Published in final edited form as:

J Phys Chem C Nanomater Interfaces. 2007 April 6; 111(17): 6245–6251. doi:10.1021/jp0702245.

Bifunctional Gold Nanoshells with a Superparamagnetic Iron Oxide-Silica Core Suitable for Both MR Imaging and Photothermal Therapy

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Abstract

We describe the synthesis, characterization, and use of hybrid nanoparticles with a superparamagnetic iron oxide (SPIO) core and a gold nanoshell. These multifunctional nanoparticles, designated SPIO-Au nanoshells, displayed superparamagnetic characteristics and a significant absorbance in the near-infrared (NIR) region of the electromagnetic spectrum. In addition, they exhibited high transverse relaxivity, r_2 , and a large r_2/r_1 ratio and therefore could be imaged by MRI to obtain T₂-weighted images. Moreover, SPIO-Au nanoshells showed efficient photo-thermal effect when exposed to NIR light. The use of SPIO-Au nanoshells, with their combination of unique magnetic and optical properties, should enhance the efficacy of nanoshell-mediated photo-thermal therapy by making it possible to direct more nanoparticles to tumors through the application of external magnetic field and by permitting real-time *in vivo* MRI imaging of the distribution of the nanoparticles before, during, and after photo-thermal therapy.

Keywords

Near-infrared; Nanoshells; Magnetic resonance imaging; Photo-thermal therapy

INTRODUCTION

The increasing availability of nanostructures with highly controlled optical properties in the nanometer size range has created widespread interest in the use of nanoparticles in biological systems for diagnostic and therapeutic applications¹.

Nanoparticles derived from gold are an attractive system for diagnostic and therapeutic applications owing to their ease of preparation, ready bioconjugation, good biocompatibility,

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and unique optical properties²⁻⁴. In particular, gold nanoshells exhibit strong absorbance with wavelength tunable in the near-infrared (NIR) region of the electromagnetic spectrum. These particles not only can be used in biomedical imaging applications but, more important, are potential candidates for localized photo-thermal therapy because they mediate strong plasmon-induced surface heat flux upon absorption of NIR light⁴⁻⁶.

Another class of inorganic nanoparticles, superparamagnetic iron oxide (SPIO) nanoparticles, have shown great promise in magnetic resonance imaging (MRI)^{7, 8}. SPIO nanoparticles have a high transverse relaxivity, r_2 , which results in negative contrast on T_2 -weighted images. SPIO-enhanced MRI has become an established technique for imaging of macrophage activity, in particular for staging of liver tumors and detection of lymph node metastasis; several products for SPIO-enhanced MRI have been approved or are being studied in clinical trials^{7, 9, 10}. Use of SPIO nanoparticles for imaging of atherosclerotic lesions^{11, 12} and for monitoring of the *in vivo* distribution of cellular trafficking¹³ is currently being investigated. In addition, magnetic nanoparticles are being studied to determine whether their use as carriers enhances delivery of therapeutic agents in the presence of external magnetic field¹⁴⁻¹⁶. In these systems, therapeutics (e.g. drugs or genes) are attached to the magnetic nanoparticles and injected near the target site. A magnetic field is then applied to the site externally to concentrate the particles at the target site.

In this paper, we describe the synthesis, characterization, and use of nanoparticles with an SPIO core and a gold nanoshell. The resulting multifunctional nanomaterial, designated SPIO-Au nanoshells, combines the attractive photo-thermal property of gold nanoshells with the magnetic property of SPIO and thus may be useful for targeted photo-thermal therapy mediated through external magnetic field and MRI guidance.

EXPERIMENTAL SECTION

Materials

The tetraethylorthosilicate (TEOS), 3-aminopropyl trimethoxysilane (APTMS), ammonia solution (30% wt, 7 ml), tetrakis(hydroxymethyl) phosphonium chloride (THPC), chloroauric acid (HAuCl_4), potassium carbonate (K_2CO_3) and formaldehyde (37%) were purchased from Sigma-Aldrich (St. Louis, MO). The water based super paramagnetic iron oxide (SPIO) particle (EMG 304) was purchased from Ferrotech (Nashua, NH). The 18 M water was obtained from a Milli-Q Synthesis system (Millipore, Billerica, MA).

