Influence of NIR Laser and Alternating Magnetic Field on Core-Shell Nanoparticles for Cell Lines Treatment

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Research Article

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Influence of NIR Laser and alternating magnetic field on \( \text{Fe}_3\text{O}_4\text{-Au } \@ \text{SiO}_2 \) Core-Shell Nanoparticles for cell lines treatment

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Abstract: Core-shell nanoparticles (CSNPs) have attracted attention in biomedical applications as they have highly useful materials with modified characteristics, such as high stability, dispersibility, higher permeability to certain target cells and reduction in consumption of precious materials. Synthesis of core-multishell nanoparticles with suitable sizes, structural characteristics and absorption using simple methods continues to be a challenge. In this study, \( \text{Fe}_3\text{O}_4\text{-Au } \@ \text{SiO}_2 \) CSNPs were synthesized in three stages to control their size and the potential for tuning their properties. FESEM images confirmed that \( \text{Fe}_3\text{O}_4\text{-Au } \@ \text{SiO}_2 \) CSNPs has a small particle size of about 22.5 nm; average crystalline size in XRD was 22.8 nm; stability was about -49.1 mV; and synthesis with magnetic and optical properties improved their biocompatibility. Treatment of CAL-51 and HBL-100 cell lines by \( \text{Fe}_3\text{O}_4\text{-Au } \@ \text{SiO}_2 \) CSNPs under NIR laser and alternating magnetic field (AMF) generated enough heat to increase cell death.

Keywords: \( \text{Fe}_3\text{O}_4\text{-Au } \@ \text{SiO}_2 \) CSNP , NIR laser , alternating magnetic field, MTT assay, optical properties , magnetic properties.

1.Introduction

Magnetic nanostructures are being used in biomedical applications because of their high magnetic susceptibilities and very low toxicity [1-4]. \( \text{Fe}_3\text{O}_4 \) NPs has been used for cancer diagnostics and treatment due to its thermal characteristics (induction of heat for destroying cancer cells), as well as certain properties of magnetic particles such as size, shape and strength of their field, and saturation magnetization [5]. Localized surface plasmon resonances (LSPR) in nanoparticles can produce strong optical resonances at visible and near-infrared wavelengths [6]. \( \text{Fe}_3\text{O}_4 \) NPs do have plasmonic properties, exhibiting LSPR due to their large electron density [7]. However, they are not as strong as gold nanoparticles. This is because of differences between the electronic structures of the two materials [8]. Gold nanoparticles (AuNPs) are used in medicine because of their unique optical properties, known as localized surface plasmon resonance (LSPR), and their high level of stability, as well as their potential to combine with biomolecules [9]. In aqueous
solutions, magnetites become corroded, agglomerated and unstable. Silica shells on the surface of the core make it dispersible in liquids, which improves biocompatibility by allowing it to be coupled with various medicines and biomolecules [10-12]. The combination of two functionalities, Fe<sub>3</sub>O<sub>4</sub> NPs magnetization and Au nanomaterial near-infrared (NIR) absorption, would allow for effective imaging and therapy for a variety of critical diseases. However, combining different surfaces is difficult, leading to low dispersion, failure to synthesize MGNPs with NIR responses and, as a result, potentially undesirable physicochemical characteristics [13]. Synthesis of core-multishell with suitable sizes, structural characteristics and absorption using simple methods continues to be a challenge [14]. Yang et al. [15] prepared Fe<sub>3</sub>O<sub>4</sub>-Au @SiO<sub>2</sub> CSNPs with spherical shape but at micro scale and over a long time, exceeding 16 h. Amatatongchai et al. [16] synthesized Fe<sub>3</sub>O<sub>4</sub>-Au @SiO<sub>2</sub>CSNPs to provide excellent features for electrochemical sensors but by complex and expensive methods, with particle size <50 nm and with non-uniform shapes. To avoid these problems, we synthesized Fe<sub>3</sub>O<sub>4</sub>-Au @SiO<sub>2</sub> CSNPs in three stages, in order to control their chemical composition, relative size and the potential for tuning their properties safely, at low cost, in a short synthesis time of about 4 h, with spherical shape and on a scale of not more than 25 nm. This was done by first synthesizing a core Fe<sub>3</sub>O<sub>4</sub> NPs using a green method, then synthesizing highly efficient Fe<sub>3</sub>O<sub>4</sub>-Au CSNPs by an ecologically friendly, sonochemical method that rapidly produces smaller particles and satisfactory properties [17], and finally coating with silica to avoid agglomeration and effectively enhance biocompatibility. MTT assay was also used to evaluate the effect of Fe<sub>3</sub>O<sub>4</sub>-Au @SiO<sub>2</sub> on CAL-51 and HBL-100 cell lines. The result showed that cytotoxic effect was increased in the presence of NIR laser and alternating magnetic field (AMF), because a good LSPR (Au NPs) absorbed NIR laser and converted to heat, and the presence of Fe<sub>3</sub>O<sub>4</sub> NPs under alternating magnetic field also generated enough heat to inactivate infected cell lines.

