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Simple synthesis of multifunctional zeolitic imidazolate frameworks-8/graphene oxide nanocrystals with controlled drug release and photothermal effect

Zhengfang Tian [a, 1], Xianxian Yao [b, 1], Yufang Zhu [a, b, *]

[a] Hubei Key Laboratory of Processing and Application of Catalytic Materials, College of Chemical Engineering, Huanggang Normal University, Huanggang 438000, China
[b] School of Materials Science and Engineering, University of Shanghai for Science and Technology, 516 Jungong Road, Shanghai 200093, China

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ABSTRACT

In this study, a simple method was developed to synthesize the zeolitic imidazolate frameworks-8/graphene oxide (ZIF-8/GO) nanocrystals with encapsulation of drug molecules simultaneously, which possess the pH-controlled drug release and photothermal effect. The structure, drug release behavior, photothermal effect of the ZIF-8/GO nanocrystals were investigated. Using fluorescein as a model drug, the results showed that the fluorescein-ZIF-8/GO nanocrystals with a particle size of 50–100 nm were monodisperse and exhibited pH-controlled release behavior. On the other hand, using breast cancer line 4T1 cells as a cellular system, the fluorescein-ZIF-8/GO nanocrystals showed negligible cytotoxicity and could be internalized into cancer cells. More importantly, the fluorescein-ZIF-8/GO nanocrystals had excellent photothermal effect by near infrared (NIR) irradiation ($\lambda = 808$ nm) to kill cancer cells with high efficacy. Therefore, the construction strategy to the fluorescein-ZIF-8/GO nanocrystals would be promising for the development of multifunctional platform with potential synergistic therapy.

1. Introduction

Metal-organic frameworks (MOFs), a class of crystalline porous hybrids built from metal ions and organic linkers, have attracted significant research interest in gas storage, catalysis, separation, biomedicine and other field due to their large surface area, tunable pore size, adjustable composition and structure, and versatile functionality [1–6]. Recent studies demonstrated that MOFs can be scaled down to nanometer size with regular morphology, and guest molecules (such as chemical drugs, biomolecules and photosensitizers) can be encapsulated in MOFs, which makes MOFs promising as nanocarriers for drug delivery [7,8].

To date, much effort has been made to investigate MOFs as carriers for drug delivery [7–23]. Ferey et al. for the first time reported MIL-100(Cr) and MIL-101(Cr) as carriers for the controlled delivery of ibuprofen (IBU), and the IBU loading capacities were 0.347 g/g and 1.376 g/g, respectively [9]. The IBU-loaded MIL-100(Cr) and MIL-101(Cr) exhibited a sustained release behavior in SBF at 37 °C and fully released the loaded IBU after 3 and 6 days, respectively. Compared to the toxic Cr-based MOFs, the Fe, Zn, Zr-based MOFs nanoparticles are more encouraging due to their low toxicity and biodegradation [10–12]. Horcajada et al. encapsulated anticancer busulfan in MIL-100(Fe), the loading capacity was 60 times that achieved with liposomes [13]. MIL-100(Fe) nanoparticles could load anticancer drug (doxorubicin, DOX) up to 9%, and a sustained release in PBS within 14 days was achieved without any burst release effect [13]. Nunzio et al. reported a “ship in a bottle” strategy to efficiently encapsulate topotecan in MIL-100(Fe) nanoparticles, which showed light triggered topotecan release behavior [14]. Sun et al. reported ZIF-8(Zn) nanoparticles for pH-controlled drug release [15]. Using 5-Fu as a model drug, slow 5-Fu release from the ZIF-8 nanoparticles was observed in PBS (pH 7.4), but the 5-Fu release rate was significantly increased in acetate buffer (pH 5.0) due to the decomposition of ZIF-8 in acidic solution. Vasconcelos et al. encapsulated anticancer drug DOX in nano ZIF-8 with a loading capacity of 0.049 g/g, which exhibited a progressive release behavior [16]. Recently, Zheng et al. demonstrated one-pot synthesis of ZIF-8 nanoparticles with encapsulated DOX molecules,

* Corresponding author. School of Materials Science and Engineering, University of Shanghai for Science and Technology, 516 Jungong Road, Shanghai 200093, China.
E-mail address: zjf2412@163.com (Y. Zhu).
[1] The first two authors contributed equally to this work.

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and the results showed that the DOX-loaded ZIF-8 nanoparticles exhibited pH-responsive release, and their efficacy on breast cancer cell lines was much higher than that of free DOX [17]. All of the results indicated that MOF nanoparticles could be carriers for potential drug delivery.

Recently, functional MOFs are attracting more and more attentions in biomedicine [24–30], because functional MOFs could not only maintain or enhance the controllability of drug delivery, but also endow MOFs with new functionality including imaging, sensing and tracking. For example, different drugs were encapsulated with high loading capacity by iron (III) carboxylate MOFs, which allowed for the controlled delivery of drugs and magnetic resonance imaging [13]. Wuttke et al. reported the synthesis of MIL-100(Fe)@lipid nanoparticles as nanocarriers, the lipid bilayer could prevent the premature release of drug molecules and stimulate cell uptake by cancer cells [24]. Wang et al. reported a MIL-101(Fe) based tumor targeting drug delivery system through the modification with a bicyclononyne functionalized β-cyclodextrin derivative, and the in vitro and in vivo results showed that this drug delivery system exhibited effective cancer cell inhibition with much reduced side effects [25]. He et al. encapsulated fluorescent carbon nanodots (C-dots) into ZIF-8 nanoparticles at room temperature, and the C-dots@ZIF-8 nanoparticles showed promising as nanocarriers for simultaneous fluorescent imaging and pH-responsive drug delivery to cancer cells [26]. Deng et al. reported the AS1411 aptamers functionalized UCNPs@MIL-100(Fe) nanoparticles for targeting drug delivery and cell imaging [27]. However, it can be found that most of functional MOFs are focused on the applications in controlled drug delivery and the combination of drug delivery and imaging.

