Research Article

Bifunctional Silica-Coated Superparamagnetic FePt Nanoparticles for Fluorescence/MR Dual Imaging

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Recently, superparamagnetic chemically disordered face-centered cubic (fcc) FePt nanoparticles have been demonstrated as superior negative contrast agents for magnetic resonance imaging (MRI). However, their low intracellular labeling efficiency has limited the potential usage and the nanotoxicity of the particles requires attention. We have developed fluorescein isothiocyanate-incorporated silica-coated FePt (FePt@SiO₂-FITC) nanoparticles that exhibited not only a significant T_1 and T_2 MR contrast abilities but also a fluorescent property without significant cytotoxicities. These results suggest that silica-coated superparamagnetic FePt nanoparticles are potential nanodevices for the combination of fluorescence and MRI contrast used for cancer diagnosis.

1. Introduction

Superparamagnetic iron oxide (SPIO) nanoparticles have demonstrated their practicability as MRI T_2 -shortening agents for noninvasive cell labeling, drug delivery or tumor detections in clinical practice [1, 2]. However, low intracellular labeling efficiency and nanotoxicity of SPIO has limited their potential usage [3, 4]. Recently, bifunctional contrast agents for both optical and MR imaging have been developed to function as good imaging probes *in vitro* and *in vivo* [5–8] and the nanotoxicity of SPIO is suppressed by particular surface modification [9]. Thus, proper modifications of SPIO have been considered as a promising strategy to improve the aforementioned problems.

Long-range ordered $L1_0$ FePt films have been studied extensively and thought to be a promising candidate for ultrahigh-density magnetic recording media due to its high magnetocrystalline anisotropy (K_u). The magnetization thermal instability or superparamagnetic effect is delayed due to their very small critical grain size of around (3–5 nm). However, when FePt nanoparticles are disordered with face-centered cubic (fcc) structure, they exhibit superparamagnetic property under critical size. Superparamagnetic

iron-platinum (FePt) nanoparticles, which show high saturation magnetization (M_s) compared to SPIO, are expected to be a high performance nanomagnet for magnetic medicine [10, 11]. In particular, the potential of FePt nanoparticles as an MRI contrast agent has been demonstrated [12]. Thus, the bifunctional contrast agent using superparamagnetic FePt nanoparticles seems to be a promising dual-modality biomedical detections material. In our strategy, silica was selected for surface coating of FePt nanoparticles to enhance the biocompatibility and easier modifications for bioconjugation or cell targeting [13]. Moreover, fluorescent dyes can be easily incorporated into a silica shell that provides a powerful tool for intracellular tracking [14]. Hence, the bifunctional fluorescein-isothiocyanate-(FITC-) incorporated silica-coated superparamagnetic FePt (FePt@SiO₂-FITC) nanoparticles were synthesized and their potential applications for dual fluorescent/magnetic imaging in this study were evaluated.

2. Experimental Procedure

2.1. Materials. For materials preparation, iron pentacarbonyl (Fe(CO)₅, 99.99%), platinum(II) acetylacetonate

FIGURE 1: XRD patterns of FePt and FePt@SiO₂-FITC nanoparticles.

(Pt(acac)₂, 97%, 1,2-hexadecanediol, fluorescence isocyanate (FITC), 3-Aminopropyltrimethoxysilane (APTMS, 97%), Triton X100, hexanol, and benzyl ether were purchased from Sigma-Aldrich (St. Louis, MO, USA). Oleylamine (80–90%) was obtained from Acros (New Jersey, USA). Oleic acid and tetraethyl silicate (TEOS, 99.9%) were obtained from Showa (Tokyo, Japan). The ethanol (99.5%) and hexane were purchased from Echo in Taiwan. The solvents were all dehydrated prior to use.

For cell culture studies, sodium phosphate dibasic (Na₂HPO₄) and sodium chloride (NaCl) were obtained from Tedia (OH, USA). Potassium chloride (KCl), potassium dihydrogenphosphate (KH₂PO₄), and sodium bicarbonate (NaHCO₃) were obtained from Showa (Tokyo, Japan). Modified Eagle's Medium (MEM), fetal bovine serum (FBS), and 0.25% trypsin-EDTA were purchased from Gibco (Gibco-BRL, USA). The penicillin-streptomycin-neomycin solution and 10% formalin were purchased from Sigma-Aldrich (St. Louis, MO, USA). Double distilled water was used in all of the aqueous solutions.