2. Experimental Details
2.1 Materials
Ferric chloride hexahydrate (FeCl<sub>3</sub>.6H<sub>2</sub>O) and Ferrous chloride tetrahydrate (FeCl<sub>2</sub>.4H<sub>2</sub>O) were procured from Panreac AppliChem in Barcelona (Spain). Hydrogen tetrachloroauric acid (HAuCl<sub>4</sub>⋅4H<sub>2</sub>O) was procured from Riedel-Dehaenag/Seelz-Hannover (Germany). Tetraethyl orthosilicate (TEOS), sodium hydroxide (NaOH), trisodium citrate dihydrate (Na<sub>3</sub>Ca<sub>6</sub>H<sub>5</sub>O<sub>7</sub>), cetyltrimethylammonium bromide (CTAB) and ammonia aqueous solution (25 wt%) were purchased from Aladdin Chemical Co. LTD (China). All solutions were synthesized with deionized water. CAL-51 (human breast cancer cell line) and HBL-100 (a breast nontumorigenic cell line) were provided by the Iraqi Center for Cancer and Medical Genetic Research (ICCMGR).
2.2 Synthesis of Fe₃O₄-Au @SiO₂ CSNPs

Three stages make up the process of synthesis: part A, synthesis of Fe₃O₄ NPs by green method; part B, synthesis of Fe₃O₄@Au by sonochemical method; part C, synthesis of Fe₃O₄-Au @SiO₂ CSNPs.

A. Fe₃O₄-NPs were synthesized by a green method using carob leaf extract. FeCl₂.4H₂O and FeCl₃.6H₂O (1/2 molar ratio) were dissolved in deionized water and heated at 80°C. Into this solution, a carob leaf extract solution was added and the yellow colour of the mix changed to brown. After that, NaOH was added to the mixture, with constant stirring to adjust the pH to 8, and the colour of the mix changed to dark brown. This was followed by constant stirring for 20 min until the reaction was complete and cooled to room temperature. Magnetite nanoparticles were washed several times with deionized water, after which they were centrifuged and the collected precipitates were oven-dried at 70°C.

B. Fe₃O₄@Au CSNPs were prepared using sonochemical method, with ultrasonic frequency at 45 kHz, 120 W. 0.01 g Fe₃O₄ NPs were dispersed in 15 mL of deionized water and ultrasonicated for 60 s. Then 25 mL (0.001 M) of HAuCl₄ solution was added, The solution was ultrasonicated for 2 min, after which 5 mL sodium citrate (0.03 M) was added. The mixture was again ultrasonicated for 20 min and heated to 45°C. The colour changed immediately to brown and gradually to dark burgundy. Next, a magnet was used to collect CSNPs, which were then washed several times with deionized water. The collected precipitates were oven-dried at 70°C.

C. Fe₃O₄-Au @SiO₂ CSNPs were prepared. 0.01 g of Fe₃O₄-Au was dispersed in 25 mL of deionised water, 30 mL of ethanol, 5 mg of CTAB (as templates) and 0.5 mL of ammonia aqueous solution (25 Wt%) in a stirrer for 30 min. After that, 0.3 mL TEOS was added drop-wise, with continuous stirring for 3 h. The colour of the solution changed immediately from burgundy and slowly to purple. The product was then collected, washed several times with ethanol and deionized water and dried in an oven at 70°C. The stock solution of Fe₃O₄-Au @SiO₂ CSNP is shown in Fig.1.

