Synthesis route and three different core-shell impacts on magnetic characterization of gadolinium oxide-based nanoparticles as new contrast agents for molecular magnetic resonance imaging

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Abstract

Despite its good resolution, magnetic resonance imaging intrinsically has low sensitivity. Recently, contrast agent nanoparticles have been used as sensitivity and contrast enhancer. The aim of this study was to investigate a new controlled synthesis method for gadolinium oxide-based nanoparticle preparation. For this purpose, diethylene glycol coating of gadolinium oxide (Gd2O3-DEG) was performed using a new supervised polyol route, and small particulate gadolinium oxide (SPGO) PEGylation was obtained with methoxy-polyethylene-glycol-silane (550 and 2,000 Da) coatings as SPGO-mPEG-silane550 and 2,000, respectively. Physicochemical characterization and magnetic properties of these three contrast agents in comparison with conventional Gd-DTPA were verified by dynamic light scattering transmission electron microscopy, Fourier transform infrared spectroscopy, inductively coupled plasma, X-ray diffraction, vibrating sample magnetometer, and the signal intensity and relaxivity measurements were performed using 1.5-T MRI scanner.

As a result, the nanoparticle sizes of Gd2O3-DEG, SPGO-mPEG-silane550, and SPGO-mPEG-silane2000 could be reached to 5.9, 51.3, and 194.2 nm, respectively. The image signal intensity and longitudinal ($r_1$) and transverse relaxivity ($r_2$) measurements in different concentrations (0.3 to approximately 2.5 mM) revealed the $r_2/r_1$ ratios of 1.13, 0.89, 33.34, and 33.72 for Gd-DTPA, Gd2O3-DEG, SPGO-mPEG-silane550, and SPGO-mPEG-silane2000, respectively. The achievement of new synthesis route of Gd2O3-DEG resulted in lower $r_2/r_1$ ratio for Gd2O3-DEG than Gd-DTPA and other previous synthesized methods by this and other groups. The smaller $r_2/r_1$ ratios of two PEGylated-SPGO contrast agents in our study in comparison with $r_2/r_1$ ratio of previous PEGylation ($r_2/r_1 = 81.9$ for mPEG-silane 6,000 MW) showed that these new three introduced contrast agents could potentially be proper contrast enhancers for cellular and molecular MR imaging.

Keywords: Nanomagnetic particle, Gadolinium-oxide, Relaxivity, DEG, mPEG-silane

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Background

Magnetic resonance imaging (MRI) is one of the various techniques used widely as imaging tools in clinical diagnosis. Unlike other two methods of computed tomography (CT) and positron emission tomography (PET), MRI has no ionizing radiation, while, with same spatial resolution (SR) as CT, also having a high SR of 0.2 to 0.3 mm compared to 3 mm of PET scan [1,2]. However, the sensitivity and intrinsic contrast of the MRI are low. Imaging contrast depends on signal intensity difference between two adjacent tissues or areas. The effective factors in the signal intensity are proton spin density (N), spin-lattice or longitudinal relaxation time (T1), and spin-spin relaxation or transverse relaxation time (T2) as shown in Equation 1:

\[ \text{SI} \propto N \cdot (1 - e^{-TR/T_1}) \cdot e^{-TE/T_2} \]  

where TR is the repetition time and TE is the echo time of MRI pulse sequence which determine the contrast between tissues [3].

Contrast agents can modify the signal intensity in different tissues and enhance intrinsic contrast. These are categorized according to the signal intensity produced on T1- and T2-weighted images: 'positive' (high signal intensity) or 'negative' (low signal intensity) [4,5].

Gd\(^{3+}\) ions are generally used as a positive contrast agent which has seven unpaired electrons and produce a magnetic moment that is significantly stronger than a proton (nearly 700 times), and its physical properties are suitable for reducing the longitudinal (T1) and transverse (T2) proton relaxation times [6]. The efficiency of the contrast agent is determined by relaxivity (r) that changes the longitudinal and transverse relaxation times. According to different absorption of agents, this change can result differences among adjacent tissues, as shown in Equation 2:

\[ \left( \frac{1}{T_i} \right)_{\text{obs}} = \left( \frac{1}{T_i} \right)_{\text{d}} + r_i [\text{Gd}^{3+}] \]  

where \((1/T_i)_{\text{obs}}\) and \((1/T_i)_{\text{d}}\) are the relaxation rates (R1 and R2, s\(^{-1}\)) of the sample and aqueous solution, respectively; r\(_i\) is longitudinal and transverse relaxivity of the sample (relaxation rates per concentration unit, s\(^{-1}\) mM\(^{-1}\)), and [Gd\(^{3+}\)] is the gadolinium concentration (mM) [7].

