Facile synthesis of ultrasmall PEGylated iron oxide nanoparticles for dual-contrast $T_1$- and $T_2$-weighted magnetic resonance imaging

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2011 Nanotechnology 22 245604
(http://iopscience.iop.org/0957-4484/22/24/245604)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 58.60.1.14
The article was downloaded on 25/07/2011 at 08:09

Please note that terms and conditions apply.
Facile synthesis of ultrasmall PEGylated iron oxide nanoparticles for dual-contrast \( T_1 \)- and \( T_2 \)-weighted magnetic resonance imaging

Fengqin Hu\(^1\), Qiaojuan Jia\(^2\), Yilin Li\(^2\) and Mingyuan Gao\(^2\)

\(^1\) College of Chemistry, Beijing Normal University, Beijing 100875, People’s Republic of China
\(^2\) Institute of Chemistry, CAS, Bei Yi Jie 2, Beijing 100190, People’s Republic of China

E-mail: fqhu@bnu.edu.cn

Received 7 January 2011, in final form 14 March 2011
Published 21 April 2011
Online at stacks.iop.org/Nano/22/245604

Abstract
The development of new types of high-performance nanoparticulate MR contrast agents with either positive (\( T_1 \)) or dual-contrast (both positive and negative, \( T_1 + T_2 \)) ability is of great importance. Here we report a facile synthesis of ultrasmall PEGylated iron oxide nanoparticles for dual-contrast \( T_1 \)- and \( T_2 \)-weighted MRI. The produced superparamagnetic iron oxide nanoparticles (SPIONs) are of high crystallinity and size uniformity with an average diameter of 5.4 nm, and can be individually dispersed in the physiological buffer with high stability. The SPIONs reveal an impressive saturation magnetization of 94 emu g\(^{-1}\) Fe\(_3\)O\(_4\), the highest \( r_1 \) of 19.7 mM\(^{-1}\) s\(^{-1}\) and the lowest \( r_2/r_1 \) ratio of 2.0 at 1.5 T reported so far for PEGylated iron oxide nanoparticles. \( T_1 \)- and \( T_2 \)-weighted MR images showed that the SPIONs could not only improve surrounding water proton signals in the \( T_1 \)-weighted image, but induce significant signal reduction in the \( T_2 \)-weighted image. The good contrast effect of the SPIONs as \( T_1 + T_2 \) dual-contrast agents might be due to its high magnetization, optimal nanoparticle size for \( T_1 + T_2 \) dual-contrast agents, high size monodispersity and excellent colloidal stability. \textit{In vitro} cell experiments showed that the SPIONs have little effect on HeLa cell viability.

Online supplementary data available from stacks.iop.org/Nano/22/245604/mmedia

1. Introduction
Magnetic resonance imaging (MRI) is currently one of the most powerful tools for biological molecular imaging and clinical diagnosis [1–4]. One of the significant advantages of MRI is the ability to acquire three-dimensional tomographic information of whole tissue samples and animals with high spatial resolution and soft tissue contrast. In addition, images are acquired without the use of ionizing radiation or radiotracers. Medical diagnosis requires enhanced contrast between normal and pathological tissues, resulting in the development of exogenous MR contrast agents.

Most of the presently commercial MR contrast agents are paramagnetic molecular complexes, such as Gd\(^{3+}\) (seven unpaired electrons) and Mn\(^{2+}\) (five unpaired electrons) chelates, which are positive (\( T_1 \)) contrast agents [5–7]. Their relaxivity ratio \( r_2/r_1 \) is commonly in the range of 1–2. Areas enriched with paramagnetic molecular complexes exhibit an increase in signal intensity and appear bright in \( T_1 \)-weighted images [1, 5]. This kind of contrast agent is limited by their nonspecificity to target, quick removal by renal excretion and short accumulation time in practical applications [8].

