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Facile synthesis of CdTe@GdS fluorescent-magnetic nanoparticles for tumor-targeted dual-modal imaging

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ABSTRACT

Multimodal imaging has made great contribution for diagnosis and therapy of disease since it can provide more effective and complementary information in comparison to any single imaging modality. The design and fabrication of fluorescent-magnetic nanoparticles for multimodal imaging has rapidly developed over the years. Herein, we demonstrate the facile synthesis of GdS coated CdTe nanoparticles (CdTe@GdS NPs) as multimodal agents for fluorescence (FL) and T_1-weighted magnetic resonance (MR) imaging. These nanoparticles obtain both prominent fluorescent and paramagnetic properties by coating the GdS shell on the surface of CdTe core *via* a simple room-temperature route in aqueous solution directly. It is shown that the as-prepared CdTe@GdS NPs have high quantum yield (QY) value of 12% and outstanding longitudinal relaxation rate (r_1) of 11.25 mM s^{-1}, which allow them to be employed as FL/MR dual-modal imaging contrast agents. They also exhibit small particle size of 5 nm, excellent colloidal stability and low cellular toxicity for concentrations up to 750 μg mL^{-1}. In addition, with the conjugation of folic acid, the nanoparticles were successfully used for tumor-targeted FL/MR dual-modal imaging *in vitro* and *in vivo*.

1. Introduction

Molecular imaging techniques, including fluorescence (FL) imaging [1–3], magnetic resonance (MR) imaging [4–8], X-ray computed tomography (CT) [9–13], positron emission tomography (PET) [14,15] and single photon emission tomography (SPECT) [16] have played important roles in the field of early detection and diagnosis of diseases, because they could provide visual, correct and positional information on the occurrence of various diseases. Depending on the different imaging mechanisms and detection source, each imaging technique (modality) has its own advantages and intrinsic limitation [17]. For instance, FL imaging can offer high sensitive, molecular level and real-time imaging information in medical imaging application, but the low spatial resolution and poor tissue penetration depth stop it from deep tissue imaging in clinic application [12,18–20]. Although MR imaging as a non-invasive imaging technique is a powerful tool in modern clinical diagnostic with unique spatial resolution, three-dimensional imaging capability to soft tissue and no tissue penetration limitation, it is difficult to obtain cellular level or real-time images by MR imaging due to its low sensitivity and long imaging time [4,17,21–23]. Owing to the radiation risk and the low sensitivity to soft tissues, CT imaging has been limited in some clinical applications, such as obstetrics [9,13,17]. Therefore, it is hard to take all complementary and reliable information at the disease site by any single-modal imaging technique.

In order to obtain accurate imaging results by gathering the benefits of each imaging modality together, multimodal imaging has been attracted great attention in medical imaging field for the early diagnosis of disease over the past two decades [24,25]. Recently, with the development of nanotechnology, fluorescent-magnetic nanoparticles have been reported as significant contrast

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agents for FL/MR dual-modal imaging [4,5,23,26–30]. Typically, magnetic ions doped quantum dots (MQDs) such as Gd-doped ZnO QDs [18], Ni-doped CdTe QDs [25], Fe-doped CdTeS QDs [26], Gd-doped CdTe QDs [31] and Gd-doped CdSe QDs [32] have been applied as contrast agents for FL and MR dual-modality imaging. These MQDs not only remain the unique fluorescence properties of high quantum yield (QY), large Stokes shift, broad excitation and narrow emission spectra from the QDs [33–36], but also gather outstanding paramagnetic properties in a small single particle. Furthermore, all these MQDs have ultra-small particle size lower than 10 nm. However, the minute quantity of the dopants in these MQDs confines the improvement of their MR imaging capability because excessive dopant ions can reduce the fluorescence of the QDs, even quench it [18,26,32].

To obtain FL/MR dual-modality imaging probes with stronger magnetic properties than those of MQDs, other types of nanomaterials based on QDs coated with a paramagnetic Gd-chelates, core–shell nanoparticles combining QDs and magnetic nanoparticles (MNPs) and fluorescence rare earths ions doped MPNs have been prepared for FL/MR dual-modality imaging applications [30]. However, the particle size of these above fluorescence-magnetic NPs is usually larger than the size of the magnetic ions doped QDs. For examples, the average diameter of Yb^{3+}/Er^{3+}:$BaGdF_5$ NPs [13], Fe_3O_4–CdZnSeS@SiO_2 NPs [37], $NaYF_4$:Yb^{3+}/Tm^{3+}@$NaGdF_4$:Yb^{3+} NPs [38] and CdSe/ZnS–Fe_3O_4 hybrid silica particles [39], is located at 12, 43.5, 65, 100 nm, respectively. The biocompatibility of the imaging probe can be decreased by its large particle size because it is hard to clean them out of the human body rapidly. In the last few years, gadolinium monosulfide (GdS) NPs have drawn much attention due to their ultra-small particle size (<10 nm) and excellent magnetic properties for bioimaging application [40–42]. Regularly, these GdS NPs were synthesized by organic or hydrothermal method with heating at a high temperature. For instances, Eu-doped GdS NPs has been reported as a noble FL/MR dual-modality imaging agent *via* heating the reaction mixture to 240 °C although the dissolvent was water [41]. And a facile method has been developed to synthesize Eu-doped GdS NPs by thermal decomposition at 200 °C in oleic acid/hexadecylamine mixture. However, if the probe was synthesized in organic phase, it is necessary to process surface modified phase-translation to enhance the water solubility and biocompatibility of the probe before the imaging application. As a result, the fluorescence properties of the probe might be decreased by these modified and phase-translation process [43]. Therefore, it is an appealing topic for fabricating FL/MR dual-modality imaging agents based on GdS NPs *via* facile aqueous routes at low temperature.