Synthesis of SPIO/gold nanoshells

In a typical procedure, 0.2 ml of water-based SPIO (EMG 304) was diluted with 6 ml of 18 M water and 80 ml of absolute ethanol. An aqueous ammonia solution (30% wt, 7 ml) and tetraethylorthosilicate (0.5 ml) were consecutively added into the SPIO solution at room temperature under continuous mechanical stirring. The clear solution turned to murky suspension in less than 30 min, indicating the formation of silica nanoparticles. The reaction was allowed to proceed at room temperature overnight. The functional groups at the surface of these unmodified silica nanoparticles are predominantly silanol (Si-OH) or ethoxy (Si-OEt) groups¹. These silica nanoparticles were then treated with 0.04 ml of 3-aminopropyl trimethoxysilane for 6 hr to introduce the amino-terminated silica surface, and then the reaction mixture was refluxed for 30 min to complete the reaction¹. After the reaction mixture was cooled down, the SPIO-embedded silica were separated from the reaction medium by centrifuging at 4000 rpm and redispersed in 100 ml of absolute ethanol. Addition of 1 ml of SPIO-embedded silica solution to 5 ml of undiluted tetrakis(hydroxymethyl) phosphonium chloride (THPC) gold solution led to the attachment of THPC gold nanocrystal onto the surface of the silica surface. This mixture was stored at 4°C overnight to maximize the surface coverage of the THPC gold nanoseeds. The

preparation of THPC gold solution involved the reduction of chloroauric acid (HAuCl_4) with THPC, which affords relatively small gold particles (e.g., 2 nm) with a net negative interfacial charge². Finally, the gold nanoshell was prepared by reduction of the K-Gold solution with formaldehyde (37%) in the presence of SPIO-embedded silica nanoparticles covered with gold nanoseeds. To prepare K-Gold solution, 2 mL of 1% (wt) H_4AuCl_4 was added into 100 mL of water containing 0.025 g of K_2CO_3 under magnetic stirring. UV-Vis absorption spectra were measured 30 min after reaction to verify the formation of nanoshells, which have significant absorbance in the near-infrared region.

Characterization Methods

Transmission electron microscopy (TEM)—To prepare the TEM sample, a small drop of the solution was transferred to the top surface of carbon-film-supported Cu grids (previously glow-discharged to achieve better dispersion) and left until dried. The TEM work was carried out in a microscope (JEOL 2010, JEOL Ltd., Tokyo, Japan) at the working voltage of 200 kV. All imaging magnifications were calibrated using standards of SiC lattice fringes (for high magnifications) and cross-line grating replica (for low magnifications). The size measurements were based on a sufficient number of samples, typically over 350.

Energy-dispersive spectroscopy (EDS)—The EDS was performed using a spectrometer (INCA, Oxford Instruments, Oxon, United Kingdom) with an ultra-thin-window Si-Li detector (capable of detecting elements with $Z \geq 5$), which was attached to the JEOL 2010 microscope.

UV-Vis spectroscopy—The UV-Vis spectroscopy of the nanoshell was taken on a Beckman Coulter DU-800 UV-Vis spectrometer (Beckman Coulter, Fullerton, CA) with a 10-mm optical path length quartz cuvette.

Magnetization measurements—The magnetization measurements were carried at 300 K and in a magnetic field (H) up to 50 kOe with a superconducting quantum-interference device magnetometer (Model MPMS, Quantum Design, San Diego, CA), which can measure a magnetic moment as low as 10^{-7} emu. For the magnetization measurement, both uncoated SPIO particles and SPIO-Au nanoshells were in the dry powder form obtained by evaporating the water in the solution. The background magnetic moments from the sample capsules (container) were found to be negligible ($\sim 10^{-5}$ emu).

Fourier transform infrared spectroscopy (FTIR)—PEG coating was investigated by using a Perkin-Elmer Spectrum GX system (Wellesley, MA).

Relaxivity—Samples prepared in water at different concentrations (CC (mM) = 8.00E-09, 1.00E-08, 2.00E-08, 4.00E-08, 8.00E-08) were poured into 4-mm-diameter nuclear magnetic resonance sample tubes (SP Industries, Inc., Warminster, PA). Axial images were obtained using a 4.7-T/40-cm MR scanner (Bruker Biospin Corp., Billerica, MA) with a 950-mT/m, 5.7-cm inner diameter actively shielded gradient coil system (19,000 mT/m-s slew rate) and a 3.5-cm inner diameter volume radiofrequency coil. Longitudinal and transversal relaxation studies were performed in axial images acquired with variable-TR (10 TR values ranging from 25 ms to 3000 ms and $\text{TE} = 10.5$ ms) and variable-TE (24 TE values ranging from 15 ms to 360 ms and $\text{TR} = 1000$ ms) multislice-multiecho sequences, respectively; other imaging parameters include a 3.2-cm field of view, 1.0-mm slice thickness, and a 64×64 matrix. Regions of interest were used to calculate signal intensities (SI) at each sample concentration. Plots of TR vs SI and TE vs SI were fit to exponential curves using a custom software program in IDL (ITT Industries, Inc.; Boulder CO) to

provide with T1 and T2 relaxation constants at each concentration. Then relaxivities r_1 and r_2 (s-1mM⁻¹) were obtained from linear fitting of the $1/T_1$ vs [CC] and $1/T_2$ vs [CC] plots.