Recently, studies have shown high efficiency and sensitivity of contrast agents when they have been used in nanoparticles form. The size of the nanoparticles that can be used in MRI is about 3 to 350 nm that might be comparable or smaller than a cell (10 to 100 μm), a virus (20 to 450 nm), a protein (5 to 50 nm), or a gene (2 nm wide and 10 to 100 nm long) [8,9].

For nanoparticles, various coating materials can reduce their toxicity and increase their biocompatibility. As a new surface covering material, this group in a previous study reported some of the primary magnetic properties of diethyleneeglycol (DEG) in combination with Gd oxide-based nanoparticles [10]. However, still further researches on the matters of the synthesis procedure, effective size, and agglomeration of gadolinium nanoparticles coated with DEG materials are needed to be done [11-13]. On the other hand, polyethylene glycol (PEG), due to its considerable physicochemical properties, has an especial interest as covering of nanoparticle surfaces [13-17]. Also, it should be noted that PEG has different molecular weights from 350 to 30,000 (and more) Da that could be used alone or in conjunction with other substances such as polylactide-polyethylene glycol and polylactide-co-glycolide [18-20]. For this reason, these two groups of surface conjugate materials (DEG and PEG) could be even useful for covering nanoparticles in biomedical cellular and molecular imaging applications.

Therefore, here in continuing our previous works, the assessment of a new supervised DEG synthesis route in addition to a gadolinium PEGylated (PEG) method in comparison to the conventionally Gd-DTPA contrast agent has been determined as the aim of this study. For this purpose, Gd\(_2\)O\(_3\)-DEG was prepared in new synthetic controlled method, and mPEG-silane grafting at the surface of a new core contrast agent (small particulate gadolinium oxide, SPGO < 40 nm) was obtained using two molecular weights of methoxy polyethylene glycol-silane: 550 and 2,000 Da as SPGO-mPEG-silane550 and SPGO-mPEG-silane2000.

Methods

The synthesis of the Gd\(_2\)O\(_3\)-DEG nanoparticles

In a new supervised polyol route, for the synthesis of gadolinium oxide nanocrystals, 2.5 mmol GdCl\(_3\)-6H\(_2\)O dissolved in 12.5 ml DEG was heated to 140°C until a clear solution was obtained. Then, 3 mmol solid NaOH was dissolved in 6 ml DEG and then added to the Gd-containing solution; the temperature of the mixture was raised to 180°C and held constant for 4 h under reflux.
and magnetic stirring, yielding a dark yellow colloid. After cooling, the nanocrystals formed were separated and purified from agglomerations or large-size particles by centrifuge filtration for 30 min at 40°C and 2,000 rpm (filters: polyethersulfone, 0.2 μm, Vivascience Sartorius, Hannover, Germany). Free Gd\(^{3+}\) ions and excess DEG in the solution were eliminated by 1,000 MW membrane (dialysis tubing, benzoylated, Sigma-Aldrich, USA) for 24 h and by 12,000 MW membrane (dialysis tubing cellulose membrane, Sigma-Aldrich, USA) for 24 h across deionized water, which these sections were not included in our previous study [13].

**The synthesis of the SPGO-mPEG-silane550 and SPGO-mPEG-silane2000**

The process of SPGO-mPEG-silane nanoparticle synthesis was performed using SPGO nanoparticles (<40 nm) purchased from Sigma-Aldrich (99.999% pure). Briefly, a solution was prepared by dissolving SPGO (1 g) and 15 mg ml\(^{-1}\) mPEG-silane (mPEG-Silane, MW550, Nanocs, Inc. (MA, USA) or mPEG-Silane, MW 2000, Laysan Bio, Inc. (AL, USA)) in deionized water (10 mL); then, the resulting solution was sonicated at 40°C for 2 h. Large-size particles were separated by centrifugation (2,000 rpm, 30 min) and the suspension was dialyzed (1,000 and 12,000 MW) as described above [21].