Superparamagnetic nanoparticles (typically iron oxide nanoparticles) are another class of MR contrast agents that was normally used as negative (\( T_2 \)) contrast agents. The nanoparticles commonly show a high \( r_2/r_1 \) ratio of at least 10, produce a decrease in signal intensity and appear dark in \( T_2 \)-weighted images [9–16]. Compared with the conventional paramagnetic agents, nanoparticle-based contrast agents have
a number of advantages due to its nanoparticulate structures: (1) the magnetic properties of the agents can be tailored by size, shape, composition and assembly; (2) the nanoparticulate agents show tunable cellular uptake; (3) the agents have large specific surface areas that facilitate conjugation with targeting molecules and other probes for achieving targeting and multimodal agents and (4) the nanoscale dimension, adjustable surface structure and shape of the agents allow varying and favorable biodistribution. Nevertheless, a negative contrast effect and magnetic susceptibility artifacts are key factors that restrict the applications of superparamagnetic nanoparticles in MRI. The resulting dark signal might mislead the clinical diagnosis in T₂-weighted MRI because the signal is often confused with the signals from bleeding, calcification or metal deposits, and the susceptibility artifacts distort the background image [17, 18]. Therefore, the development of new types of nanoparticulate MR contrast agents with either T₁ or T₁ + T₂ dual-contrast ability is urgently needed.

For the above reasons, nanoparticles of Gd₂O₃ [19–22], GdF₃ [23], GdPO₄ [24] and MnO [18] have been investigated as T₁ MR contrast agents in the past few years. However, the sophisticated synthesis procedures and low r₁ values make them far from optimal for positive MRI. Recently, superparamagnetic iron oxide nanoparticles with ultrasmall sizes (<6 nm) were found to be good candidates for T₁ or T₁ + T₂ dual MR contrast agents [25–27]. Monodisperse ultrasmall iron oxide nanoparticles were mostly synthesized in non-polar organic solvents. They are only dispersible in non-polar organic solvents, and thus need surface modification with hydrophilic and biocompatible ligands before biomedical applications. For example, hydrophilic ultrasmall iron oxide nanoparticles with potential as dual MR contrast agents [25–27]. Monodisperse ultrasmall iron oxide nanoparticles were mostly synthesized in non-polar organic solvents. They are only dispersible in non-polar organic solvents, and thus need surface modification with hydrophilic and biocompatible ligands before biomedical applications. For example, hydrophilic ultrasmall iron oxide nanoparticles with potential as dual MR contrast agents [25–27]. Monodisperse ultrasmall iron oxide nanoparticles were mostly synthesized in non-polar organic solvents. They are only dispersible in non-polar organic solvents, and thus need surface modification with hydrophilic and biocompatible ligands before biomedical applications. For example, hydrophilic ultrasmall iron oxide nanoparticles with potential as dual MR contrast agents [25–27].

Monodisperse ultrasmall iron oxide nanoparticles were mostly synthesized in non-polar organic solvents. They are only dispersible in non-polar organic solvents, and thus need surface modification with hydrophilic and biocompatible ligands before biomedical applications. For example, hydrophilic ultrasmall iron oxide nanoparticles with potential as dual MR contrast agents [25–27]. Monodisperse ultrasmall iron oxide nanoparticles were mostly synthesized in non-polar organic solvents. They are only dispersible in non-polar organic solvents, and thus need surface modification with hydrophilic and biocompatible ligands before biomedical applications. For example, hydrophilic ultrasmall iron oxide nanoparticles with potential as dual MR contrast agents [25–27].

The colorimetric MTT assay was performed to determine the cytotoxicity of the SPIONs. Specifically, HeLa cells were first plated into a 96-well plate and cultured for about 24 h in Dulbecco's Modified Eagle Medium (DMEM, high glucose, Gibco, C11995) supplemented with 10% fetal bovine serum (FBS, Thermo, SH3007003). Then, the cells were washed with PBS and incubated with 100 μl 1-sulphosalicylic acid (5 mg ml⁻¹) MTT (Amresco, 98%, code 0793) was added for 3 h to allow the cells to react with the reagent to form a formazan dye that can be quantified by a spectrophotometer. The absorbance of each well was measured at 570 nm on a SpectraMax M5 microplate reader.

2.2. Cell viability experiments
The colorimetric MTT assay was performed to determine the cytotoxicity of the SPIONs. Specifically, HeLa cells were first plated into a 96-well plate and cultured for about 24 h in Dulbecco’s Modified Eagle Medium (DMEM, high glucose, Gibco, C11995) supplemented with 10% fetal bovine serum (FBS, Thermo, SH3007003). Then, the cells were washed with PBS and incubated with 100 μl 1-sulphosalicylic acid (5 mg ml⁻¹) MTT (Amresco, 98%, code 0793) was added for 3 h to allow the cells to react with the reagent to form a formazan dye that can be quantified by a spectrophotometer. The absorbance of each well was measured at 570 nm on a SpectraMax M5 microplate reader.

