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Full Length Article

Synthesis and characterization of polymer-coated manganese ferrite nanoparticles as controlled drug delivery

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ABSTRACT

In this study, monodisperse and superparamagnetic manganese ferrite ($MnFe_2O_4$) nanoparticles have been synthesized by a one-pot sonochemical method using polyvinylpyrrolidone (PVP) as stabilizer. The as-prepared $MnFe_2O_4$ nanoparticles were investigated systematically by TEM, XRD, FTIR, XPS, SQUID and MTT. The TEM observation showed that the PVP-coated $MnFe_2O_4$ nanoparticles had uniform dispersion with narrow particle size distribution. The magnetization curves demonstrated superparamagnetic properties of the coated $MnFe_2O_4$ nanoparticles with good hydrophilicity at room temperature. The *in vitro* cytotoxicity experiments exhibited negligible cytotoxicity of the obtained PVP-coated $MnFe_2O_4$ nanoparticles even at the high concentration of 150 μg/mL after 24 h treatment. More importantly, anti-cancer model drug of doxorubicin hydrochloride (DOX) was loaded on the surface of $MnFe_2O_4$ nanoparticles. The drug loading capacity of the developed nanocarrier reached 0.45 mg/mg and the loaded DOX exhibited interesting pH-dependent release behavior. In conclusion, the as-prepared PVP-coated $MnFe_2O_4$ nanoparticles were proposed as a potential candidate for controlled drug delivery.

1. Introduction

Recently, manganese ferrite ($MnFe_2O_4$) nanoparticles with unique properties have been the subject of extensive research, and have been widely applied in different areas including biomedicine, catalysis, adsorbent and water treatment [1–4]. One of the most important and interesting applications of $MnFe_2O_4$ nanoparticles is biomedical fields, such as magnetic resonance imaging, controlled drug delivery and cancer hyperthermia therapy [5–8]. In order to achieve these biomedical applications, appropriate surface modification is necessary for $MnFe_2O_4$ nanoparticles to enhance biocompatibility and decrease aggregation. The bare $MnFe_2O_4$ nanoparticles appear to agglomerate toward the larger clusters with increased sizes [9,10]. In the presence of external magnetic field, the clusters will be further magnetized and result in a stronger attraction between the magnetic nanoparticles, and consequently producing increased cytotoxicity [11]. It has been reported that $MnFe_2O_4$ nanoparticles with suitable surface modification not only can prevent such aggregations and clusters, but also stay for a longer time in the circulation of blood vessels and are less recognized by the human immune system known as reticulo-endothelial system (RES) [9,12].

Many research groups have recently concentrated on developing different methods to reduce aggregation and improve biocompatibility. It has been proved to be effective using a polymeric coating enwrapped on the surface of $MnFe_2O_4$ nanoparticles. Chitosan as a biocompatible polymer was utilized to treat $MnFe_2O_4$ nanoparticles, and the magnetic properties, heat behavior and particle size of the surface-coated $MnFe_2O_4$ nanoparticles were also examined [7]. Shah's group investigated the potential of surface-treated $MnFe_2O_4$ nanoparticles in hyperthermia therapy and controlled drug delivery. The multifunctional carrier was prepared by modifying with poly-N-isopropylacrylamide (PNIPAm) and polyethylene glycol (PEG) & folic acid (FA), respectively [8,13]. Lee et al. reported hyaluronic acid (HA) surface-treated $MnFe_2O_4$ nanoparticles served as magnetic resonance contrast agents. And they further investigated the magnetic properties, biocompatibility and CD44 targeting efficiency of HA-$MnFe_2O_4$ nanoparticles [5]. These scientists have made a great contribution for the development of $MnFe_2O_4$ nanoparticles in biomedical applications. However, to promote practical purposes, this is a time of great chal-

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lenges for $MnFe_2O_4$ nanoparticles to enhance size homogeneity and bio-safety.

Herein, the present work reported monodisperse and superparamagnetic $MnFe_2O_4$ nanoparticles in the presence of polyvinylpyrrolidone (PVP) using a sonochemical method. Then, the effects of PVP on the morphology, structure and magnetic properties of $MnFe_2O_4$ nanoparticles were examined in detail. The *in vitro* cytotoxic activity was systematically studied by MTT assays with varied sample concentrations and incubation time. Moreover, doxorubicin hydrochloride (DOX) was loaded onto the surface of PVP-coated $MnFe_2O_4$ nanoparticles, and the drug capacity and release behavior of DOX from the drug-loaded $MnFe_2O_4$ nanoparticles were also studied.

2. Experimental

2.1. Materials

Ferric chloride hexanydrate ($FeCl_3{\cdot}6H_2O$, 98%), manganese chloride tetrahydrate ($MnCl_2{\cdot}4H_2O$, 98%), polyvinylpyrrolidone (PVP K30, M_n = 30,000) and sodium hydroxide (NaOH, AR) were supplied by Sinopharm Chemical Reagent Co., Ltd. Doxorubicin hydrochloride (DOX, >99%) was purchased from J&K Chemical Co., Ltd. All the other chemical reagents were directly used without further treatment.