**Characterization of the contrast materials**

Nanoparticle size measurements were performed three times repeatedly by dynamic light scattering (DLS, Brookhaven Instruments, USA). Also the morphological information of the nanoparticles was done by transmission electron microscopy (TEM, CM120 model, Koninklijke Philips Electronics, Netherlands).

The effects of surface coating in composition with nanomagnetic particles, received from their spectra, was recorded by FTIR spectrometer (Tensor27, Bruker Cor., Germany) over a range between 400 and 4,000 cm\(^{-1}\) at room temperature (26°C ± 1°C). Moreover, structural characterization of the SPGO was collected on an X-ray diffractometer (XRD, PW1800, Philips). After filtration and dialysis, the nanoparticle concentrations were determined by induced coupled plasma-atomic emission spectroscopy (Varian-Liberty 150 AX Turbo, USA). In addition, magnetic strength measurements of SPGO and Gd\(_2\)O\(_3\)-DEG were executed with commercial vibrating sample magnetometer (VSM, 7400 model, Lakeshore Cryotronics Inc, OH, USA).

**Relaxivity measurements**

The signal intensity (SI) and longitudinal (\(T_1\)) and transverse (\(T_2\)) relaxation times were measured by 1.5 T MRI scanner (Siemens AG, Germany) using the head coil. After both types of dialyses (1,000 and 12,000 Da), nanomagnetic concentration measurements done by ICP, then \(T_1\) and \(T_2\) changes in aqueous solution for Gd-DTPA, and three synthesized nanomagnetic particles of Gd\(_2\)O\(_3\)-DEG, SPGO-mPEG-silane550 and 2000 were accomplished by diluting them in 5 ml water with Gd concentration at a range of 0.1, 0.3, 0.6, 0.9, 1.2, 1.5, 2, and 2.5 mM (mmol/L). \(T_1\) relaxation time for each sample was obtained by varying repetition times (TR = 100, 200, 400, 600, 2,000 ms) with fixed echo time at TE = 15 ms. Similarly, \(T_2\) relaxation times were measured by varying echo times (TE = 30, 60, 90, 120 ms) and fixed TR = 3,000 ms, and imaging parameters of slice thickness of 5 mm, 1 mm gap, 512 × 384 matrix size, and 25 cm\(^2\) field of view. Signal intensities were obtained with manually drawn regions of interest for each sample. Relaxation rates of \(R_1\) (1/\(T_1\)) and \(R_2\) (1/\(T_2\)) were calculated by exponential curve fitting of the signal intensity vs. time (TR or TE) according to Equation 1. After relaxation rate determination for different concentrations, the \(R_1\) or \(R_2\) vs. concentration curve were plotted and, thereby, the relaxivities \((r_1\) and \(r_2\)) as the slope of Equation 2 could be calculated.

**Results**

**Characterization of the contrast materials**

Table 1 shows the size and polydispersity index (PdI) measurements using DLS; thereby, Gd\(_2\)O\(_3\)-DEG nanoparticles had a hydrodynamic diameter distribution of 5.9 ± 0.13 nm with a PdI of 0.390, while SPGO-mPEG-silane550 and 2000 were 51.3 ± 1.46 nm and 194.2 ± 22.1 nm with PdI of 0.350 and 0.225, respectively. The results showed that when molecular weight increases, the nanoparticle size increase as well. However, despite their different sizes, PdIs of nanoparticles (as an index of the nanoparticle dispersion) had acceptable ranges of less than 0.5.

Figure 1 shows the morphology of three wrapped around nanoparticles, while specifically, just images of Gd\(_2\)O\(_3\)-DEG are sharp and uniform such that spherical or ellipsoidal shape of Gd nanomagnetic particles could be visualized separately with clear grains in nano dimensions. The images of two other PEGylated nanoparticles, because of large molecular weights, were agglomerated such that they could not been viewed as sharp as Gd\(_2\)O\(_3\)-DEG nanoparticles among their surface covers.