![Figure 1: The solution of Fe₃O₄-Au @SiO₂ CSNPs](image)
2.3 MTT assay

The MTT assay was utilized to test the cytotoxic effect of Fe$_3$O$_4$&mdash;Au@SiO$_2$ CSNPs. CAL-51 and HBL-100 cell lines were cultured into 96-well plate ($1 \times 10^4$ cells/well) that contain a mixture of RPMI medium and fetal calf serum (10%). The cells were cultured for 24 h to ensure cell adhesion to the wells. The cell lines were treated with different concentrations of Fe$_3$O$_4$-Au@SiO$_2$ (3.1, 6.25, 12.5, 25 and 50 μg/mL) in the absence and irradiated with NIR laser (808 nm laser, 0.5 W·cm$^{-2}$, 20 min) and again when applying an alternating magnetic field (0.3 T for 25 min). Untreated cell lines were cultured in a well plate to serve as the control. Cell viability was measured after 72 h of incubation. The media were discarded from the plate and washed three times with PBS. 28 μL of 2 mg/mL solution of MTT stain was added to each well and the plate was kept at 37°C. After 2.5 h, the MTT solution was removed with 130 μL of DMSO (Dimethyl Sulphoxide). After this, the plates were incubated for 15 min at 37°C with shaking. The optical density of Fe$_3$O$_4$-Au@SiO$_2$ and of the control for each well were read using a FLUO star OPTIMA device at 492 nm. The cell growth inhibition rate and percentage of cytotoxicity of Fe$_3$O$_4$-Au@SiO$_2$ CSNPs were calculated according to Equation (1) [18].

\[
\text{Inhibition rate} = \frac{A - B}{A} \times 100 \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (1)
\]

where A represents the optical density of the control (cells only) and B represents the optical density of the samples.

Images of CAL-51 and HBL-100 cells, treated with Fe$_3$O$_4$-Au@SiO$_2$ at a chosen concentration of 12.5 μg/mL, were taken with a digital camera connected to an inverted microscope at 100× magnification.

3. Characterisation

LSPR of Fe$_3$O$_4$-Au@SiO$_2$ was determined with a UV-Vis spectrooscope (the Shimadzu UV-1601 spectrophotometer). X-ray diffractometer (XRD) (Shimadzu XRD 6000, Cu Kα radiation source) was utilized to analyze the structure of Fe$_3$O$_4$-Au@SiO$_2$. Field Emission Scanning Electron Microscope (FESEM) (model: £IGMA Series-ZEISS Company) was used to analyze the NPs' size and morphological properties. Zetaplus device (from Brookhaven) was used to analyze the electric charge on the nanoparticles surface and the stability of the nanoparticles. The magnetization was measured at RT with a vibrating sample magnetometer (VSM, BVH-55).
4. Result and Discussion

Fig. 2 shows the XRD patterns of the synthesized Fe$_3$O$_4$ NPs, Fe$_3$O$_4$@Au NPs and Fe$_3$O$_4$-Au@SiO$_2$ NPs. The Fe$_3$O$_4$ peaks are at 2θ = 30.56°, 35.86°, 43.46°, 54.01°, 57.38°, 63.00°, and 74.46°, are assigned to (220), (311), (400), (422), (511), (440), and (533) respectively, matching the data of ICSD file no: 98-002-7899 [19]. Fe$_3$O$_4$@Au nanoparticles have peaks identical to those of Fe$_3$O$_4$ nanoparticles but with additional peaks at 38.2°, 44.3°, and 64.5° ascribed to the fcc Au locations of (111), (200) and (220) planes respectively (ICSD file no: 98-005-2700) [20]. These results are consistent with those of Maximenko et al. [21]. The XRD pattern of the Fe$_3$O$_4$-Au@SiO$_2$ CSNPs is identical to the pattern of Fe$_3$O$_4$@Au NPs, with the exception of the broad peak at 2θ = 15–25, which is due to the amorphous SiO$_2$ [22]. This implies that the SiO$_2$ shell around Fe$_3$O$_4$-Au has no effect on the initial structure of Fe$_3$O$_4$-Au due to its good protective function. The average crystalline size of synthesized Fe$_3$O$_4$ NPs, Fe$_3$O$_4$@Au NPs and Fe$_3$O$_4$-Au@SiO$_2$ NPs can be estimated as 14, 22 and 22.8 nm respectively. These were calculated using the Debye–Scherrer equation.