From viewpoint of therapeutic efficiency in cancer treatment, controlled drug delivery could enhance therapeutic efficiency and reduce side effects of toxic anticancer drugs, but the multidrug-resistance of cancer cells in chemotherapy is a serious problem [31,32]. Therefore, more and more studies proposed the synergistic therapy strategy through the combination of controlled drug delivery with other therapeutic approaches, such as photothermal therapy, magnetic hyperthermia, gene therapy [33–35]. For example, photothermal therapy is a minimally invasive local treatment of cancers, which utilizes photothermal conversion agents (such as gold nanorods, carbon dots, graphene, and copper chalcogenides) to generate heat in tumor tissue or after the internalization by cancer cells, resulting in tumor inhibition or cancer cell apoptosis [36–39]. However, to the best of our knowledge, there are rare reports describing the construction of functional MOFs for synergistic therapy with controlled drug delivery and photothermal therapy.

Graphene and graphene oxide (GO) have attracted great attention on drug/gene delivery due to their unique morphology, easy surface modification, low toxicity and excellent biocompatibility [40]. To date, graphene and GO as nanocarriers have been reported to load a variety of therapeutics, including anti-cancer drugs, poorly soluble drugs, antibodies, proteins and genes [41–44]. For example, Liu et al. reported a phospholipid monolayer membrane functionalized graphene and the functionalized nanocomplex exhibited pH-controlled drug release behavior with a high drug loading capacity of 70% [43]. Chen et al. designed a gene delivery system based on GO chemically functionalized with branched PEI (PEI-GO), and the PEI-GO exhibited an excellent ability to load DNA at low mass ratio and effectively deliver plasmid DNA into cells and be localized in the nucleus [44]. On the other hand, graphene and GO show good near infrared (NIR) absorbance, high photothermal conversion efficiency and excellent thermal conductivity, which could be applied in photothermal treatment of tumor tissue [45,46]. For example, Yang et al. reported that the PEGylated graphene nanosheets exhibited ultrahigh in vivo tumor uptake and efficient photothermal therapy properties in mice under low-power NIR laser irradiation (2 W/cm^2) [45]. Therefore, we speculate that the combination of MOF nanoparticles with graphene or GO could be promising for synergistic therapy with controlled drug delivery and photothermal therapy.

Many studies recently reported the MOF/graphene composite materials for different applications [47–50]. For example, Chen et al. reported a simple and in situ synthesis method to prepare GO/ZIF-8 composites in aqueous solution, which showed enhanced CO_2 adsorption energy and significant CO_2 uptake capacity [47]. Xu et al. fabricated a layered nanoarchitecture composed of photoactive UiO-66-NH_2 and graphene, and the layered hybrids exhibited excellent photocatalytic oxidation of benzyl alcohol under visible light [48]. However, there are no reports on describing the construction of MOF/GO or MOF/graphene composite nanoparticles for synergistic drug delivery and photothermal therapy.

In this work, we report on simple synthesis of ZIF-8/graphene oxide (ZIF-8/GO) nanocrystals with encapsulation of fluorescein molecules (fluorescein-ZIF-8/GO). Here, fluorescein was used as a model drug due to its absorbance wavelength at 493 nm and luminescence emission at 520–530 nm, which is easy to monitor drug loading and release, as well as cell uptake. As shown in Fig. 1, the fluorescein-ZIF-8/GO nanocrystals synergistically combine pH-controlled drug release owing to the pH-sensitive decomposition of ZIF-8 nanocrystals and photothermal effect of GO, which is a potential multifunctional platform for synergistic cancer therapy.

2. Experimental

2.1. Materials

2-Methylimidazole (99% purity), $Zn(NO_3)_2.6H_2O$ (99% purity), methanol (HPLC grade) and fluorescein were purchased from Sigma-Aldrich. Graphene oxide (GO, 1 mg/ml, average dimensional size of 7.5 nm) was obtained from Nanjing XFNANO Co. Ltd. Ultrapure water was obtained from Millipore pure water system. All chemicals were of analytical-reagent grade and used without further purification.

2.2. Synthesis of fluorescein-encapsulated ZIF-8/GO (fluorescein-ZIF-8/GO) nanocrystals

The fluorescein-ZIF-8/GO nanocrystals were synthesized according to a previous report with some modifications [18]. For a typical synthesis, 0.19 g of $Zn(NO_3)_2.6H_2O$ was completely dissolved in 100 ml of methanol, and 1.2 ml of fluorescein solution (2 mg/ml in methanol) was added into the $Zn(NO_3)_2$ solution. Subsequently, 0.4 g of 2-methylimidazole was dissolved in 100 ml of methanol, and then added into the mixed solution of $Zn(NO_3)_2$ and fluorescein at room temperature with magnetic stirring for 30 min. Then, 2 ml of GO suspension was added into the above mixture solution. After further magnetic stirring for 1 h, the nanocrystals were collected by centrifugation, washed several times with methanol, and dried under vacuum at 60 °C for 6 h.

As controls, the ZIF-8/GO nanocrystals were synthesized similar to that of the fluorescein-ZIF-8/GO nanocrystals without the addition of fluorescein solution. ZIF-8 nanocrystals were synthesized following the above procedure without the addition of fluorescein solution and GO suspension.

2.3. Characterization

The X-ray diffraction (XRD) patterns were obtained on a D8 ADVANCE powder diffractometer using Cu Kα1 radiation