2.3. Characterization
TEM images and selected-area electron diffraction patterns were obtained on a JEM-2010 operated at an accelerating potential reaction. The produced SPIONs show excellent colloidal stability in the physiological buffer, present an impressive saturation magnetization of 94 emu g⁻¹ Fe₃O₄ and a r₁ of 19.7 mM⁻¹ s⁻¹ as well as a r₂/r₁ ratio of 2.0 at 1.5 T. To the best of our knowledge, these are the highest r₁ and lowest r₂/r₁ ratio at 1.5 T reported so far for PEGylated iron oxide nanoparticles, indicating that the SPIONs are promising T₁+T₂ dual-contrast agents for a variety of MRI applications.
Figure 1. (a) TEM (inset is HR-TEM) images, (b) size distribution histogram and (c) electron diffraction patterns of the 5.4 nm SPIONs. The scale bar is 20 nm in the TEM image and 2 nm in the HR-TEM image.

Figure 2. Powder x-ray diffractogram of the 5.4 nm SPIONs. Bottom: JCPDS card (19-0629) data for magnetite.

Voltage of 200 kV. HR-TEM images were obtained on a JEOL JEM-2100F FAST TEM operated at an accelerating voltage of 200 kV. Samples for TEM were prepared by spreading a drop of the solution sample on copper grids coated with a carbon film followed by evaporation under ambient conditions. XRD measurements were carried out on a powder sample of the SPIONs using a Regaku D/Max-2500 diffractometer. DLS measurements were performed with a Malvern Instruments Zetasizer Nano Series Nano-ZS. FTIR spectra were obtained with a Thermo Nicolet NEXUS 870 Fourier transform spectrometer. The transmission spectra of the SPIONs were taken after making pellets with KBr powder. A universal ATR sampling accessory was used to record the attenuated total reflection spectra of pure liquid TREG and HOOC–PEG–COOH (600 g mol\(^{-1}\)). Magnetic susceptibility measurements were carried out on a Quantum Design MPMS SQUID magnetometer. Samples were dispersed in 0.1 M sodium citrate and frozen under a nitrogen environment. Longitudinal and transverse relaxation times were measured at 1.5 T (60 MHz) and 37 °C on a Bruker mq60 NMR Analyzer. An inversion–recovery pulse sequence was used to measure the longitudinal relaxation times and a spin echo pulse sequence was used to measure the transverse relaxation times. MR phantom images were acquired on a Siemens 3 T TIM Trio clinical imaging system at ambient temperature (~25 °C). A \(T_1\)-weighted image was acquired using a \(T_1\)-weighted spin echo pulse sequence with \(TR = 500\) ms, \(TE = 11\) ms, \(FOV = 75 \times 100\) mm\(^2\), data matrix = 192 \times 256, slice thickness = 2 mm and four signal averages. A \(T_2\)-weighted image was acquired using a \(T_2\)-weighted spin echo pulse sequence with \(TR = 1500\) ms, \(TE = 75\) ms, \(FOV = 75 \times 100\) mm\(^2\), data matrix = 192 \times 256, slice thickness = 2 mm and four signal averages. The iron concentration of each sample for SQUID and relaxivity was measured with a Quantum Design MPMS SQUID magnetometer. Samples were prepared by heating a mixture of 1.5 mmol Fe(acac)\(_3\), 6 g HOOC–PEG–COOH (600 g mol\(^{-1}\)) and 20 ml TREG at 260 °C for 30 min. Figure 1(a) shows the representative TEM and HR-TEM images of the SPIONs. The histogram of the nanoparticle size based on statistical results is shown in figure 1(b). The average nanoparticle size is 5.4 nm. A standard deviation of 0.7 nm demonstrates the high monodispersity of the SPIONs prepared with this procedure. Selected-area electron diffraction patterns shown in figure 1(c) reveal that the SPIONs are of high crystallinity. The lattice spacings (calculated on the basis of the XRD) are in agreement with those of bulk inverse spinel iron oxide such as magnetite (JCPDS 19-0629, \(\gamma\)-Fe\(_2\)O\(_3\)) or maghemite (JCPDS 39-1346, \(\gamma\)-Fe\(_2\)O\(_3\)). The chemical composition of the SPIONs was demonstrated in the following FTIR spectra.

