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Fluorescent carbon dot gated hollow mesoporous carbon for chemo-photothermal synergistic therapy

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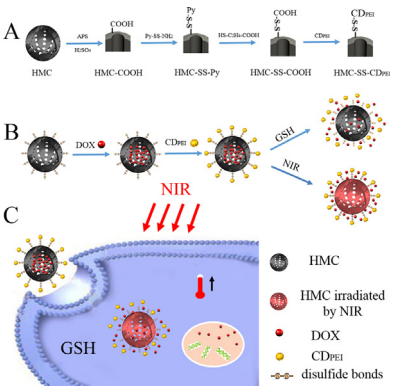
GRAPHICAL ABSTRACT



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ABSTRACT

An efficient and intelligent nano-carrier that combines cell imaging with near infrared (NIR) light and redox dual-responsive drug delivery was successfully prepared. The hollow mesoporous carbon (HMC) nanoparticles with high photothermal conversion ability were developed to increase the drug loading efficiency and realize chemotherapy and photothermal synergetic therapy. The photo-stable and luminescent carbon dots (CDs) were prepared from branched polyethyleneimine (PEI) by hydrothermal reaction. The PEI CDs (CD_{PEI}) were grafted on the openings of HMC as the "gatekeepers" via disulfide units (HMC-SS-CD_{PEI}) to prevent the premature release of doxorubicin (DOX). In the presence of GSH, the CD_{PEI} separated from HMC due to the breakage of disulfide bonds, thus triggering the rapid release of the encapsulated drug. In addition, the release rate of DOX could be further accelerated by NIR light irradiation due to the increased temperature which would decrease the interaction between HMC and DOX. The fluorescence of the CD_{PEI} is quenched when being attached to the HMC, while it is recovered when the CD_{PEI} breaking away from HMC. Hence, the fluorescent CD_{PEI} not only act as a gatekeeper to control drug release but also play a vital role in monitoring the process of the drug delivery. The developed HMC-SS-CD_{PEI} showed dual-responsive drug release property and could be used as visible nano-platforms for chemo-photothermal synergistic therapy.

1. Introduction

There has been a rapid development of anticancer nanomedicine in recent years. However, limitations are becoming more

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and more apparent, such as severe toxicity, side effects, poor bioavailability and large dosage requirement. Thus we want to design a multifunctional drug delivery platforms (MFDDPs) to achieve controlled and targeted drug delivery that can improve treatment efficacy to a large extent.

Photothermal therapy is a physical therapy, in which light could be converted into cytotoxic heat to eliminate tumor cells [1]. Near-infrared (NIR) light, working as a burgeoning in vitro physical method shows great promise in assisting drug delivery and improving therapeutic efficacy [2]. NIR light with a wavelength from 700 to 1100 nm, is noninvasive for normal tissues and possesses a long penetration depth [3]. To achieve better ablation of tumor cells and overcome side effects caused by traditional chemical drugs, the combination of chemotherapy and photothermal therapy which is called chemo-photothermal therapy has attracted wide attention [4,5]. The novel combination of therapy can induce synergistic effects by delivering cytotoxic heat and chemical agents to cancer sites synchronously and locally [6]. In addition, under the circumstance of high temperature, the toxicity of chemical drugs are improved [7] and tumor cells are more sensitive to chemotherapeutic agents [8], thus the dosage requirement and side effects are reduced to a large extent.

Up to now, a wide variety of functional materials have been explored as NIR-absorbing drug carriers. Among them carbon nanomaterials such as fullerene, carbon nanotubes [9–11] and graphene [12–14] have attracted wide attention. Mesoporous carbon nanoparticles (MCN), as an original carbon-based carrier exhibit excellent great potential working as MFDDPs due to their unique physiochemical properties, such as the high photothermal conversion capability, large surface area, tunable pore size, low toxicity, and easily-modified surface [15–17]. The attractive channels are especially important for drug loading and protecting therapeutic agents inside the mesopores. Compared with conventional MCN, hollow mesoporous carbon (HMC) with a hollow core inside the carrier show higher drug encapsulation efficiency. Moreover, HMC showed better photothermal conversion efficacy than MCN [18].

Premature drug release is another obstacle that we need to work out. Fortunately, stimuli-responsive MFDDPs have made great progress in recent years. A key advantage of such MFDDPs is their capacity to regulate drug release behavior under specific stimuli, which can largely improve the treatment efficacy at the tumor sites and reduce systemic side effects. Stimuli including pH [19], redox potential [20], light [21], temperature, and enzymes [22] could trigger drug release at the specific target tissues. Among these stimuli, redox potential [23] is popular intracellular stimulus at cancer sites. There is a significant difference in the glutathione (GSH) concentration between the extracellular (2 μM) and intracellular (10 mM) environments [22]. And the concentration of intracellular GSH levels in most tumors is at least 4 times higher than that in normal cells.