With this mind, we developed GdS coated CdTe nanoparticles (CdTe@GdS NPs) as an excellent agent for FL and T_1-weighted MR dual-modality imaging by a facile aqueous route at room-temperature in this work. The as-prepared CdTe@GdS NPs with a ultra-small particle size of approximately 5 nm have high quantum yield (QY) value of 12% and outstanding longitudinal relaxation rate (r_1) of 11.25 mM s^{-1}. The coating of the GdS shell on the surface of the CdTe core not only provided both prominent fluorescent and paramagnetic properties for the as-prepared CdTe@GdS NPs, but also reduced the toxicity and increased the biocompatbility of the CdTe@GdS NPs. With the conjugation of folic acid, the nanoparticles were successfully used for tumor-targeted FL/MR dual-modal imaging *in vitro* and *in vivo*.

2. Materials and methods

2.1. Materials

$GdCl_3 \cdot xH_2O$ (98%+), thioacetamide (TAA, 99%+) and glutathione (GSH, 99%+) were purchased from Alfa Aesar (Tianjin, China). $Na_2TeO_3 \cdot xH_2O$ (99%+) was purchased from Sigma Aldrich (Shanghai, China). $CdCl_2 \cdot 2.5H_2O$ (98%+), $NaBH_4$ (98%+), dimethyl sulfoxide (DMSO, 99%), folic acid (FA, 98%+), 1-ethl-3-(3-dimethylaminopropyl) carodiimide hydrochloride (EDC, 98%), $N_2H_4 \cdot H_2O$ (80%) and N-hydroxysuccinimide (NHS, 98%) were purchased from Beijing J&K Scientific Ltd. (Beijing, China). PBS buffer solution (20X) and 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT, 98%) were purchased from Sangon Biotech Ltd. (Shanghai, China). All reagents were used without further purification. And the stock solutions of chemicals were prepared in deionized water which was obtained from an Aquapro AWL-0502-U super pure water system (Chongqing, China).

2.2. Instrumentation and characterization

The particle size and morphology of the as-prepared CdTe@GdS NPs was characterized by transmission electron microscopy (TEM) and high-resolution transmission electron microscopy (HRTEM) images which were acquired on a Philips Tecnai G2 F20 S-TWIN transmission electron microscopy (Philips, Holland) using 200 kV electron source. XPS spectra were recorded using a Kratos Axwas Ultra DLD spectrometer employing a monochromated Al-Ka X-ray source (hv=1486.6 eV), hybrid (magnetic/electrostatic) optics and a multi-channel plate and delay line detector (DLD). All XPS spectra were recorded using an aperture slot of 300×700 μm^2, survey spectra were recorded with a pass energy of 160 eV, and high-resolution spectra with a pass energy of 40 eV. Powder X-ray diffraction (XRD) patterns were collected on a Rigaku D/max-2500 X-ray diffractometer (Rigaku, Japan) with Cu Kα radiation. Fourier-transform infrared (FTIR) spectra (4000–500 cm^{-1}) in KBr were recorded by using a Vector 22 FTIR spectrophotometer (Bruker, Germany). The metal compositions were determined on an ICP-9000(N+M) inductively coupled plasma atomic emission spectroscope (ICP-AES) (TJA, America). The absorption spectra of all samples were obtained from a UV-2450 UV–vis spectrophotometer (Shimadzu, Japan). The fluorescence emission spectra of all samples were performed using an F-4500 fluorescence spectrophotometer (Hitachi, Japan) equipped with a plotter unit and a quartz cell (1 cm × 1 cm). The slit widths of excitation and emission were both 5 nm. All optical measurements were performed at room temperature under ambient conditions. The quantum yield (QY) of the CdTe@GdS NPs was determined by a reference method using Rhodamine 6 G (QY=95%) as the reference.

2.3. Synthesis of the CdTe@GdS NPs

2.5 mL red CdTe QDs solution was added into a 100 mL conical flask, then 10.0 mL 0.02 mol L^{-1} $GdCl_3$, 5.0 mL 0.1 mol L^{-1} GSH, and 10.0 mL deionized water were added into the reaction system. After 2 min stirring, 10.0 mL 0.02 mol L^{-1} TAA and 30.0 mL 80% $N_2H_4 \cdot H_2O$ were introduced into the reaction mixture. Afterwards, the reaction mixture was stirred at room-temperature for 2 h, and it was changed from red to milky, which indicated the CdTe@GdS NPs were established. Before the further modification and bioapplication, the as-prepared CdTe@GdS NPs were purified by centrifugation with 12,000 r/min from the alkalinous reaction mixture, and they were washed by deionized water and ethanol. Afterwards, they were dried at 60 °C in vacuum for 12 h.

2.4. Synthesis of FA conjugated CdTe@GdS NPs

FA was conjugated to the amino group of the CdTe@GdS NPs by the activation of EDC and NHS for establishing the targeted imaging probe of FA-CdTe@GdS NPs. FA was added into an EDC/NHS