3. Results and discussion

A polyol process was designed to synthesize SPIONs by using Fe(acac)\(_3\) as the iron precursor, HOOC–PEG–COOH as the stabilizer and TREG as the solvent and reducing agent. Typically, 5.4 nm SPIONs were prepared by heating a mixture of 1.5 mmol Fe(acac)\(_3\), 6 g HOOC–PEG–COOH (600 g mol\(^{-1}\)) and 20 ml TREG at 260 °C for 30 min. Figure 1(a) shows the representative TEM and HR-TEM images of the SPIONs. The histogram of the nanoparticle size based on statistical results is shown in figure 1(b). The average nanoparticle size is 5.4 nm. A standard deviation of 0.7 nm demonstrates the high monodispersity of the SPIONs prepared with this procedure. Selected-area electron diffraction patterns shown in figure 1(c) reveal that the SPIONs are of high crystallinity. The lattice spacings (calculated on the basis of the XRD) are in agreement with those of bulk inverse spinel iron oxide such as magnetite (JCPDS 19-0629, \(\gamma\)-Fe\(_2\)O\(_3\)) or maghemite (JCPDS 39-1346, \(\gamma\)-Fe\(_2\)O\(_3\)). The crystal structure was also investigated by powder x-ray diffraction (XRD). As shown in figure 2, the position and relative intensity of the strong diffraction peaks of the SPIONs correspond to a cubic structure of the inverse spinel iron oxide. The average particle size calculated with Debye–Scherrer’s formula is 5.1 nm, which is quite close to the TEM result. Note that, it is very difficult to distinguish between these two spinel structures (magnetite and maghemite) with selected-area electron diffraction and XRD patterns. The chemical composition of the SPIONs will be demonstrated in the following FTIR spectra.
The polyol method possesses both merits of the syntheses in non-polar organic solvent and in aqueous solvent. The former provides a monodisperse particle diameter, whereas the latter provides an easy synthesis for water solubility and biocompatibility. As expected, the 5.4 nm SPIONs showed high monodispersity with a standard deviation of 0.7 nm, and can be readily dispersed in aqueous media without any further surface modification. The SPIONs can also form a stable dispersion in PBS at the same pH value and ionic strength as physiological conditions. This colloid remains stable at room temperature for several months without noticeable precipitation, as shown in figure 3(a). The colloidal stability of the SPIONs was further investigated through dynamic light scattering (DLS). As shown in figure 3(b), the hydrodynamic diameter of the SPIONs freshly dispersed in PBS is 10.1 nm, which remains unchanged after placement of the solution for 9 months. This indicates that the SPIONs prepared with the current procedure show excellent colloidal stability in PBS, which is promising for in vitro and in vivo biomedical applications.

The surface chemical structure of the SPIONs was characterized by Fourier transform infrared (FTIR) spectroscopy. The FTIR spectra of the SPIONs, TREG and HOOC–PEG–COOH were shown in figure 4. The characteristic bands of HOOC–PEG–COOH at 1103 cm$^{-1}$ (C–O–C stretch) and 2868 cm$^{-1}$ (CH$_2$ stretch) appear in the spectrum of the SPIONs, indicating that HOOC–PEG–COOH is present on the SPION nanocrystal surfaces. The distinct spectral difference between HOOC–PEG–COOH and the SPIONs is that the carboxyl band at 1751 cm$^{-1}$ for HOOC–PEG–COOH is shifted to a lower wavenumber, 1630 cm$^{-1}$, accompanied by the appearance of a new band at 1419 cm$^{-1}$ in the spectrum of the SPIONs. This spectral change indicates that the carboxylate group interacts with the iron on the SPION surface [30]. In addition, the spectrum of the SPIONs exhibits characteristic peaks centered at 595 cm$^{-1}$ that are attributed to lattice absorption of the SPIONs [31–33]. It has been demonstrated that magnetite and maghemite can be identified from each other through their lattice absorption peaks in the FTIR spectra. The lattice adsorption peaks of the SPIONs centered at 595 cm$^{-1}$ indicate that the SPIONs are probably magnetite [33, 34]. After the PEG-coated SPIONs were dispersed in sodium citrate or PBS, both FTIR spectra and colloidal stability suggest that citrate or phosphate has been modified on the SPION surfaces even though PEG is still the primary surface coating ligand (figure S1 available at stacks.iop.org/Nano/22/245604/mmedia).