2.2. Synthesis of FePt Nanoparticles. The synthesis of fcc FePt nanoparticles involving simultaneous chemical reduction of Pt(acac)₂ and Fe(CO)₅ by 1,2-hexadecanediol at high temperature was described as previous report [15]. Briefly, Pt(acac)₂ (0.48 mmol) was dissolved in 10 mL of benzyl ether and the solution was heated to 100°C under nitrogen atmosphere. The surfactants of oleylamine (0.5 mmol) and oleic acid (0.5 mmol) were added into the reaction and subsequently the Fe(CO)₅ (1 mmol) was injected. The mixture solution was then heated to 297°C under refluxing for 30 minutes. Finally, the reaction system was cooled down to room temperature and the FePt nanoparticles were purified using ethanol washing and then collected by centrifugation.

2.3. Synthesis of Silica-Coated FePt Nanoparticles. The bifunctional magnetic silica-coated FePt (FePt@SiO₂) nanoparticles were synthesized by a water-in-oil microemulsion method as previous reports [13, 16]. First, the *N*-1-(3-triethoxysilylpropyl)-*N*-fluoresceyl thiourea (FITC-APTMS) was prepared by stirring 5 mg FITC in 5 mL ethanolic APTMS solution (10 v/v%) for 24 hours. The monodisperse hydrophobic FePt nanoparticles were also redissolved in cyclohexane at room temperature and Triton X-100, hexanol

and distilled water were added into the solution with stirring to generate a microemulsion. Then the TEOS, APTMS, and FITC-labeled APTMS were added into the system to form the functional silica shell structure. The sol-gel growth of silica was limited in the water domain in this w/o microemulsion. All procedures were carried out in subdued light. To remove free surfactants and unreacted chemicals, the as-synthesized silica-coated FePt nanoparticles solution was centrifuged and washed with ethanol and deionized water. All procedures were repeated twice and the final silica-coated FePt nanoparticles were stored in deionized water for following experiments.

These FePt@SiO₂-FITC nanoparticles were evaluated by the X-ray diffraction (XRD), transmission electron microscope (TEM), vibration sample magnetometer (VSM), fluorescence spectroscopy, *T*₂ enhancing relaxivity, and determine the iron content of FePt@SiO₂-FITC nanoparticles by inductively coupled plasma atomic emission spectroscopy (ICP-AES).

2.4. Characterizations of FePt Nanoparticles and FePt@SiO₂-FITC Nanoparticles. The FePt nanoparticles were further characterized by XRD (Bruker MXP-III) with a 2.0 kW Cu tube and a Sol-X energy dispersive detector. The XRD sample was mounted with Vaseline on a glass substrate, and the data were collected from 20°–80° 2θ (step size = 0.6° and time per step = 1 s) at room temperature.

The size and morphologies were observed under the TEM (JEM 1200, JEOL Ltd., Japan). Samples for TEM analysis were prepared as dilute dispersions in hexane/water with a small amount of surfactants. The size distributions were evaluated by dynamic light scattering (DLS, ZS-90, Malvern).

The magnetic properties and performance were characterized by VSM. Magnetization curves as a function of applied field were measured with fields up to 1.2 kOe at room temperatures. The relaxation times (*T*₁ and *T*₂) were measured by NMR (300 MHz, Varian) at room temperature. The iron concentrations of samples were determined by ICP-AES (ICAP 9000, Jarrell-Ash, USA). The MRI images were all taken by the clinical 3T MR scanner (Signa Excite 3 T, GE Healthcare, USA).

The cytotoxicity of FePt and FePt@SiO₂-FITC nanoparticles was evaluated by MTT assay using human cervical

FIGURE 2: The TEM images of (a) FePt and (b) FePt@SiO₂-FITC nanoparticles.

FIGURE 3: Room-temperature magnetization curves of FePt and FePt@SiO₂-FITC nanoparticles.

epithelioid carcinoma (HeLa) cells. The intracellular localization of FePt@SiO₂-FITC nanoparticles in HeLa cells was examined using a confocal microscope after costaining with LysoTracker Red (Invitrogen) as our previous report [17].