The localized surface plasmon resonance (LSPR) can be determined using UV-Vis spectroscopy. The shape and position of the LSPR peak provides information on the scale, size, structure and stability of metal nanoparticles in aqueous solution [23]. Fig. 3 shows the UV-Vis SPR spectra of Fe$_3$O$_4$ NPs, Fe$_3$O$_4$@Au NPs and Fe$_3$O$_4$-Au@SiO$_2$ CSNPs. Magnetite NPs have plasmonic properties but they are not as powerful as gold NPs. This is because of the two materials' different electronic structures. The UV-Vis SPR spectrum of Fe$_3$O$_4$ is absent in the visible region. The LSPR of Fe$_3$O$_4$@Au CSNPs normally appears at 530 nm but this peak shifted towards large wavelengths (red shift) due to SiO$_2$ shell around Fe$_3$O$_4$@Au. The plasmon absorption shows up at 545 nm.
Fe₃O₄ NPs, Fe₃O₄@Au CSNPs and Fe₃O₄-Au@SiO₂ CSNPs were morphologically analysed using FESEM. Figs.4a-c depict the FESEM images of all the samples. Fig.4a shows Fe₃O₄ NPs with many spherical particles and a particle size of about (10-2) nm. The image of the Fe₃O₄@Au CSNPs sample is shown in Fig.4b and it appears that the particle size has increased with coating Fe₃O₄ by Au, having an average particle size of 17.3 nm. As illustrated in Fig.4c, Fe₃O₄-Au CSNPs coated with SiO₂ shell appear darker, with particle sizes of about 22.5 nm. Fig.4d is the TEM image of Fe₃O₄-Au@SiO₂ CSNPs that will be used for biomedical application. The image shows that it is spherical, with a particle size of 20 nm.
When the $\text{Fe}_3\text{O}_4$ NPs are small enough (less than 30 nm), they become superparamagnetic at room temperature [24]. The shell coated core causes increase in particle size that was proved by the XRD and the FESEM analyses. Particle size influences the magnetic characteristics of NPs. It is also reflected in the structure of the spin from the surface of the NPs. The magnetic properties of NPs increase as their size increases due to reduced surface effects. The decrease in surface area causes a decrease in surface disorder and an increase in inter-particle interactions, resulting in higher magnetic characteristics such as high saturation magnetization, agreeing with Silva et al. [25], while coating the NPs with the shell layer helps decrease the surface effect. The spins on the surface of the NP shells are no longer aligned, due to the action of the exchange or superexchange interaction (disorder structure) with the spins from the core of the nanoparticles that are aligned. The noncollinearity of the spins from the surface of the nanoparticles causes a decrease in saturation magnetization. Due to the mass contribution from the diamagnetic material ($\text{SiO}_2$-Au) shell, CSNPs have much lower saturation magnetization ($M_s$) than $\text{Fe}_3\text{O}_4$ NPs, agreeing with Stafford et al. [26]. Fig.5 shows that the saturation magnetization $M_s$ and remanent magnetization $M_r$ decrease while coercive force increases by coating the NPs with Au and $\text{SiO}_2$. The increase of coercivity may be related to the impact of the spin disorder at the $\text{Fe}_3\text{O}_4$-Au interface and to the weak interchange of surface and core spins, (shown in Table 1).

![Figure 5: Hysteresis loops of $\text{Fe}_3\text{O}_4$ NPs, $\text{Fe}_3\text{O}_4$ @Au NPs and $\text{Fe}_3\text{O}_4$ –Au@$\text{SiO}_2$ nanoparticles synthesized at RT](image)

### Table 1. Magnetic parameters

| Sample           | $M_s$ \([\text{emu/g}]\) | $M_r$ \([\text{emu/g}]\) | $H_c$ \(\text{Oe}\) | Particle size from FESEM \([\text{nm}]\) |
|------------------|--------------------------|---------------------------|-------------------|---------------------------------|
| $\text{Fe}_3\text{O}_4$ | 26.6                     | 1.4                       | 8                 | 9                               |
| $\text{Fe}_3\text{O}_4$ @Au | 17                      | 1.8                       | 15                | 17.3                            |
| $\text{Fe}_3\text{O}_4$–Au@$\text{SiO}_2$ | 10                      | 1.1                       | 21                | 22.5                            |
Measurement of zeta potential gives information on surface function, particle stability and the interaction of dissolved compounds with the surface. The zeta potential magnitude reflects sample stability whereas the zeta potential sign shows whether the surface is dominated by positive or negative charges [27]. The zeta potential was utilized to analyze the stability of the prepared Fe₃O₄-Au @SiO₂ NPs. The Fe₃O₄-Au @SiO₂ CSNPs had a stable dispersion of about -49.1 mV, as shown in Fig.6. The nanoparticles that have zeta potential values higher than ± 30 mV are used in medical applications due to good dispersity and high suspension stability.