The magnetic properties of the SPIONs were measured using a superconducting quantum interference device (SQUID). Figure 5 shows the magnetization loops measured at 5 and 250 K. At 250 K, the SPIONs exhibit superparamagnetic behavior without magnetic hysteresis and remanence, whereas ferromagnetic behavior with a coercivity of 220 Oe is observed at 5 K since thermal energy is insufficient to induce moment randomization. The saturation magnetization of the SPIONs at 250 K is 94 emu g$^{-1}$Fe$_3$O$_4$, which is close to the value of bulk magnetite (98 emu g$^{-1}$). This value is quite impressive and well above the ones reported previously [29, 35].
higher the saturation magnetization is, the more important is the material for practical applications. The high saturation magnetization value found in the SPIONs might be related to the high crystallinity of the SPIONs and the nature of the surface coating material (HOOC–PEG–COOH) used. It was demonstrated that acids can decrease the spin disorder at the surface of the nanoparticles and enhance the saturation magnetization value. This kind of behavior has also been observed in Fe₂O₃ nanoparticles coated with oleic acid [36].

\[ T₁ + T₂ \] dual-contrast agents require a high \( r₁ \) and a \( r₂ \) which is not significantly larger than \( r₁ \). The use of iron oxide nanoparticles as \( T₁ + T₂ \) dual-contrast agents is, in most cases, limited due to the large \( r₂/r₁ \) ratio although the \( r₁ \) is often higher compared to paramagnetic chelates. Therefore, to achieve the successful use of iron oxide nanoparticles in dual-contrast \( T₁ \)- and \( T₂ \)-weighted MRI, one should try to maximize \( r₁ \) while keeping \( r₂ \) as small as possible. MR measurements were performed in order to investigate the ability of the SPIONs to shorten the \( T₁ \) and \( T₂ \) and thus evaluate whether it is suitable as \( T₁ + T₂ \) dual-contrast agents. \( T₁ \) and \( T₂ \) of the SPIONs at different Fe concentrations were measured on a 1.5 T (60 MHz) relaxometer at 37°C. The \( r₁ \) and \( r₂ \) of the SPIONs were determined by calculating the slope of a plot of \( 1/T₁ \) and \( 1/T₂ \) versus Fe concentration. As shown in figure 6, the \( r₁ \) and \( r₂ \) of the SPIONs are 19.7 and 39.5 mM⁻¹ s⁻¹, respectively. Therefore, the \( r₂/r₁ \) ratio of the as-developed contrast agents is 2.0. These are the highest \( r₁ \) and lowest \( r₂/r₁ \) ratios at 1.5 T reported so far for PEGylated iron oxide nanoparticles (see table S1 available at stacks.iop.org/Nano/22/245604/mmedia). It is worth noting that the \( r₂ \) of the SPIONs is 1.7 times higher than that of the recently reported PEG-coated Fe₂O₃ \( T₁ \) contrast agents (7.3 mM⁻¹ s⁻¹, 1.5 T) and even 4.5 times higher than that of magnevist (3.6 mM⁻¹ s⁻¹, 1.5 T), which is a typical \( T₁ \) contrast agent based on gadolinium as a clinical standard [26]. The high \( r₂ \) as well as low \( r₂/r₁ \) ratio makes the as-developed SPIONs an ideal candidate for \( T₁ + T₂ \) dual-contrast agents at clinically relevant magnetic fields.

To further validate the potential of the SPIONs as \( T₁ + T₂ \) dual-contrast agents, we acquired \( T₁ \)- and \( T₂ \)-weighted MR images as a function of iron concentration using a 3.0 T MRI scanner. As shown in figure 7, the SPIONs induced a bright signal enhancement in a concentration-dependent manner in the \( T₁ \)-weighted MR image. Compared to a commercially available Feridex, which is also an iron oxide nanoparticle-based contrast agent, the SPIONs exhibited much better \( T₁ \) positive contrast. In the \( T₂ \)-weighted MR image, the SPIONs also displayed a significant signal reduction with increasing nanoparticle concentration. The MR images indicate that the SPIONs could be utilized as high-performance \( T₁ + T₂ \) dual-contrast agents.