**Table 1 DLS size and PdI measurements for the three nanoparticle contrast agents**

| Nanoparticle          | Hydrodynamic diameter/nm | PdI  |
|-----------------------|--------------------------|------|
| Gd\(_2\)O\(_3\)-DEG   | 5.9 ± 0.13               | 0.387|
| SPGO-mPEG-silane550   | 51.3 ± 1.46              | 0.350|
| SPGO-mPEG-silane2000  | 194.2 ± 22.1             | 0.225|

The results show a direct relationship between size and molecular weight.
FTIR spectra were employed to detect the characteristic bands of different ligands after coating Gd$_2$O$_3$ nanoparticles. Figure 2 shows a comparison of the FTIR spectrum of pure diethylene glycol with the DEG-coated Gd$_2$O$_3$ nanocrystals prepared by the polyol method. The bands in DEG at 2,876 and 1,460 cm$^{-1}$ correspond to the symmetric stretching and bending of CH$_2$ (Figure 2b). A band at 1,127 cm$^{-1}$ corresponds to C-O stretch, and the broad band of O-H stretch was observed in the 3,100 to 3,500 cm$^{-1}$ range. There are no significant differences between FTIR spectra in Figure 2d, c due to the presence of extra DEG molecules; after the coated Gd$_2$O$_3$ was cleaned up by dialysis and centrifuge, unreacted DEG has been removed. After coating Gd$_2$O$_3$ with DEG, shifts in the bands of DEG can be observed in the Gd$_2$O$_3$-DEG surface. It seems that shifts in the position of CH$_2$ and C-O stretching of DEG are due to bonding to Gd$_2$O$_3$ molecules. Furthermore, the peak shifts from 1,127 to 1,120 cm$^{-1}$ suggest a new configuration for DEG molecules, which oxygen bind to the two Gd atoms and had also been observed by Pedersen et al. [22].

FTIR spectrum for mPEG-silane550 is compared with that of the SPGO-mPEG-silane550 in Figure 3a, d, respectively. The FTIR spectrum of the mPEG-silane550 (Figure 3a) displays a peak at 1,284 cm$^{-1}$ corresponding to Si-C stretching vibration. The bands at 2,876 and 1,458 cm$^{-1}$ correspond to the symmetric stretching and bending of CH$_2$. The bands at 1,627, 1,107, and 3,100 to 3,500 cm$^{-1}$ correspond to C=O stretching vibration, C-O ether, and N-H stretching vibration, respectively. The band at 1,551 cm$^{-1}$ corresponds to -NH bending vibration in the amide link between the silane and the PEG. The shifts of the characteristic peaks of the mPEG-silane550 to 1,247.21 and 2,925 cm$^{-1}$ (Figure 3d) are strong evidences that PEG bonded to the surface of Gd$_2$O$_3$ through a reaction of mPEG-silane550 with the nanoparticles surface also been observed by Wu et al. [23]. The bands at 850 and 1,500 cm$^{-1}$ are common between mPEG-silane550 and SPGO-PEG-silane550 after coating SPGO with mPEG-silane550. The spectrum of SPGO-PEG-silane2000 is very similar with that of SPGO-PEG-silane550, and they have very little differences most likely due to size effects or molecular weight (Figure 3b, e).

The structural properties of SPGO in Figure 4 showed XRD electron diffraction patterns of nanoparticles that compared with reference code 00-012-0797 of CSD-Profan database in 25°C, included are diffraction angles and intensities that are consistent with standard reference pattern.
The magnetic properties of the SPGO and Gd$_2$O$_3$-DEG nanoparticles were measured by VSM at room temperature. The relative magnetization curves vs. applied field were plotted in Figure 5. For paramagnetic, diamagnetic, and superparamagnetic materials, when the applied magnetic field is removed, they should exhibit no coercivity and remanence. Also, paramagnetic materials have a linear relationship between magnetization ($M$) and applied field ($H$) with positive slope. As shown in Figure 5a, SPGO particles revealed paramagnetic properties. Also, magnetization curve with S shape (sigmoidal) of Gd$_2$O$_3$-DEG nanoparticle is shown in Figure 5b, which is similar to superparamagnetic materials. Thereby, the difference between SPGO and Gd$_2$O$_3$-DEG in relation to covering Gd$_2$O$_3$ with DEG could be seen clearly in Figure 5b.
Relaxivity measurements

Nanoparticle tubes were prepared by certain concentrations (Figure 6). \( R_i (1/T_i, i = 1, 2) \) vs. Gd concentration curve were plotted, and the slope of the curve or relaxivity \( (r_i) \) was obtained for each nanoparticle (Table 2). Gd concentration shows a linear relationship up to 1.5 mM with a good of fit \( r > 0.98 \) according to Equation (Figure 7).