Temperature Elevation Induced by NIR Laser Irradiation—The laser was a continuous wave GCSLX-05-1600m-1 fiber-coupled diode laser (DHC, China Daheng Group, Inc. Beijing, China) with a center wavelength of 808 ± 10 nm. It was powered by a DH 1715A-5 dual-regulated power supply (DHC, China Daheng Group, Inc.). A BioTex LCM-011 optical fiber (5 meters in length) was used to transfer laser power from the laser unit to the target. This fiber had a lens mounting at the output that allowed the laser spot size to be changed by changing the distance from the output to the target. The output power was independently calibrated using a handheld optical power meter (Newport Model 840-C) and was found to be 1 W for a spot diameter of 3.5 mm and a 2-amp supply current. The end of the optical fiber was attached to a retort stand by a movable clamp and positioned directly above the cell cultures. The laser spot size was focused down to fit inside the individual compartments containing sample.

RESULTS AND DISCUSSION

Synthesis and PEG coating of SPIO-Au nanoshells

The synthesis of the SPIO-Au nanoshells was a multistep procedure (Scheme 1). First, silica-coated SPIO (Fe₂O₃) nanoparticles were synthesized according to the well-known Stöber process¹⁷. We used commercially available SPIO (average diameter, 10 nm) nanoparticles stabilized with oleic acid in water. The magnetic nanoparticles were easily coated with amorphous silica via the sol-gel process because the iron oxide surface has a strong affinity for silica. No primer was needed to promote the deposition and adhesion of silica. The thickness of the silica sphere could be tuned from 2-100 nm by simply changing the concentration of the sol-gel precursor, tetraethylorthosilicate (TEOS)¹⁸. Next, the surface of the silica shell was functionalized with amine groups by treatment with NH₄OH and 3-aminopropyltrimethoxysilane. Then gold nanocrystal seeds (2-3 nm) were attached to the amino groups on the silica sphere by reduction of chloroauric acid (HAuCl₄) with tetrakis(hydroxymethyl) phosphonium chloride (THPC)¹⁹. Since the gold nanoseeds had net negative surface charges, they firmly attached to the amino groups on the silica sphere, which were positively charged when pH was acidic. Finally, the attached gold nanoseeds were used to nucleate the growth of a gold overlayer on the silica surface to form a gold nanoshell. The nanoshells were isolated by centrifugation and washed with deionized water. The nanoshells were then resuspended in sodium citrate buffer (33 mM) to stabilize the particle solution. To control the thickness of the gold shell, we varied the concentration of gold-seeded, SPIO-containing silica particles while keeping the concentration of gold precursor (HAuCl₄ in 2.5% K₂CO₃ solution) constant.

In our synthesis scheme, the silica layer served the same role as the silica core in conventional gold nanoshells—it provided a dielectric interface for shifting the plasma resonance to the NIR wavelength region. In addition, functionalizing the outer surface of the silica layer with free amine groups facilitated the initial growth of the gold nanoseeds, which in turn facilitated the subsequent growth of the outermost gold shell.

In the last step, the nanoshells were coated with polyethylene glycol (PEG) because of its known high biocompatibility. PEG coating was achieved by treated SPIO-Au nanoshells with monofunctional PEG precursor MeO-PEG-SH (Mw 5,000), resulting in stable nanoparticles. The PEG coating was confirmed using Fourier transform infrared spectroscopy, which showed peaks characteristic of PEG around 2918 cm⁻¹, 1453 cm⁻¹, and 1026 cm⁻¹ corresponding to the C-H stretching, the C-H bending, and the C-O stretching vibrations, respectively (Figure 1).