The high saturation magnetization (94 emu g⁻¹Fe₂O₃) of the SPIONs is a factor in its high \( r₁ \) value [25]. Optimal core size with good monodispersity is also very important for nanoparticle \( T₁ + T₂ \) dual-contrast agents: it should be both large enough to offer a high \( r₁ \), and small and monodisperse enough to cause a small \( r₂/r₁ \) ratio [37]. It has been suggested that a core size of approximately 5 nm is optimal to form a \( T₁ + T₂ \) dual-contrast agent based on iron oxide nanoparticles [26]. Besides nanoparticle size, size uniformity also affects the \( r₂/r₁ \) ratio of the magnetic nanoparticles. An increase of nanoparticle size leads to an increase in both \( r₁ \) and \( r₂ \). However, this effect on \( r₂ \) is much more significant than that on \( r₁ \). Therefore, a small increase of nanoparticle size results in a large increase of \( r₂/r₁ \) ratio. Therefore, high monodispersity of nanoparticle size is desired for \( T₁ + T₂ \) dual-contrast agents. The SPIONs we produced are with the optimal diameter of 5.4 nm and high size monodispersity (SD = 0.7 nm), resulting in its high \( r₁ \) and low \( r₂/r₁ \) ratio.

Excluding aggregation of magnetic nanoparticles is essential to obtain high-performance \( T₁ + T₂ \) dual-contrast agents since the transverse relaxation effect is enhanced while \( T₁ \)-shortening is weakened when agglomeration occurs [38]. So far, a lot of work has been done on the use of PEG as a ligand for iron oxide nanocrystals [39, 40]. However, the coating of nanoparticles with PEG often results in large hydrodynamic diameters and the formation of small amounts of aggregates, which in turn enables these systems to act as \( T₂ \) while not as \( T₁ \) contrast agents. In this work, the hydrodynamic diameter of the 5.4 nm SPIONs is 10.1 nm, which is slightly larger than the superposition of an iron oxide core and PEG
coating since counterions and water form a diffuse layer which moves with the SPIONs. This indicates that the SPIONs are individually dispersed. Furthermore, the hydrodynamic diameter of the SPIONs has excellent stability during the 9 month measurement period. The excellent dispersity of the SPIONs in aqueous solution could be another factor for its high $r_1$ and low $r_2/r_1$ ratio.

The cytotoxicity of the SPIONs was determined using the colorimetric MTT assay on HeLa cells. For this study, HeLa cells were incubated with 15.6, 31.3, 62.5, 125, 250 μg Fe ml$^{-1}$ of the SPIONs for 24 h. As shown in figure 8, after 24 h incubation, the viability of HeLa cells was still $>90\%$ at all Fe incubation concentrations. These results demonstrate that the SPIONs show little cytotoxicity, indicating that they have potential in in vivo MRI applications.

4. Conclusions

In summary, a facile one-pot reaction was developed to synthesize 5.4 nm water-soluble PEG-coated SPIONs which can act as high-performance $T_1 + T_2$ dual MR contrast agents. The SPIONs produced with this procedure are highly crystalline, superparamagnetic at room temperature, and can be individually dispersed in the physiological buffer with high stability. The SPIONs present an impressive saturation magnetization value of 94 emu g$^{-1}$ Fe$_3$O$_4$ and a $r_1$ of 19.7 mM$^{-1}$ s$^{-1}$ as well as a $r_2/r_1$ ratio of 2.0 at 1.5 T. $T_1$- and $T_2$-weighted MR images demonstrated that the SPIONs could be utilized as high-performance $T_1 + T_2$ dual-contrast agents. High magnetization, optimal nanoparticle size for $T_1 + T_2$ dual-contrast agents, high size monodispersity and excellent colloidal stability might be factors for the good contrast effect of the SPIONs as $T_1 + T_2$ dual-contrast agents. The cell viability assay showed that the SPIONs have little effect on HeLa cell viability. The novel SPIONs should have great potential in dual-contrast $T_1$- and $T_2$-weighted MRI for molecular imaging and diagnostic applications.

Acknowledgments

This work was supported by the initial funding of science research from the College of Chemistry, Beijing Normal University, the Fundamental Research Funds for the Central Universities, and the Youth Science Foundation of Beijing Normal University (no. 105501GK).

References


Figure 8. Viability of HeLa cells after 24 h incubation with the 5.4 nm SPIONs at various Fe incubation concentrations.