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Synthesis and Cell Imaging of a Near-Infrared Fluorescent Magnetic "CdHgTe–Dextran-Magnetic Layered Double Hydroxide–Fluorouracil" Composite

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ABSTRACT

In this article, a water-soluble near-infrared quantum dots of CdHgTe were prepared and subsequently combined with the drug delivery system "dextran-magnetic layered double hydroxide–fluorouracil" (DMF) to build a new nanostructure platform in form of CdHgTe@DMF, in which the fluorescent probe function of quantum dots and the magnetic targeting transport and slow-release curative effect of DMF were blended availably together. The luminescent property particle size, and internal structure of the composite were characterized using fluorescence spectrophotometer, ultraviolet spectrophotometer, laser particle size distribution, TEM, X-ray diffraction, and Fourier transform infrared. The experimental study on fluorescent tags effect and magnetic targeting performance of the multifunctional platform were performed by fluorescent confocal imaging. The results showed that the CdHgTe could be grafted successfully onto the surface of DMF by electrostatic coupling. The CdHgTe@DMF composite showed super-paramagnetic and photoluminescence property in the near-infrared wavelength range of 575-780 nm. Compared with CdHgTe, the CdHgTe@DMF composite could significantly improve the cell imaging effect, the label intensity increased with the magnetic field intensity, and obeyed the linear relationship $D_{mean} = 1.758 + 0.0075M$ under the conditions of magnetic field interference. It can be implied that the CdHgTe@DMF may be an effective multifunction tool applying to optical bioimaging and magnetic targeted therapy.

Introduction

The magnetic nanoparticles have been used widely in the biomedical field, which generates a profound impact on biomedical research. Some magnetic nanoparticles have been developed for tumor tissue imaging and therapy with a plenty of advantages over traditional medical material. It can bring medicines to infected organs and combine the drug delivery systems with the target tumor cells or tumor microenvironment to realize visualization treatment by imaging technology.[1-5] The near-infrared quantum dots (QDs) are one of the research studies concentrating point toward bioimaging owe to their excellent optical properties, low background interference, and strong tissue penetration. As a kind of fluorescent probe, it is widely used *in vivo* and *in vitro* imaging and biomarkers. Balalaeva[6] studied the vital fluorescence imaging of tumor using 2 contrast agents prepared with QDs, including polyethylene glycol–coated bioinert QDs and anti-HER2/neu scFv antibodies combined QDs. With nude mice inoculated HER2/neu-positive breast cancer tumor were used as a model, the results showed that bioinert QDs and tumor targeting QDs probes could successfully implement visualization for nude mouse tumor. Modern magnetic targeting drug delivery system established with Fe_3O_4,[7-10] can be composited with QDs to synthesize the multifunctional nanoparticles for fluorescent tracer and magnetic targeted delivery. Wang[11] prepared a new kind of Fe_3O_4/CdTe nanocomposite by hydrothermal coprecipitation of ferric and ferrous ions, followed by surface modification with TMAOH and chemical activation with aspartic acid. Then, the surface-modified Fe_3O_4 nanoparticles were covalently coated with CdTe QDs to synthesize Fe_3O_4/CdTe composite of magnetic luminescent. Yang[12]

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prepared a system of microfluidic emulsification through encapsulating anticancer drug tamoxifen, Fe_3O_4 nanoparticles and CdTe QDs into size-controlled polycaprolactone microcapsules, combined magnetic targeting, fluorescence imaging, and drug controlled release properties together. Shen[13] developed a novel nanoparticles CFLMNPs composed with folate, carboxymethyl chitosan ferroferric oxide, and CdTe QDs.

However, Fe_3O_4 only acts magnetic steering role in these studies mentioned previously, the drug loading will rely on the chemical bonding or carrying of macromolecular organic polymer. This way is not only complicated for the synthesis process but also difficult to take into account for design the slow-release drugs. At the same time, the degradation problem of the carrier cannot be solved. To overcome these disadvantages, we developed new dual-function carrier, that is, a magnetic layered double hydroxide (MLDH) in form of $[Fe^{II}_xFe^{III}_2(OH)2(x+2)](A^{y-})_{2/y}\cdot(1\sim2x)H_2O$ to integrate magnetic targeting and slowly release functions.[14-17] Based on MLDH, a supramolecular drugs delivery system of "dextran-magnetic layered double hydroxide—fluorouracil" (DMF) was established.[14-17] To certify intuitionally the magnetic targeting, slow-release effect, and therapeutic effect of DMF, we prepared water-soluble near-infrared CdHgTe QD as a fluorescent agent to combine and trace the DMF system. In this article, we characterized the basic structure and properties of the CdHgTe@DMF composite and investigated the cell imaging effect. This would be significant for development of a targeted diagnostic and therapeutic agent.

Experimental Parts

Materials

3-mercaptopropionic acid (MPA), $Cd(NO_3)_2\cdot4H_2O$ (99%), $NaBH_4$ (99%), Te powder (99.9%), and $Hg(NO_3)_2\cdot4H_2O$ (99%) were obtained from Tianjin Damao Chemical Reagent Co. (China). Rhodamine 6G (99.9%) was purchased from Aladdin (China). Roswell Park Memorial Institute-1640 medium, Hyclone fetal calf serum, and Hyclone phosphate-buffered saline (PBS) were obtained from Beijing Thermo Fisher child Biochemical Products Co. (China). Mixing biologicals of trypsin-ethylenediaminetetraacetic acid (0.25%) and penicillin-streptomycin were purchased from Beijing Boao. Antifluorescence decay seal tablet was purchased from Beijing Puli Lai Gene Technology Co.