![Figure 6: zeta potential measurement of Fe₃O₄-Au @SiO₂](image)

Use of the MTT assay to study the cytotoxic effect of Fe₃O₄-Au @SiO₂ CSNPs dispersed in deionized water at different concentrations (3.125, 6.25, 12.5, 25 and 50 μg/mL) is shown in Fig.7. Exposure of cell lines to Fe₃O₄-Au @SiO₂ CSNPs caused a reduction in the viability of cancer cells. The cytotoxic effects of these cell lines increased with the increase of Fe₃O₄-Au @SiO₂ CSNP concentration. The results show that Fe₃O₄-Au @SiO₂ CSNPs have the ability to inhibit the proliferation of cancer cells and cell death when comparing cell lines with tumours (CAL-51) and normal cell lines (HBL-100), as the tumour cell death in CAL-51 was approximately 70%, contrasting with approximately 13% in HBL-100 at the highest Fe₃O₄-Au @SiO₂ concentration (the black bars in Fig.7). To achieve more cell death, the cell lines with the NPs were irradiated for 20 min with NIR of 808 nm wavelength and at 0.5 W cm⁻². The irradiation light is absorbed by LSPR (Au NPs) and converted to heat and forms a hot metallic lattice by electron-electron relaxation and electron-phonon relaxation. Heat energy is precipitated in the tumour cell lines, causing them to inhibit the proliferation of cancer cells and therefore their death (the red bars of Fig.7). Photothermal effect of Fe₃O₄-Au @SiO₂ results in a significant reduction of the tumour, since cell lines are sensitive to heat. Higher tumour cell killing was noticed with the use of NIR radiation. Tumour cell killing was approximately 75% for CAL-51 and about 15% for the HBL-100, at the highest Fe₃O₄-Au @SiO₂ concentration. The cytotoxic effect was increased under laser irradiation due to increased absorption, induced by the distinct properties of LSPR. Furthermore, because of the smaller particle size, the larger light energy from the NIR laser was converted to heat energy, agreeing with Huang et al. [28]. Applying an alternating magnetic field (AMF) (0.3 T) for 25 min caused even
more cancer cell death (higher cytotoxicity) (the green bars in Fig.7). Applying an alternating magnetic field (AMF) (0.3 T) for 25 min caused even more cancer cell death (higher cytotoxicity) (the green bars in Fig.7). AMF causes the Fe₃O₄ in cancer cells to spin back and forth, thus generating a significant amount of heat and causing the death of the tumour cells. The highest tumour cell death was about 85% for CAL-51 and about 16% for HBL-100 at the highest Fe₃O₄-Au @SiO₂ concentration. The magnetite centre could still spin and create heat in a magnetic field. Current findings indicate that the photothermal effect of Fe₃O₄-Au @SiO₂ with the application of AMF achieves the highest rate of tumour cell death. Both NIR radiation and AMF cause greater death in tumour cells containing Fe₃O₄-Au @SiO₂ CSNPs, as these resulted in a rapid increase in temperature inside the cell lines.

![CAL-51 cells](image1.png) ![HBL-100 cells](image2.png)

Figure 7: Cytotoxic effect on two cell lines with Fe₃O₄-Au@SiO₂ (without, +NIR, +AMF)

Treating CAL-51 and HBL-100 cell lines with Fe₃O₄-Au @SiO₂ CSNPs, in the presence of laser and AMF produced cellular damage. This is most likely because of the photothermal effect. Changes in morphology and cell viability, as compared with the control, were noticed from the microscope images as presented in Fig.8.
5. Conclusions

In this study, Fe$_3$O$_4$-Au @SiO$_2$ was synthesized in a short time, with desired physicochemical characteristics and effective biocompatibility. In UV-Vis spectroscopy, the shift in LSPR peak to a longer wavelength (red shift) confirmed that the core-shell had formed. A LSPR peak of Fe$_3$O$_4$@Au appears at 530 nm and shifts to 545 nm when coated with SiO$_2$. The particle size was obtained from the FESEM image and XRD analysis, showing the increase in size of particles with a shell. In addition, the TEM images show a spherical shape, with a particle size of 20 nm, with a clear appearance of Fe$_3$O$_4$-Au @SiO$_2$ CSNPs. VSM indicated that the magnetization was decreased due to being coated by Au and SiO$_2$. Exposure of cell lines to Fe$_3$O$_4$-Au @SiO$_2$ CSNPs caused a reduction in the viability of cancer cells. The application of NIR radiation caused greater cell death, at around 70% for CAL-51 and about 20% for HBL-100. The application of alternating magnetic field also caused increased cell death, at around 80% for CAL-51 and about 30% for HBL-100.

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