Characterization of SPIO-Au nanoshell

Figure 2 shows typical transmission electron microscopy images of nanoparticles at different stages of SPIO/Gold nanoshell synthesis. After synthesis of silica-coated SPIO nanoparticles, SPIO nanoparticles (dark contrast) were clearly observed inside the spherical silica (Fig. 2A). Most of these particles contained 1 to 4 single SPIO nanoparticles or clusters of SPIO nanoparticles. The mean diameter of silica-coated SPIO nanoparticles was estimated to be 66.0 ± 9.5 nm. After treatment with HAuCl_4 and THPC, gold nanoseeds on the silica surface were clearly observed (densely distributed dark spots; Fig. 2B). The SPIO-Au nanoshells had an average diameter of 82.2 ± 9.7 nm, and the gold shell had a thickness of ~ 8 nm. The gold coating was not continuous with topographical roughness on the nanometer scale (Fig. 2C). Energy-dispersive spectroscopy of the PEG-coated SPIO-Au nanoshells across the entire image area showed the presence of C, O, Si, Fe, and Au (Fig. 2D). As discussed before, the most attractive property of gold nanoshells is their strong absorption at near-infrared region. UV-Vis spectroscopy of the aqueous solution of PEG coated SPIO-Au nanoshells showed that the surface plasma band of the nanoshells peaked at around 825-910 nm (Fig. 3), more than 300 nm towards the infrared compared to the peak for conventional gold nanoparticles²². Theoretical calculations have shown that the plasmon resonance of noble metal nanoshells can vary over hundreds of nanometers, the position of the resonance dictated by both the shell thickness and the size of the dielectric core²². The broad absorbance between 825 nm and 910 nm suggested that SPIO-Au nanoshells would be suitable for photo-thermal therapy with light in the NIR region, where there is minimum light absorption in tissues.

Magnetic property of SPIO-Au nanoshells

To determine whether the SPIO-Au nanoshells possessed a magnetic property that could potentially be used for magnetic field-guided targeting, we dispersed SPIO-Au nanoshells in pure water. An Nd-Fe-B magnet (~ 0.3 T) was then used to separate the nanoshells. The solution of SPIO-Au nanoshells, which was initially dark, was almost transparent after 15-min exposure to the magnetic field (Fig. 4A and 4B). The particles were precipitated to one side of the vial wall. UV-Vis spectroscopy revealed that more than 85% of the nanoshells were removed from the solution. Figure 4C shows the room-temperature magnetization curve of the SPIO-Au nanoshells obtained using a superconducting quantum interference device. For comparison, the magnetization curve of the commercial SPIO nanoparticles (average diameter, 10 nm) used in the preparation of SPIO-Au nanoshells is also presented. The insets are the plot of $M(H)$ in the zoomed region between -2 kOe and 2 kOe. The $M(H)$ hysteresis loop for the SPIO-Au nanoshells was almost completely reversible (Fig. 4C). The saturation moment per unit mass, M_s , for SPIO-Au nanoshells was 3.5 emu/g at 20 kOe, which was about 5.9% of the M_s for SPIO. This value for SPIO-Au is in accordance with previously reported data for silica-magnetite nanoparticles²⁰. These data indicated that SPIO-Au nanoshells exhibit superparamagnetic characteristics.

Magnetic Resonance (MR) relaxation study of SPIO-Au nanoshells

Since SPIO nanoparticles are effective T_2 MRI contrast agents^{7, 8}, we evaluated the T_2 relaxation of SPIO-Au nanoshells. The relaxivity data measured at 4.7 T in water showed a high r_2 value of 152 S^{-1} per mM of Fe_2O_3 , a very low r_1 value of $0.65 \text{ S}^{-1}\text{mM}^{-1}$, and thus a high r_2/r_1 ratio of 234 . In comparison, the commercial Resovist® SPIO nanoparticles exhibits a r_1 , r_2 , and r_2/r_1 values of $188 \text{ S}^{-1}\text{mM}^{-1}$, $12 \text{ S}^{-1}\text{mM}^{-1}$, and 9.6 , respectively²¹. It is not clear at the present time as to why SPIO-Au nanoshells showed such a high r_2/r_1 ratio. Nevertheless, the MR relaxivity data was in agreement with the magnetization data obtained with the superconducting quantum interference device and indicated that SPIO-Au nanoshells have excellent superparamagnetic characteristics. Figure 5 shows the results of MRI of SPIO-Au nanoshell solutions of various concentrations. The T_2 -weighted images

became noticeably darker with increasing nanoparticle concentrations, while the T_1 -weighted images showed little change in signal intensity with change in nanoparticle concentration. This result agreed with the relaxivity data indicating that SPIO-Au nanoshells have a high r_2/r_1 value and thus function as negative contrast agents.

