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A smart nanoporous theranostic platform for simultaneous enhanced MRI and drug delivery

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ABSTRACT

Use of inorganic nanoparticles is expectedly improving the prospects of chemotherapy and diagnosis. Here, we report a facile approach to synthesize water dispersible, superparamagnetic manganese ferrite ($MnFe_2O_4$) nanoparticles at relatively low temperature. Subsequently, these $MnFe_2O_4$ nanoparticles are integrated with acid degradable mesoporous ZnO nanoparticles to attain a platform for simultaneous magnetic resonance imaging (MRI) and acid triggered anticancer drug delivery. Drug release was evaluated by tuning the pH of buffer solutions to mimic intracellular environment, which demonstrated a bio-relevant acid sensitive release behavior. In vitro cell study congruently demonstrated an excellent concentration-dependent cytotoxicity on pancreatic cancer cells, with IC_{50} of 3 μg/mL composite concentration. As far as imaging results are concerned, relaxivity value (r_2) value of our system was found to be measurably higher than commercial T_2 MRI contrast agent Ferridex (63.5 mM^{-1} s^{-1}).

This smart nanosystem can be a step forward towards the realization of concurrent effective therapy, monitoring of nanocarrier distribution and disease evolution.

1. Introduction

Nanoscale therapeutics has recently garnered an immense research interest in order to tackle debilitating diseases [1,2]. Cancer therapy which ubiquitously results in numerous intolerable side effects indeed necessitates the development of effective drug delivery systems. In this respect, recent innovations in nanotechnology have luckily provided us unprecedented possibilities to successfully meet the requirement to combat this predicament [3–6]. Moreover, nanoparticulated diagnostics agents have also reached the commercial market to diagnose diseases in initial stages.[7]. Thus, integration of diagnostics and therapeutics at nanoscale is highly tempting biomedical research area. To date, myriad and diverse nanotheranostics devices have been designed to take advantage of the hypervascularized tumour lesion for achieving site specific release and diagnosis [8]. Among those theranostic constructs, nanoporous inorganic nanoparticles are recently explored to simultaneously ferry anticancer drug and contrast agent, because of their excellent stability, high loading capacity and versatile physicochemical properties [9,10]. Besides just integration, focus is now shifted towards the development of 'smart' or 'intelligent' materials. Stimuli responsive or smart materials can perceive the prevalent biological trigger and accordingly respond by displaying transformation in their physical or chemical behaviour to release the loaded cargo for efficacious therapy. Since there are considerable pH variations in various body parts and in pathological conditions, pH-responsive [11–16] materials are more appropriate choice among various explored stimuli. Zheng et al. has recently evaluated hollow mesoporous zirconia nanocapsules as effective carriers for anti-cancer drug delivery in response to mildly acidic conditions of tumours [17]. Another study explored monodispersed mesoporous magnetite for pH sensitive release of doxorubicin (DOX) [7]. More recently, our group reported a pH triggered release of chemotherapeutic drug from ZnO quantum dots to the neoplastic cells.[18]

As far as diagnosis goes, multiple imaging techniques, such as optical imaging, ultrasound imaging, magnetic resonance imaging (MRI), positron emission and X-ray tomography, are clinically used to diagnose the diseases at early stages. However, MRI has been recognized as one of the most powerful non-invasive imaging modality at the cellular or molecular level [19–23].

In the course of MRI recording procedure, contrast agents are normally required to shorten the longitudinal (T_1) or transverse

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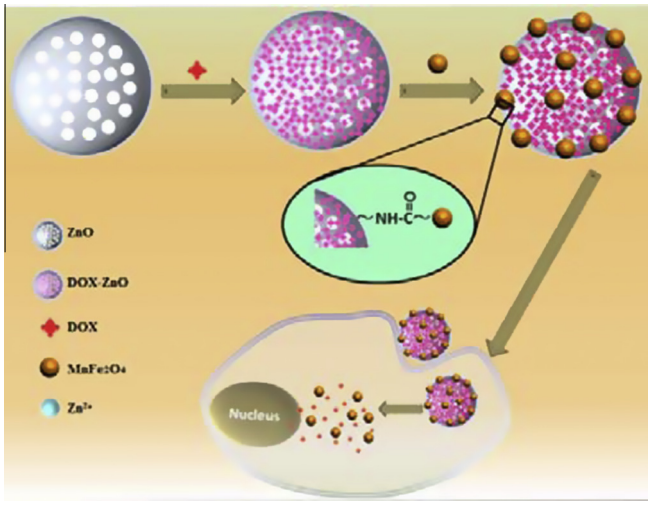

Scheme 1. Schematic illustration of the synthetic procedure and responsive intracellular drug release of DOX-ZnO@$MnFe_2O_4$.

(T_2) relaxation times for highlighting and enhancing the image quality. The currently available MRI contrast agents are of two types. Positive contrast agents (T_1), consisting of paramagnetic species, produce brighter images, while negative contrast agents (T_2) generate a darker contrast in the tissue where they are concentrated.