Figure 7a shows the longitudinal relaxation rates \( (1/T_1) \) for the used materials. Gd\(_2\)O\(_3\)-DEG had longitudinal proton relaxivity at least 2.5 times higher than Gd-DTPA, whereas \( r_1 \) for SPGO-mPEG-silane550 and 2000 was less compared with Gd-DTPA. That is why, unlike Gd\(_2\)O\(_3\)-DEG and Gd-DTPA, \( R_1 \) relaxation rates of SPGO-mPEG-silane550 and 2000 did not change considerably with concentration. In Figure 8b, for all of nanoparticle materials and Gd-DTPA, the change of Gd concentration led to the increase of transverse relaxation rates \( (1/T_2) \), while this effect is significantly higher for SPGO-mPEG-silane550 and 2000 compared to Gd\(_2\)O\(_3\)-DEG and Gd-DTPA (Figure 7b, Table 2).

### Discussion

Contrast agents can modify the signal intensity in different tissues to enhance their contrast and improve the low sensitivity of magnetic resonance imaging. The efficiency of the contrast agents according to different absorption of agents is determined by \( r_i \) that changes the longitudinal and transverse relaxation times to result differences among adjacent tissues. These changes are categorized according to the signal intensity produced on \( T_1 \) and \( T_2 \)-weighted images: ‘positive’ known as high signal intensity or ‘negative’ as low signal intensity. Recently, studies have shown high efficiency and sensitivity of contrast agents when they have been used in nanoparticle forms. To have higher relaxivity, reduce toxicity, increase biocompatibility and half-life, besides preventing the nanoparticle aggregations, contrast agents in MRI should be coated with various materials. Different factors could affect the sizes of nanoparticles including type of the core, coating molecular weights, nanoparticle aggregation and, thereby, the synthesis route. Theoretically, by increasing molecular weights of nanoparticle coatings, their average size could be increased as well [24]. For this reason, in this study, we investigated magnetic properties of three Gd-based nanoparticles with different coatings of DEG, mPEG-silane550, and mPEG-silane2000 comparing to conventionally extracellular Gd-DTPA contrast agent. For nanoparticle synthesis, two different methods were used. Firstly, the preparation and coating of Gd\(_2\)O\(_3\) by previous polyl route besides

### Table 2 Results of relaxometry for three nanoparticle contrast agents and Gd-DTPA

| Nanoparticle               | \( r_2/r_1 \) | \( r_2 \) (mM\(^{-1}\) s\(^{-1}\)) | \( r_1 \) (mM\(^{-1}\) s\(^{-1}\)) |
|---------------------------|--------------|-------------------------------|-------------------------------|
| Gd-DTPA                   | 1.13         | 5.14                          | 4.55                          |
| Gd\(_2\)O\(_3\)-DEG      | 0.89         | 11.81                         | 13.31                         |
| SPGO-mPEG-silane550      | 33.34        | 26.34                         | 0.79                          |
| SPGO-mPEG-silane2000     | 33.72        | 33.72                         | 1.00                          |

Longitudinal relaxivity \( (r_i) \) of Gd-DTPA PEGylated nanoparticles (SPGO-mPEG-silane550 and 2000) was smaller than that of Gd\(_2\)O\(_3\)-DEG.
0.2-μm filtration, and two 1,000 and 12,000 Da dialysis membranes led to reach the good and desirable smaller size of approximately 5 nm of gadolinium crystal nanoparticles covered by DEG in Gd2O3-DEG compounds. Secondly, for mPEG-silane550 and mPEG-silane2000, despite using filtration and sonication after PEG coating method for elimination aggregated particles prior to DLS measurement, PEGylated nanoparticles even still had relatively larger sizes of approximately 51.3 and approximately 194.2 nm. For this, part of that increase size should be due to the effect of their molecular weights. In our study, molecular weights of three materials were as follows: MWSPGO-mPEG-silane2000 > MWSPGO-mPEG-silane550 > MW Gd2O3-DEG. As seen in Table 1, the measured particle sizes have an incremental behavior as the molecular weight has increased, which are in accordance with their appearance in related TEM images.

