. FeSO₄ (0.8×10^{-5} mol) and FGO (5 mg) were added in 6 mL of DI water, and ammonia was added to adjust the pH to 9.5. Then the solution was transferred into autoclave and heated at 180 °C for 2 h. The product was washed and dried through vacuum freeze drying.

More experimental data and details can be found in the [Supplementary Information](#).

3. Results and discussion

The key procedure for successful modification of FG is introducing oxygen functional groups onto the carbon skeleton, which finally changes FG from hydrophobic to hydrophilic and provides the binding sites for Fe₃O₄ nanoparticles. By pre-treating FG using a F-sacrificing strategy based on our previous work with some modifications [9], chemically inert FG becomes active and can be oxidized by our newly developed oxidation method. As shown in [Fig. S1](#), the solubility of FG greatly improved after oxidation, and FTIR spectrum in [Fig. 1a](#) indicate that while C–F bonds (1213 cm^{-1}) was retained, oxygen groups in the forms of C–O (1387 cm^{-1}), C–O–C (1112 cm^{-1}), O=C=O (1726 cm^{-1}) are successfully introduced. The successful synthesis of FGO/Fe₃O₄ nanocomposite was first confirmed by element analyses. XPS ([Fig. 1b](#)) and FTIR spectra ([Fig. S2](#)) indicate that Fe₃O₄ has been successfully loaded on the surface of FGO layers. High resolution XPS spectrum ([Fig. 1c–f](#)) is employed to study the composition and the nature of chemical bonds. The C1s spectrum of FGO/Fe₃O₄ ([Fig. 1c](#)), six fitted peaks are found, corresponding to C=C (284.6 eV), C–C (285.5 eV), C–O (286.7 eV), C=O (287.8 eV), C–F (288.9 eV), and w-C–F (290.2 eV) groups [9], respectively. The O1s spectrum ([Fig. 1e](#)) indicates oxygen have been grafted onto the surface of FG sheets. The F1s spectrum ([Fig. 1d](#)) located at about 688.6 eV, clearly shows the presence of fluorine atoms. [Fig. 1f](#) shows two peaks located at 711.6 eV (Fe 2p_{3/2}) and 726.0 eV (Fe 2p_{1/2}) indicating the formation of Fe₃O₄ [10].

To obtain detailed structural information, XRD pattern ([Fig. 2a](#)) was further analyzed and for FGO samples, the (001) peak near 14° is considered as the reflection of a high fluorine level in hexagonal system [11], and the broad (002) reflection peak ($2\theta = 26^\circ$) shows the stack sequences of the samples along the stacking direction [12]. The peaks at 41° can be assigned to the (100) reflections that represent the C–C in-plane length in the reticular system [13]. As for the nanocomposite, the peak of FGO is almost overlapped by