Recently, carbon dots (CDs) as a new class of fluorescent materials have attracted many researchers' attention due to their superior properties such as good luminescence [24], low toxicity [25], photo-stability, hydrophilic and biocompatibility [26]. Thus, it could be explored as bio-sensing and bio-imaging [27,28] candidate to monitor the drug delivery process [29]. Moreover, controllable size made it working as gatekeepers of mesopores that can prevent drug leakage efficiently. Considering the unique properties of HMC, NIR and CDs, it is desirable integrate NIR light and CDs with the biocompatible stimuli-responsive HMC to develop novel type of MFDDPs.

In this work, HMC was used as the drug carrier as well as the NIR absorbing material to realize the synergistic treatment of chemotherapy and photothermal therapy. The fluorescent carbon dots CD_{PEI} with a diameter of 3 nm was fabricated using the hydrothermal polymerization method. The CD_{PEI} were grafted on the mesoporous openings of HMC via disulfide bonds to prevent the premature drug release as shown in Scheme 1. Doxorubicin (DOX) was employed as model drug to investigate drug loading capacity and stimuli-responsive drug release property of HMC-SS-CD_{PEI}/DOX. Moreover, the supernatant fluorescence intensity with or without GSH were explored to understand mechanism of redox-responsive release behavior. Stability, hemolysis and cytotoxicity assays were performed to evaluate biocompatibility of HMC-SS-CD_{PEI}. Furthermore, cell viability experiments were taken to estimate the synergistic effects of HMC-SS-CD_{PEI}/DOX by combination of chemotherapy and phototherapy. All in all, the novel MFDDPs can not only achieve better inhibition of tumor cells, but also serve as a good platform for real-time imaging of nano-carriers.

2. Materials and Experimental conditions

2.1. Materials

Tetraethoxysilane (TEOS) and cetyltrimethylammoniumbromide (CTAB) were supplied by Tianjin Bodi Chemical Industry Co. The branched polyethyleneimine (PEI), 3-mercaptopropionic, glutathione (GSH), 3-mercaptoprhopyltrimethoxysilane (MPTMS, 95%), N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC), N-hydroxysuccinimide (NHS) and doxorubicin hydrochloride (DOX) were obtained from Aladdin Chemical Inc. (Shanghai, China). Cell culture medium dulbecco's modified eagle medium (DMEM), trypsin-EDTA solution (0.25%), fetal bovine serum (FBS) and penicillin–streptomycin were obtained from GIBCO, Invitrogen Co. (Carlsbad, NM, USA). 3-(4,5-Dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) were supplied by Amresco (USA). Fluorescent 4′,6-diamidino-2-phenylin dole (DAPI) was obtained from Biyuntian Co. (Nanjing, China). All other chemicals were of analytical grade and used without further purification.

2.2. Synthesis of CD_{PEI}

The functionalized CD_{PEI} are prepared by a route as reported previously [26]. 0.1 g branched PEI (Mw 25 kDa) was dissolved in 20 mL deionized water. Then, 0.4 g citric acid (CA) was added to obtain a homogeneous solution under vigorous stirring at room temperature. Subsequently, it is transferred to an autoclave and kept at 180 °C for 10 h. Finally, the resulting solution was centrifuged at 15000 rpm to produce a bright yellow solution which is then dialyzed against deionized water for 1 day.

2.3. Preparation of HMC-SS-COOH

The synthesis of S-(2-Aminoethylthio)-2-thiopyridine hydrochloride (Py-SS-NH_2) was performed on the basis of our previous work [30]. And HMC-COOH was prepared by the previous method [31]. Firstly, HMC-COOH (100 mg) was dispersed in 30 mL PBS (pH = 7.4) and mixed with NHS and EDC for 1 h under stirring at room temperature. Secondly, Py-SS-NH_2 (40 mg) was added to the above suspension and stirred for 12 h. Afterwards, the mixture solution was centrifuged at 13000 rpm for 15 min and supernatant was discarded. The precipitates were washed with purified water and ethanol in sequence. The products were named as HMC-SS-Py.

The preparation of HMC-SS-COOH was performed by dispersing 80 mg of HMC-SS-Py in 25 mL ethanol. Subsequently, 3-mercaptopropionic acid (40 μL) was added into the above suspension and the reaction mixture was stirred for 24 h. Finally, HMC-SS-COOH was obtained by a centrifugation, washed with ethanol and dried under vacuum.