3. Results and Discussions

FePt nanoparticles were synthesized by heating the Pt(acac)₂ and Fe(CO)₅ precursors with the surfactants at 297°C for 30 minutes to form the black suspension. The as-synthesized FePt nanoparticles were washed and centrifuged for the following characterization and evaluations. Figure 1 showed the XRD patterns of oleic acid/oleylamine-capped FePt nanocrystals with or without the functionalized SiO₂ coating. It is known that the FePt nanoparticles were

TABLE 1: Longitudinal and transverse relaxivities and relaxivity ratios of FePt and FePt@SiO₂-FITC nanoparticles.

Material	r_1 (s ⁻¹ mM ⁻¹)	r_2 (s ⁻¹ mM ⁻¹)	r_2/r_1
FePt	5.7	396.1	69.5
FePt@SiO ₂ -FITC	6.8	102.3	15.0

generated rapidly as the temperature rises from 250 to 297°C. Saita and Maenosono had also reported the effects of heating rate on the synthesized FePt nanoparticles [18]. Thus, we set the reaction temperature at 297°C for 30 min in this study to avoid formation of γ -Fe₂O₃ (or Fe₃O₄). As shown in Figure 1(a), the (111), (200), and (220) peaks of typical chemically disordered fcc-phase FePt crystallite without being annealed were evidently observed and there was no (311) peak observed around $2\theta = 35^\circ$ [18–20]. These FePt nanocrystals were coated with SiO₂ using water-in-oil microemulsions method and NH₄OH was used to catalyze the decomposition of TEOS to silica over the course of 48 hrs. XRD patterns of FePt@SiO₂-FITC nanoparticles confirmed the existence of fcc-phase FePt after SiO₂ coating (Figure 1(b)). Due to the amorphous SiO₂ coating, the broaden peak was found in the low diffraction angle (indicated by *) [21]. It is noticed that the (111) FePt fundamental peak was shift slightly to the high angle. To prepare the FePt@SiO₂ and FePt@SiO₂-FITC nanoparticles, the multiple-surface modifications were carried out under air condition, and thus the surface oxidation of FePt might be occurred. In the XRD study, the shifted peak to high angle (from $\sim 40^\circ$ to $\sim 41.7^\circ$) may be due to the coupling of FePt crystallite with the oxidized product on the FePt nanoparticle surface, in which the peak at about 41.7 is near to the reflection peak of FeO (200) at $\sim 42^\circ$ according to the assignment of JPCDS No. 86–2316 [22, 23]. Further investigations of FePt nanoparticles for structure changes are being undertaken at our lab.

FIGURE 4: The MRI images of FePt@SiO₂ and FePt@SiO₂-FITC nanoparticles evaluated by clinical 3T MR scanner.

Figure 2 shows the TEM images of FePt and FePt@SiO₂-FITC nanoparticles and the sizes were analyzed by SigmaScan Pro software. The size of FePt nanoparticles was 4.59 ± 0.80 nm with sphere/cubic shape (Figure 2(a)). The FePt@SiO₂-FITC nanoparticles revealed 48.98 ± 6.41 nm thick silica structure that was coated around several FePt nanoparticles from TEM observation (Figure 2(b)). The polydispersity of FePt@SiO₂-FITC nanoparticles observed by DLS was 0.182.

The room-temperature magnetic hysteresis curves of FePt and FePt@SiO₂-FITC nanoparticles were all normalized to emu per gram of Fe content as shown in Figure 3. Clearly, the fcc-phase FePt nanoparticles sustain their superparamagnetic property in the silica composites at room temperature [20]. However, the lower and unsaturated magnetization of FePt@SiO₂-FITC nanoparticles observed under the applied field of 1.2 T may be due to the surface loose density of FePt component in the silanized particles or the surface dead layer around SiO₂ [24–26]. The significant difference in M_s among nanoparticles capped with varied ligands and the dead layer thickness have been estimated as previous report [27]. Thus, the electron donation from ligands to the Fe d band may reduce the magnetization. The possible FeO formation may also reduce M_s of nanoparticles.