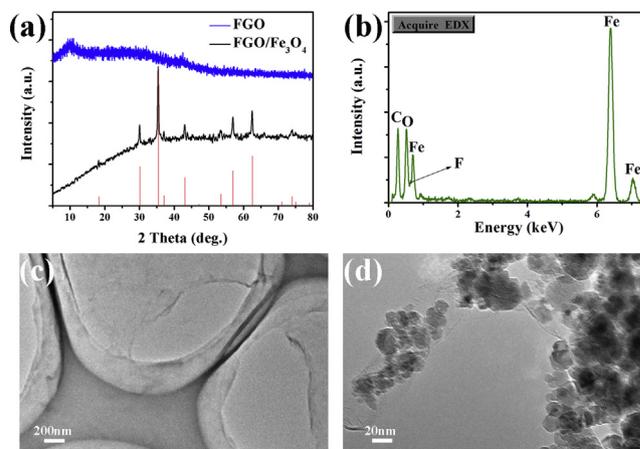


Fig. 2. (a) XRD pattern for FGO (black) and FGO/Fe₃O₄ (blue). (b) Energy dispersive X-ray (EDX) spectrum of FGO/Fe₃O₄. TEM images of (c) FGO sheet and (d) FGO/Fe₃O₄. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fe₃O₄ nanoparticles, which show intense peaks at $2\theta = 30.2^\circ$, 35.6° , 43.3° , 53.7° , 57.3° and 62.8° , and these data fit well to the JCPDS card (65-3107). The chemical element analyses from EDX spectrum ([Fig. 2b](#)) indicate exist of fluorine, carbon, oxygen and iron elements in the sample, and these results corresponded well to the XPS data in [Fig. 1b](#). In addition, the FGO/Fe₃O₄ nanocomposite can excellently accumulate through magnet (see photos in [Fig. S3](#)). Brunauer-Emmett-Teller (BET) measurements ([Fig. S4](#)) indicate that FGO/Fe₃O₄ nanocomposite have a large surface area of $149.35 \text{ m}^2/\text{g}$. TEM observation is performed to investigate the morphology and structure. [Fig. 2c](#) clearly shows that transparent and thin FGO sheets with corrugated structure were observed. Besides, the nano-sheets possess a very stable nature even under electron beam. Fe₃O₄ nanoparticles with uniform sizes were successfully attached to FGO sheets, which can be seen in [Fig. 2d](#) and the average size of Fe₃O₄ is about 20 nm.

The photothermal conversion capabilities of FGO sheets, Fe₃O₄ and FGO/Fe₃O₄ nanocomposites were investigated and shown in [Figs. S5](#) and [3](#). The temperature of FGO/Fe₃O₄ ($70 \mu\text{g}/\text{mL}$) can easily reach 52.2°C at a low power density of $1 \text{ W}/\text{cm}^2$ for 600 s. Compared to FGO and Fe₃O₄ ([Fig. S5](#)), they could not reach 50°C under the same conditions. Therefore, the FGO/Fe₃O₄ nanocomposites exhibited superior photothermal behavior, and showed concentration-dependent behavior ([Fig. 3b](#)). Moreover, the nanocomposited showed nice stability against photothermal

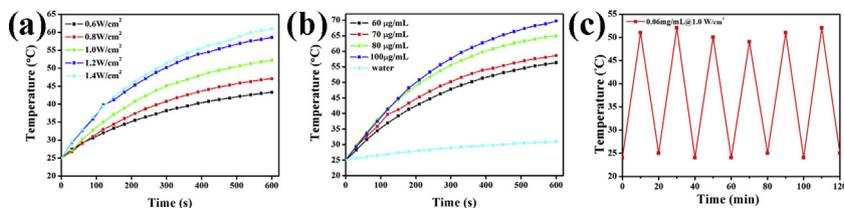


Fig. 3. Photothermal performance of FGO/Fe₃O₄ solution exposed to 808 nm laser (a) at different power densities (70 µg/mL), and (b) different concentration at 1.2 W/cm². (c) Warming cycles of the composite.

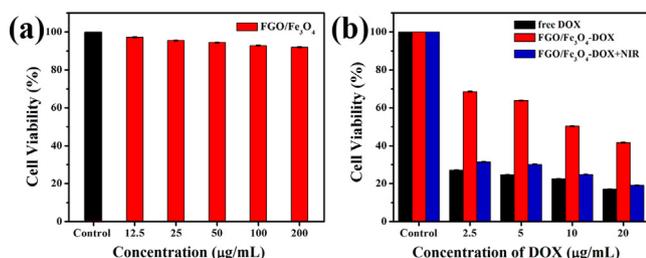


Fig. 4. (a) Cell viability of FGO/Fe₃O₄. (b) Cell viability of Hela cells with different concentration of free DOX, FGO/Fe₃O₄-DOX and FGO/Fe₃O₄-DOX with NIR for 24 h.

heating after cycles of warming procedure (Fig. 3c). These results indicated the FGO/Fe₃O₄ nanocomposites possessed satisfying photothermal stability and excellent photothermal performance.