Magnetic properties in MRI were related to relaxivities ($r$), especially, $r_2/r_1$ ratio that defines the potential for being a positive or negative contrast agent. Meanwhile, several studies have investigated the size effects on magnetic properties and relaxivities, e.g., SPIO nanoparticles with hydrodynamic diameters of 9, 12, and 15 nm had $r_2/r_1$ ratio of 2.75, 5.95, and 13.08, respectively [22,23]. Some other studies have also showed that the $r_2/r_1$ ratio increases with larger sizes of nanoparticles [14,25,26]. Consequently, in this study, the changes of coating materials with various molecular weights on a similar core were also studied in terms of $r_2/r_1$ ratios which have been shown in Table 2. Thereby, it is clear that those $r_2/r_1$ ratios for Gd2O3-DEG were much lower than that of other two PEGylated materials. Meanwhile, even for SPGO-mPEG-silane2000, the said ratio was a bit higher than SPGO-mPEG-silane550.

For positive contrast agents, $r_2/r_1$ ratio is described to be 1 to 2 and for negative ones; however, it is between 2 and 40 [21]. Thus, in our study, Gd$_2$O$_3$-DEG (with $r_2/r_1$ ratio = 0.89) could reveal good results as a positive contrast agents even better than Gd-DTPA (with $r_2/r_1$ ratio = 1.13) [10-12], that is in part because of such small size nanoparticles that could be yielded in the new synthetic method in this research. However, $r_2/r_1$ ratios for PEGylated nanoparticles are relatively high. In one study, PEGylated SPGO with higher MW (MW = 6,000 Da) resulted to an $r_2/r_1$ ratio equal to 81.6 [20]. In this study, we used polymers with a lower molecular weight (i.e., 550 and 2,000) and so the $r_2/r_1$ ratios could be reached to 33.34 and 33.72, respectively. These
decreased ratios in our study should be mostly related to the selected lower molecular weight materials. Furthermore, the relaxivity results in Figure 7a, b indicate that Gd₂O₃-DEG nanoparticles (with lower $r_2/r_1$ ratio) as positive contrast agents are clearly more appropriate than Gd-DTPA. SPGO-mPEG-silane550 and 2000 due to having both high $r_2$ and high $r_2/r_1$ ratio appear to be proper contrast agents for $T_2$-weighted MR imaging methods, as well.

According to Equations 1 and 2, signal intensities change with $T_1$, $T_2$, and the concentration of contrast agents. Therefore, short $T_1$ leads to a signal increase, whereas, short $T_2$ decreases the signal. A maximum signal occurs at intermediate concentrations; such expectations could be seen clearly in Figure 8a, b. In addition, the maximum signal intensity for Gd₂O₃-DEG occurred at similar daily clinical concentration relative to Gd-DTPA with similar intensity (0.6 mM near to 0.1 mM; Figure 8a). Also, signal intensities for SPGO-mPEG-silane550 and SPGO-mPEG-silane2000 were much less than the two other contrast agents (Figure 8b). This is another conformation that they can be considered as negative or $T_2$-weighted contrast agents. This could be remained for future experiment for them to be compared with other negative contrast agents such as iron oxide-based ones.

**Conclusions**

The synthesis controlled method making use of dialysis, filtration, and sonication could have direct effect on the nanosize scale and magnetic characterization of nanoparticles, consequently on their $r_2/r_1$ ratio as providing and giving them a positive or negative signal properties of contrast agents. Thereby, in our study, the Gd₂O₃-DEG

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**Figure 8 Signal intensities for contrast agents.** Relative signal intensities in (a) Gd-DTPA and Gd₂O₃-DEG. (b) SPGO-mPEG-silane550 and SPGO-mPEG-silane2000 (TR = 600 ms and TE = 15 ms). Maximum signal intensity for Gd₂O₃-DEG was obtained (0.6 mM), whereas it was 1.5 mM for Gd-DTPA.
with $r_2/r_1$ lower than Gd-DTPA and other previously synthesized Gd$_2$O$_3$-DEG could be achieved. Moreover, for preparation of PEGylated contrast agents, polymers with lower molecular weights could potentially have better contrast properties as behaving like negative contrast agents that should be compared with other similar negative ones.

Therefore, among different group coating materials, DEG and PEG, due to their considerable properties and not having fixed sizes (different molecular weights), were selected as useful surface covering of nanomagnetic particles that could reveal noticeable relaxivity, magnetic property, and signal intensity that are proper for cellular and molecular MRI applications that would be remained for future in vivo studies.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
GA and NRA designed the study, carried out all of the experimental work and data acquisitions, and drafted the manuscript. SH and EG performed the synthesis and the interpretation of nanoparticles’ chemical structure. HRM contributed in drug regulations consultancy. RZ participated in material characterizations. SR carried out the magnetic resonance imaging protocols. All authors read and approved the final manuscript.