Here we report a facile strategy to judiciously integrate therapeutic and imaging functionalities into a single nanocarrier. Synthetically, acid sensitive mesoporous ZnO nanoparticles are first prepared to serve as a nanocarrier for highly potent anticancer drug Doxorubicin (DOX). DOX is then loaded onto the ZnO nanoparticles by capitalizing on its complex formation tendency. Manganese ferrite ($MnFe_2O_4$) nanoparticles, T_2 relaxation enhancement agent, are also tethered onto the surface of ZnO nanoparticles via amidation reaction to impart imaging functionality. Instability of DOX-Zn^{2+} complex and porous ZnO nanoparticles in mildly acidic conditions, as found in endosomes or cancerous tissues, results in the release of DOX in cancerous cells. Most importantly, following ZnO dissolution and drug release, the contrast agents can provide the opportunity to assess the therapeutic response of chemotherapy. The pictorial presentation of this intelligent and multifunctional nanoarchitecture is illustrated in Scheme 1.

2. Experimental

2.1. Materials

Chemical reagents used in this study are of analytical grade and used as received. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and 3-aminopropyltriethoxysilane (APTES) were purchased from Aladdin-reagent Co. Ltd. 2-[2-(2-Hydroxyethoxy)ethoxy]ethanol (TEG) was purchased from Beijing chemical reagent Co. 3-[4,5-dimethylthialzol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) was bought from Sigma–Aldrich. Doxorubicin hydrochloride was obtained from Yuancheng tech. development Co.,Wuhan.

2.2. General Synthesis procedures

2.2.1. Synthesis of amine-functionalized ZnO nanoparticles

Mesoporous ZnO nanoparticles were synthesized according to literature with slight modification [24]. Briefly, 3.0 mmol of zinc acetate dihydrate was added into 30 mL of TEG. The solution was then heated to 160 °C and stirred for 30 min. The resulting precipitate was isolated by centrifugation, washed with nanopure water and ethanol, and afterwards air-dried. To improve the water dispersibility, precipitated ZnO nanoparticles (200 mg) were dispersed in 20 mL of anhydrous N, N-dimethylformamide (DMF) while sonicated, followed by the addition of 50 μL of 3-aminopropyltriethoxysilane (APTES). The temperature was raised to 130 °C. After 30 min, amine-functionalized ZnO (ZnO–NH_2) nanoparticles were centrifuged and washed twice with ethanol.

2.2.2. Synthesis of carboxylic acid functionalized $MnFe_2O_4$ nanoparticles

Five mmol of manganese (II) chloride ($MnCl_2{\cdot}4H_2O$) and 10 mmol of iron (III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) were added into 50 mL of TEG in 100 mL three-neck flask. The mixture was magnetically stirred at room temperature under N_2. Separately, 40 mmol of NaOH was dissolved in 20 mL of TEG at 120 °C. Once the precursors were completely dissolved in TEG, the base solution was added through a syringe. The reaction temperature was then raised to 200 °C and held for 12 h. $MnFe_2O_4$ nanoparticles were separated by adding acetone, and then washed with water and ethanol mixture until the supernatant became colourless. To attain water dispersible magnetic nanoparticles, as-prepared $MnFe_2O_4$ nanoparticles (50 mg) and 150 mg of citric acid were dispersed in 20 mL of water, and the mixture was sonicated until colloidal solution was formed. The functionalized $MnFe_2O_4$–COOH nanoparticles were isolated by a magnet, followed by redispersion in 5 mL of water to give a transparent black solution for further use.

2.2.3. Doxorubicin loading and conjugation of ZnO with $MnFe_2O_4$ nanoparticles

ZnO-NH_2 powder (50 mg) was dispersed in ethanolic solution (5 mL, 1 mg mL^{-1}) of doxorubicin and stirred overnight. The mixture was centrifuged to give a residue, which was dispersed in 10 mL of water.

To conjugate magnetic nanoparticles with drug loaded ZnO nanoparticles, EDC (20 mg), as carboxyl activating agent, was added into the $MnFe_2O_4$–COOH nanoparticle solution under sonication. Then, this solution was added to the DOX loaded ZnO nanoparticles solution and the mixture was stirred for 10 min. The desired product was later collected by a magnet.

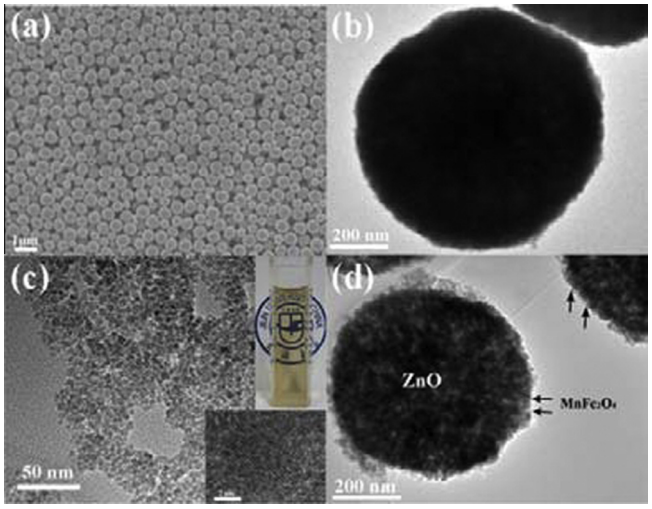

Fig. 1. (a) SEM and (b) TEM images of synthesized mesoporous ZnO. (c) TEM images of $MnFe_2O_4$ nanoparticles, inset: high-resolution TEM image (bottom), photograph of the aqueous dispersion of nanoparticles (top). (d) TEM of synthesized ZnO–$MnFe_2O_4$.