The T_1 and T_2 values obtained from FePt or FePt@SiO₂-FITC nanoparticles dispersed in pure water are summarized in (Table S1 and Figure S1 in Supplementary Material available online at doi:10.1155/2012/631584) and the inverse relaxation times were almost linearly proportional to the concentration of nanoparticle similar to previous report [12]. Consequently, the r_1 (longitudinal relaxivities) and r_2 (transverse relaxivities) values of dispersed in pure water were determined to be 5.8 and 396.1 for FePt or 6.8 and 102.3 s⁻¹ mM⁻¹ for FePt@SiO₂-FITC nanoparticles, respectively (Table 1). For a T_2 contrast agent, a higher r_2/r_1 ratio has a better contrast efficacy [28] and thus FePt@SiO₂-FITC nanoparticles with $r_2/r_1 = 15$ can be potentially

used for MR contrast. The MRI images of FePt@SiO₂ and FePt@SiO₂-FITC nanoparticles were evaluated by clinical 3T MR scanner and the results were shown in Figure 4. Unexpectedly, FePt@SiO₂ and FePt@SiO₂-FITC nanoparticles revealed bright T_1 -weighted imaging, whereas T_2 -weighted imaging of both nanoparticles became dark as the Fe concentration increased. FePt nanoparticle has been demonstrated as potential T_2 -weighted contrast agent for MR imaging due to its magnetization [29, 30]. For the T_1 contrast enhancement, it is possible that the generation of FeO surface coating on the FePt nanoparticle may provide additional assistance for the spin-lattice relaxation process.

The fluorescence spectrum of FePt@SiO₂-FITC nanoparticles was shown in Figure S1. Clearly, the property of FITC was observed in FePt@SiO₂-FITC nanoparticles which exhibited strong fluorescence at 535 nm with the excitation wavelength at 488 nm. Thus, FePt@SiO₂-FITC nanoparticles could be observed directly inside the cells by the fluorescence of the FITC. Figure 5 showed the intracellular localization of FePt@SiO₂-FITC nanoparticles in HeLa cells. After 12 hours incubation, the colocalization of fluorescence (Figure 5(c)) of FePt@SiO₂-FITC nanoparticles (Figure 5(a)) and LysoTracker (Figure 5(b)) was observed in HeLa cells. It is speculated that FePt@SiO₂-FITC nanoparticles were internalized into cells and entrapped presumably in the endosomes/lysosomes, as suggested by confocal microscopic observation. This result indicated that the FePt@SiO₂-FITC nanoparticles might be taken up by cells via endocytosis. The dose-dependent cytotoxicity of FePt and FePt@SiO₂-FITC in HeLa cells was demonstrated in Figure 6. No significant cytotoxicity was observed after 500 μM FePt@SiO₂-FITC nanoparticles incubation for 24 h or 72 h, whereas FePt nanoparticles induced cell toxicity at 500 μM for 72 h incubation (62% cell survival). Thus, the cytotoxicity of FePt nanoparticles was potentially suppressed with silica coating.

The introduction of APTMS and FITC-labeled APTMS in synthetic procedure of silica-coated nanoparticle not only

FIGURE 5: Comparative intracellular localization of FePt@SiO₂-FITC nanoparticles with LysoTracker Red observed by confocal laser scanning microscopy.

FIGURE 6: Cytotoxicity of FePt and FePt@SiO₂-FITC nanoparticles. Cells were incubated for 24 h or 72 h at 37°C ($n = 4$).

provide the fluorescent property but produce the positive surface charge of FePt@SiO₂-FITC nanoparticles (Figure S2) that facilitate attachment and internalization of the particles [31]. Moreover, the amino groups of APTMS can be further conjugated using hydrophilic polyethylene glycol that results in steric hindrance to the phagocyte, system, and prolongation of blood circulation time [32]. Developing multiple imaging modalities in one nanoparticle is a promising field for biomedical applications. Chou et al. reported the dual modal biomedical imaging by using the FePt nanoparticles as simultaneous CT and MRI contrast agent [29]. Malvindi et al. also reported the dual mode imaging of the FePt-iron oxide and silica nanoparticles combination as the MRI and ultrasonography contrast agent [30]. These reports showed the advantages of these highly potential dual-mode imaging contrast agents for biomedical applications. Further investigations of FePt@SiO₂-FITC nanoparticles for simultaneous fluorescence/MR imaging *in vivo* are ongoing at our lab.

4. Conclusion

The longitudinal and transverse proton relaxation times obtained with silica-coated superparamagnetic FePt nanoparticles was measured. Unexpectedly, FePt@SiO₂ and FePt@SiO₂-FITC nanoparticles revealed bright T₁-weighted imaging, whereas T₂-weighted imaging of both nanoparticles became dark as the Fe concentration increased. Moreover, the surface coating using silica successfully suppressed the nanotoxicity of FePt. These results suggest that silica-coated superparamagnetic FePt nanoparticles are potential nanodevices for the combination of simultaneous fluorescence and MRI contrast for cancer diagnosis.

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