The cytotoxicity of material is a key factor that affects its further application in biological fields, and the successful construction of FGO/Fe₃O₄ nanocomposite allows us for the first time to evaluate its cytotoxicity. It was found that cell viability remained above 90% even at a very high concentration of 200 µg/mL (Fig. 4a). Then a broad-spectrum anti-cancer drug, Doxorubicin (DOX), was loaded and accordingly a magnetic composite possessing cancer photo-chemotherapy was constructed. The successful drug loading was confirmed by characteristic peaks of DOX in the FTIR spectrum (Fig. S6). The cell experiment and drug release data in Fig. S7 clearly indicate that compared to free DOX, the composite shows obviously sustained drug release performance and dose dependent effects (Fig. 4b). And undoubtedly, when combined NIR irradiation the composite exhibits greatly improved cancer-killing property even at very low concentration (2.5 µg/mL), which is significant in keeping good cancer therapy while reducing the drug dosage to decrease side effects. The reproducibility of this work has been confirmed by repeated experiment, such as photo-thermal performance (Fig. S8) and cell viability (Fig. S9). The mechanism of the excellent photo-chemotherapy effect is supposed to an enhanced cytotoxicity of DOX in elevated temperature and increasing heat sensitivity [14]. And this in turn reflects that the constructed FGO/Fe₃O₄ nanocomposite enjoys distinguished advantages and is potentially valuable in cancer photo-chemotherapy.

4. Conclusions

In summary, a novel FGO/Fe₃O₄ nanocomposite have been designed and first constructed in a mild and operationally simple

strategy. Elements and morphology of the composite is carefully investigated, and it exhibits excellent photothermal performance and good biocompatibility. Moreover, cell viability experiments confirm the composite enjoys excellent photo-chemotherapy effect in cancer therapy. Considering the outstanding properties and high synthesis efficiency, the constructed FGO/Fe₃O₄ nanocomposite holds great promise in future cancer photo-chemotherapy.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (21671118), the Taishan Scholar Foundation of Shandong Province, Natural Science Foundation of Shandong Province (ZR2016EMB04), and Project of Shandong Province Higher Educational Science and Technology Program (J16LA03).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.matlet.2017.02.103>.

References

- [1] R.R. Nair, W. Ren, R. Jalil, I. Riaz, V.G. Kravets, L. Britnell, et al., *Small* 6 (2010) 2877–2884.
- [2] A. Avsar, J.H. Lee, G.K.W. Koon, B. Özyilmaz, *2D Mater.* 2 (2015) 044009.
- [3] M. Inagaki, F. Kang, *J. Mater. Chem. A* (2014) 13193–13206.
- [4] A.L. Walter, H. Sahin, K.J. Jeon, A. Bostwick, S. Horzum, et al., *ACS Nano* 8 (2014) 7801–7808.
- [5] X. Liang, J. Guo, S. Liang, C. Hong, Y. Zhao, *Mater. Lett.* 135 (2014) 92–95.
- [6] R. Stine, W.K. Lee, K.E. Whitener, J.T. Robinson, P.E. Sheehan, *Nano Lett.* 13 (2013) 4311–4316.
- [7] X. Yang, X. Zhang, Y. Ma, Y. Huang, Y. Wang, Y. Chen, *J. Mater. Chem.* 19 (2009) 2710–2714.
- [8] J. Li, X. Zeng, T. Ren, E. van der Heide, *Lubricants* 2 (2014) 137–161.
- [9] P. Gong, J. Wang, W. Sun, D. Wu, Z. Wang, Z. Fan, et al., *Nanoscale* 6 (2014) 3316–3324.
- [10] L. Ren, S. Huang, F. Wei, T. Liu, *Appl. Surf. Sci.* 258 (2011) 1132–1138.
- [11] M. Zhang, L. Liu, T. He, G. Wu, P. Chen, *Mater. Lett.* 171 (2016) 191–194.
- [12] Q. Feng, N. Tang, F. Liu, Q. Cao, W. Zheng, et al., *ACS Nano* 7 (2013) 6729–6734.
- [13] X. Wang, Y. Dai, W. Wang, M. Ren, B. Li, et al., *ACS Appl. Mater. Interfaces* 6 (2014) 16182–16188.
- [14] Z. Meng, F. Wei, R. Wang, M. Xia, Z. Chen, H. Wang, et al., *Adv. Mater.* 28 (2016) 245–253.