Synthesis of Near-Infrared CdHgTe

The synthesis of CdHgTe was performed by methods reported previously.[18] One mL of $Cd(NO_3)_2\cdot4H_2O$ (0.01725M) and 21.5 μL of MPA were dissolved in 100-mL water followed by adjusting the pH to 8.0 ~ 9.0 through dropwise addition of 1-M NaOH. The solution mentioned previously was prepared in a 3-necked flask, and O_2 was removed on bubbling N_2 for 30 min. Under stirring, 1 mL of freshly prepared NaHTe solution (generated by the reaction of 4.8-mg Te powder, 120-mg $NaBH_4$, and 10-mL water under N_2 atmosphere at 50°C) was added into the reaction system. Before refluxing, 862 μL of $Hg(NO_3)_2$ solution (0.01 M) was added under nitrogen atmosphere, which contributed to the red shift of QDs to NIR range. The CdHgTe precursors were formed at this stage, accompanied by the solution color changing to brown. The precursors were converted to CdHgTe QDs by refluxing for 7 h at 100°C under nitrogen atmosphere. The QDs of CdHgTe obtained previously were purified with the absolute ethyl alcohol, followed by centrifugation and vacuum drying. The yield of this reaction step was 76.4%. The quantum yield of CdHgTe was 10%.

Synthesis of CdHgTe@DMF

After the formation of CdHgTe QDs, the CdHgTe@DMF composite was prepared using the DMF particles as infrastructure (a detailed description about the synthesis of DMF, the drug loading ratio of the system and the release profile of fluorouracil over time is given in the Supporting Information). Six milligrams of CdHgTe powder and 3-mg DMF powder were placed in mortar and grinded to mix well, followed by dissolving in 50-mL ultrapure water and ultrasonic dispersion for 3 h, during the processes the CdHgTe QDs and DMF were linked by electrostatic binding accompanying with the increase in particles surface area. The ultrasonicate solution mentioned previously was then undergone magnetic separation to remove unbound QDs. The separated CdHgTe@DMF samples were purified with the absolute ethyl alcohol and centrifuged for 15 min with the rotation speed of 5000 $r\cdot min^{-1}$. About 4.5 mg of dry samples obtained from vacuum desiccation were composed of the following components by weight percentage: 33% of CdHgTe QDs and 67% of DMF. The recombination rate of the CdHgTe QDs was 25%.

Characterizations of Samples

The UV-visible absorption spectra were taken on a Shimadzu UV spectrophotometer—UV2450. Photoluminescence spectra (PL)

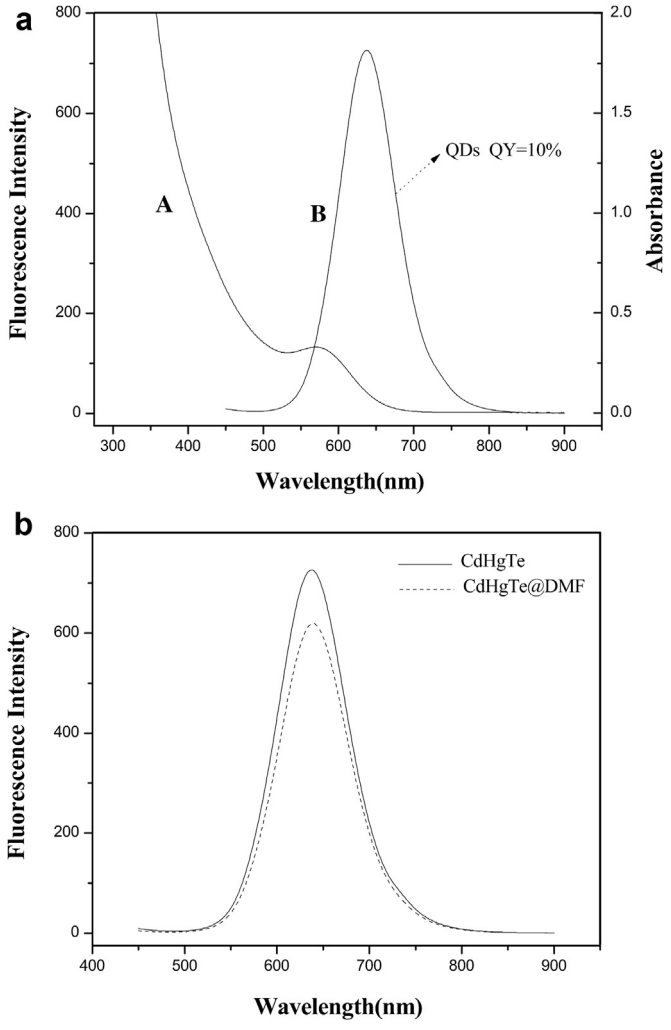

Figure 1. UV absorption spectrum (a-A), fluorescence emission spectra (b-B) of CdHgTe solution in distilled water. Fluorescence emission spectra (b) of CdHgTe and CdHgTe@DMF solution in distilled water.