Photothermal study on SPIO-Au nanoshell

As a potential photothermal mediator, the photothermal effect of the SPIO-Au nanoshells has to be evaluated. In order to investigate temperature elevation of SPIO-Au nanoshells induced by NIR laser irradiation, we used a continuous-wave fiber-coupled diode laser with a center wavelength of 808 ± 10 nm. Figure 6A shows the experimental setup. Experiments in aqueous solution showed that the temperature increased with increasing power output (data not shown). Moreover, at lower nanoshell concentrations (0.125 – 0.5 times the concentration of the stock solution—i.e., 0.125×10^{11} – 0.5×10^{11} particles/ml), the temperature change over the first 5 min increased with increasing nanoshell concentration. At higher nanoshell concentrations (0.5 – 1 times the concentration of the stock solution—i.e., 0.5×10^{11} – 1×10^{11} particles/ml), temperature elevation did not increase with increasing nanoshell concentration (Fig. 6B and 6C). For all concentrations tested, temperature elevation plateaued within about 5 min of light exposure. At a concentration of 0.75×10^{11} particles/ml, a temperature elevation of 16.3°C was achieved during 5 min of light exposure with a power output of 1 W. These data indicated that SPIO-Au nanoshells acted as an efficient photothermal mediator.

CONCLUSION

In summary, we have succeeded in synthesizing gold nanoshells with a SPIO core. These nanoparticles formed a stable solution in water when coated with PEG, were superparamagnetic, and had high r_2 and r_2/r_1 values and therefore could be imaged with MRI to obtain T_2 -weighted images. Moreover, these nanoparticles exhibited the strong NIR absorbance of regular gold nanoshells and exhibited efficient photo-thermal effect. These multifunctional SPIO-Au nanoshells, which have both magnetic and optical properties, should enhance the efficacy of nanoshell-mediated photo-thermal therapy by making it possible to direct more nanoparticles to tumors through the application of external magnetic field and by permitting real-time *in vivo* MRI imaging of the distribution of the nanoparticles before, during, and after photo-thermal therapy. Further studies to investigate the *in vivo* diagnostic and therapeutic potential of this novel material are in progress.

Acknowledgments

The work at U. T. M. D. Anderson Cancer Center was supported by the National Cancer Institute (Grant R01 CA119387) and by the John S. Dunn Foundation. The work at Sam Houston State University was supported by a grant from the SHSU EGR program and by an award from the Research Corporation. The work at the University of Texas at Austin was supported by the Welch Foundation under Grant F-1191 and by the National Science Foundation under grant DMR-0605828. We thank Stephanie Deming for editorial assistance.

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Figure 1.
FT-IR spectrum of PEG-coated SPIO-Au nanoshells.

Figure 2.

Typical transmission electron microscopy (TEM) images of (A) silica-coated SPIO nanoparticles, (B) silica-coated SPIO nanoparticles with gold nanoseeds on the surface, and (C) SPIO-Au nanoshells. Arrows: SPIO embedded in silica. Arrowheads: gold nanoseeds. (D): Energy-dispersive spectroscopy of SPIO-Au nanoshells across the entire image area. The signal of Cu was from the Cu grids of the TEM sample.

Figure 3.
UV-Vis spectrum of SPIO-Au nanoshells

Figure 4.

Photographs of a vial containing SPIO-Au nanoshells (1×10^{11} particles/ml) in pure water before (A) and after (B) magnetic separation for 15 min. (C) Magnetization curves of commercial SPIO nanoparticles and SPIO-Au nanoshells measured at 300 K.

Figure 5. T1-weighted (left) and T2-weighted (right) MRI images of SPIO-Au nanoshells in water at 0.8, 1.0, 2.0, 4.0, and 8.0 mM (vials 1-5, respectively, concentrations in terms of Fe_2O_3 moiety).

Figure 6.

(A) Photograph of experimental setup for measuring temperature changes mediated by SPIO-Au nanoshells. NS: aqueous solution containing the nanoshells in a quartz cuvette (100 μ L). Arrow: optical fiber delivering NIR laser light through the cuvette window. Arrowhead: thermocouple. (B) Temperature measured over a period of 15 min of exposure to NIR light at various nanoshell concentrations, which are expressed in terms of dilution factor of the concentration of the stock solution (1×10^{11} particles/mL). (C) Temperature change (ΔT) over the first 5 min as a function of nanoshell concentration, expressed in terms of the concentration of the stock solution.

Scheme 1.

Synthesis of gold nanoshells with superparamagnetic iron oxide (SPIO) cores. TEOS, tetraethylorthosilicate; APTMS, 3-aminopropyltrimethoxysilane; THPC, tetrakis(hydroxymethyl) phosphonium chloride.