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NRA was born in 1960 in Shiraz, Iran, received her BSc in Nuclear Physics from Shiraz University, Shiraz, Iran, in 1986, his MSc and Ph.D. in Medical Physics (Medical Imaging) from Nagoya University, Nagoya, Japan in 1995. At present, he is a professor in the Medical Physics at the Department of Medical Physics & Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences (TUMS). His research interests during Ph.D. graduation was in computer-aided diagnostic (CAD) systems for the detection of cancer on digital mammograms, leading to development of software algorithms and CAD systems for mammographic cancer detection. As a PIP member of the American Association in Medical Physics (AAPM) and other scientific forums, he published many articles and several books in Medical Imaging aspects, achieved awards in innovation, scientific hypothesis and inventions, and paper awards in world conferences. Recently, his research interests have been focusing on the development of nanomagnetic particles for MRI applications. The development of the present work in combination with the magnetoliposomes as tumor cell tracking and drug delivery system for liver specific target detection has been accepted and will be presented in RSNA2012.

SH was born in 1960 in Abadan, Iran, and received her BSc and MSc in Analytical Chemistry from Shiraz University, Shiraz, Iran, in 1990, and her Ph. D. in Pharmaceutics from Nagoya University in Japan in 1995. Her Ph.D. research was related to pharmacokinetics of drugs, especially drug characterization in brain distribution. At present, she is an associate professor in the Pharmaceutical Department, Food & Drug Laboratory Research Center, Food & Drug Organization (FDO), Ministry of Health, Tehran, Iran. She is the head of QC approving of herbal medicine and supplements in Iran FDO and also has been the lecturer of GMP and GLP at the universities while performing many workshops for drug factories. Her recent research interest is in the synthesis and analytical method development of nanosized molecules for drug delivery applications. HRM received his Pharm D from Tabriz University and his Ph.D. in Pharmaceutics from the University of Bradford, England in 1995. He has been a member of the Fellowship in Liposomal Gene Delivery in Cancer, University of Alberta, Canada. At present, he is a professor of Pharmaceutics in School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. His research interests have been related to transdermal drug delivery, modeling biological barriers, gene delivery, liposomal drug delivery, and lyotropic liquid crystals. He has been also the Director General of some drug factories.

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BR received his BSc in Radiology from Iran Medical University in 1990 and his MSc in Medical Physics from Iran Medical University in 2001. At present, he is an employee of Medical Imaging Center in Enam Hospital Complex, School of Medicine. He has been contributing to so many researches with different departments and researchers; he is qualified in developing different MRI imaging protocols. At present he is responsible for performing new and proper MRI data acquisitions in nanomagnetic contrast agents and MRI neuroimaging applications.