2.2. Synthesis of PVP-coated $MnFe_2O_4$ nanoparticles

The PVP-coated $MnFe_2O_4$ nanoparticles were prepared by a one-step sonochemical method. In a typical reaction, 1.62 g $FeCl_3{\cdot}6H_2O$, 0.59 g $MnCl_2{\cdot}4H_2O$ and calculated PVP were totally dissolved in deionized water (150 mL) under magnetic stirring. The obtained homogeneous solution was added into a beaker containing 3.5 M NaOH solution. The beaker was placed in a self-made ultrasonic bath with power and frequency of 100 W and 20 kHz, respectively. During this procedure, the pH value was adjusted to 11 and the mixture solution was allowed to sonicate for 1 h. The final products were collected by a strong magnet and rinsed with absolute ethanol and deionized water for several times. The polymer-coated $MnFe_2O_4$ nanoparticles were named as PVP-$MnFe_2O_4$-1/10, PVP-$MnFe_2O_4$-1/1 and PVP-$MnFe_2O_4$-2/1, respectively. For comparison, bare $MnFe_2O_4$ nanoparticles were synthesized by the same experiment process without PVP.

2.3. Characterization

A Tecnai G2 F20 transmission electron microscopy (TEM) was used to observe the morphology with an operating voltage of 160 kV. The crystallographic analysis was performed by a Rigaku Dmax-Ultima$^+$ X-ray diffraction system with Cu radiation. The functional groups were examined in a Nicolet Magna 750 Fourier transform infrared spectrometer (FTIR). The surface analysis was carried out with a Thermo Scientific Escalab 250Xi X-ray photoelectron spectroscopy (XPS) equipped with a hemispherical analyzer. The magnetization properties were studied by using a Quantum Design MPMS-XL-7 superconducting quantum interference device (SQUID).

2.4. In vitro *cytotoxicity*

To examine the cytotoxicity of the magnetic nanoparticles, an *in vitro* cytotoxicity experiment was performed using HeLa Cells. The amounts of viable cells were determined by the estimation of mitochondrial reductase activity using standard methyl thiazolyl tetrazolium (MTT, Sigma-Aldrich) assay. The cells were seeded in a RPMI-1640 culture media with 100 U/mL penicillin at 20000 cells/mL and cultured with 5% CO_2 at 37 °C for 24 h. At the end of the incubation time, the HeLa cells were treated with PVP-$MnFe_2O_4$ solutions with different concentrations (from 0 to 150 μg/mL) and further incubated for 12 h and 24 h, respectively. Cell viability was defined as the ratio between the amount of formazan determined for cells treated with the different PVP-$MnFe_2O_4$ solutions and for control non-treated cells.

2.5. In vitro *loading and release of DOX*

In brief, the weighted PVP-$MnFe_2O_4$-1/1 was ultrasonically dispersed in PBS solution (200 mL, pH 7.4) containing different amounts of DOX. After mechanical stirring for 24 h under dark conditions, the drug-loaded nanoparticles were centrifuged and washed with fresh PBS solution for several times. The washed supernatants were collected and the residual drugs were measured by UV–vis measurement (TU-1810) at an excitation wavelength of 479 nm. The loading capacity was calculated based on the standard curve with different known drug concentrations.

Release kinetics of the loaded DOX from drug-loaded $MnFe_2O_4$ was measured by using the dialysis devices. In brief, the prepared DOX-loaded PVP-$MnFe_2O_4$ nanoparticles were sonicated in PBS solution (5 mL) with varied pH values (4.0, 7.4 and 9.0). The dialysis devices were incubated in a shaking table under gentle shaking (100 r/min) at constant temperature. At given time intervals, a certain amount of release medium (5 mL) was removed for analysis and then poured back to the release system. The percentage of released DOX was calculated by UV–vis spectroscopy.

3. Results and discussion

The preparation procedure of PVP modification of $MnFe_2O_4$ nanoparticles is shown in Fig. 1. This biocompatible polymer of PVP is regarded as an ideal candidate for surface modification of nanoparticles, which is benefit for $MnFe_2O_4$ nanoparticles to deal with the existing problems of dispersion and biocompatability. As the salt solution was added into NaOH solution, the color changed rapidly from initially yellow to dark black. The tiny $MnFe_2O_4$ nanocrystals were produced in aqueous medium following a sonochemical mechanism. In addition, bare $MnFe_2O_4$ nanoparticles were also synthesized for comparison by the same experiment process without PVP. Considering the potential application environments of the PVP-coated $MnFe_2O_4$ nanoparticles as drug delivery, the PBS solutions with different pH values (4.0, 7.4 and 9.0) are chose as the solution media to study the dispersion stability. As shown in Fig. S1, the aqueous solutions of PVP-$MnFe_2O_4$ at different pH values (4.0, 7.4 and 9.0) keep stable at the high concentration of 25 mg/mL. No precipitation is observed even in the period of 28 days except that the color is a little darker, showing a good long-term aqueous stability. The morphology of bare $MnFe_2O_4$ and PVP-$MnFe_2O_4$-1/1 was examined by TEM. The un-modified $MnFe_2O_4$ nanoparticles show obvious agglomeration from the representative TEM image (Fig. 2a). As for the PVP-treated $MnFe_2O_4$ nanoparticles, it can be clearly observed from Fig. 2b that the nanoparticles have good dispersion and homogeneous shape, with a narrow particle size distribution (inset of Fig. 2b). It is noteworthy that steric and electrostatic interactions between the amide groups of coated PVP molecules hinder serious aggregation of $MnFe_2O_4$ nanoparticles.

The crystalline structure of the PVP-coated $MnFe_2O_4$ nanoparticles was determined by XRD, as shown in Fig. 3. The XRD curves of PVP-coated $MnFe_2O_4$ with different concentrations of PVP display representative diffraction peaks of bare $MnFe_2O_4$, which confirms that the surface-treatment does not change the crystalline structure of manganese ferrite. It should be noted that no diffraction