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References
1. Pereira GA, Geraldes CFGC: Design and optimization of gadolinium based contrast agents for magnetic resonance imaging. Ann Magn Reson 2007, 6(1):1–33.
2. Hengerer A, Grimm J: Molecular magnetic resonance imaging. Biomed Imaging Interv J 2006, 2(2):1–7.
3. Kuriashkin IV, Losonsky JM: Contrast enhancement in magnetic resonance imaging using intravenous paramagnetic contrast media: a review. Vet Radiol Ultrasound 2000, 41(4):4–7.
4. Gould F: Nanomagnetism shows in vivo potential. Nano Today 2006, 1(4):34–39.
5. Laurent S, Elt LV, Muller RH: Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. Contrast Med Mol Imaging 2006, 1(3):128–137.
6. Frame EM, Uzgiris EE: Gadolinium determination in tissue samples by inductively coupled plasma mass spectrometry and inductively coupled plasma atomic emission spectrometry in evaluation of the action of magnetic resonance imaging contrast agents. Analyst 1998, 123(4):675–679.
7. McDonald MA, Watkin KL: Investigations into the physicochemical properties of dextran small particulate gadolinium oxide nanoparticles. Acad Radiol 2006, 13(4):421–427.
8. Waters EA, Wickline SA. Contrast agents for MRL. Basic Res Cardiol 2008, 103(2):114–121.
9. Pankhurst QA, Connolly J, Jones SK, Dobson J. Applications of magnetic nanoparticles in biomedicine. J Phys D: Appl Phys 2003, 36:167–181.
10. Söderlind F, Pedersen H, Petrol RM Jr, Käll PO, Uvdal K. Synthesis and characterization of Gd2O3 nanoparticles functionalized by organic acids. J Colloid Interface Sci 2005, 288(1):140–148.
11. Engström M, Klasson A, Pedersen H, Vahlberg C, Käll PO, Uvdal K. High proton relaxivity for gadolinium oxide nanoparticles. MAGMA 2006, 19(4):180–186.
12. Klasson A, Ahlén M, Hellqvist E, Söderlind F, Rosén A, Käll PO, Engström M. Positive MRI enhancement in THP-1 cells with Gd2O3 nanoparticles. Contrast Media Mol Imaging 2008, 3(3):106–111.
13. Riyahi-Alam N, Behrouzkia Z, Seifalian A, Haghgoo Jahromi S. Properties evaluation of a new MRI contrast agent based on Gd-loaded nanoparticles. Biol Trace Elem Res 2010, 137(3):324–334.
14. Faucher L, Gossuin Y, Hocq A, Fortin MA. Impact of agglomeration on the relaxometric properties of gadolinium oxide nanoparticles. Nanotechnology 2011, 22(29):295103.
15. Kamaly N, Pugh JA, Kalber TL, Bunch J, Miller AD, McLeod CW, Bell JD. Imaging of gadolinium spatial distribution in tumor tissue by laser ablation inductively coupled plasma mass spectrometry. Mol Imaging Biol 2010, 12(6):361–366.
16. Döron AL, Chu K, Ali A, Brannon-Peppas L. Preparation and initial characterization of biodegradable particles containing gadolinium-DTPA contrast agent for enhanced MRI. Proc Natl Acad Sci U S A 2008, 105(45):17232–17237.
17. Schipper ML, Iyer G, Koh AL, Cheng Z, Steinberg Y, Aharoni A, Keren S, Bentorilla LA, Li J, Rao J, Chen X, Banin U, Wu AM, Sinclair R, Weiss S. Gumbhir SS. Particle size, surface coating, and PEGylation influence the biodistribution of quantum dots in living mice. Small 2009, 5(1):126–134.
18. Mulder WJ, Strijkers GJ, McLeod CW, Bell JD. Imaging of gadolinium spatial distribution in tumor tissue by laser ablation inductively coupled plasma mass spectrometry. Mol Imaging Biol 2010, 12(6):361–366.
19. Oyewumia MO, Yolke RA, Jay M, Coakley T, Mumper RJ. Comparison of cell uptake, biodistribution and tumor retention of folate-coated and PEG-coated gadolinium nanoparticles in tumor-bearing mice. J Control Release 2004, 95(1–2):613–626.
20. Nelson J, Bennett LH, Wagner MJ. Solution synthesis of gadolinium nanoparticles. J Am Chem Soc 2002, 124(12):2979–2983.
21. Fortin MA, Petoral RM, Söderlind F, Klasson A, Engström M, Veres T, Käll PO, Uvdal K. Polyethylene glycol-covered ultra-small Gd2O3 nanoparticles for positive contrast at 1.5 T magnetic resonance clinical scanning. Nanotechnology 2007, 18(39):395501–395510.
22. Pedersen H, Söderlind F, Petrol RM Jr, Uvdal K, Käll PO, Ojamäe L. Surface interactions between Y2O3 nanocrystals and organic molecules - an experimental and quantum-chemical study. Surface Sci 2005, 592(1–3):124–140.
23. Wu Y, Zuo F, Zheng Z, Ding X, Peng Y. A novel approach to molecular recognition surface of magnetic nanoparticles based on host-guest effect. Nanoscale Res Lett 2009, 4(7):738–747.
24. Casula MF, Corrias A, Arosio P, Lascialfari A, Sen T, Floris P, Bruce IJ. Design of water-based ferrofluids as contrast agents for magnetic resonance imaging. J Colloid Interface Sci 2011, 357(1):50–55.
25. Casula MF, Floris P, Innocenti C, Lascialfari A, Marinone M, Corti M, Sperling R, Parak WJ, Sangregorio C. Magnetic resonance imaging contrast agents based on iron oxide superparamagnetic ferrofluids. Chem Mater 2010, 22:1739–1748.
26. Li Y, Pei Y, Zhang X, Gu Z, Zhou Z, Yuan W, Zhou J, Zhu J, Gao X. PEGylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. J Control Release 2001, 71(2):205–211.

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