BNL-108300-2015-CP

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advanced theranostics: synthesis, modeling and experiment***

Masoud Masoumi

Ya Wang ¹, Mingzhao Liu ², Mahder Tewolde ¹, Jon Longtin ¹

Dept. of Mechanical Engineering, Stony Brook University, Stony Brook, NY,
²Center of Functional Nanomaterials, Brookhaven National Laboratory, Upton, NY,

ACTIVE AND PASSIVE SMART STRUCTURES AND INTEGRATED
SYSTEMS 2015

Presented by: SPIE – San Diego, CA

March 9 -12, 2015

Center for Functional Nanomaterials

Brookhaven National Laboratory

**U.S. Department of Energy
Office of Basic Energy Sciences**

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Multifunctional magneto-plasmonic nanotransducers for advanced theranostics: synthesis, modeling and experiment

Masoud Masoumi ^a, Ya Wang ^{*a}, Mingzhao Liu ^b, Mahder Tewolde ^a, Jon Longtin ^a

^aDept. of Mechanical Engineering, Stony Brook University, Stony Brook, NY, USA 11790

^bCenter of Functional Nanomaterials, Brookhaven National Laboratory, Upton, NY, USA 11973

ABSTRACT

In this work, nano-transducers with the superparamagnetic iron oxide (SPIO) core have been synthesized by the preparation of precursor gold nanoseeds loaded on SPIO-embedded silica to form a gold nanoshell. The goal is for such nano-transducers to be used in theranostics to detect brain tumors by using MRI imaging and then assist in their treatment by using photothermal ablation. The iron oxide core provides for the use of a magnetic-field to guide the particles to the target (tumor) site. The gold nanoshell can be then readily heated using incident light and/or an alternating magnetic-field. After synthesis of nano-transducer samples, Transmission Electron Microscopy was employed to analyze the formation of each layer. Then, UV spectroscopy experiments were conducted to examine the light absorbance of the synthesized samples. The UV-visible absorption spectra shows a clear surface plasmon resonance (SPR) band around 530 nm, verifying the presence of gold coating nanoshells. Finally, photothermal experiments using a high-power laser beam with a wavelength of 527 nm were performed to heat the samples. It was found that the temperature reaches 45° C in 12 minutes.

Keywords: Theranostic nanomedicine, SPIO, cancer treatment, UV-spectroscopy, photothermal experiment

1. INTRODUCTION

Effective cancer treatment remains a challenging and complex research challenge [1]. As attempts to develop multifunctional medicines for different types of diseases, researchers have been focused on promoting new drugs with the synergistic effects of therapeutic and diagnostic capabilities [2]. In recent years, nanoparticle-based platforms for drug delivery have gained attention due to their capabilities to impart more accurate cancer cell targeting to the medical treatments. Numerous multilayered nanostructures have been synthesized and evaluated to compare the effects of different types of juxtaposition of magnetic iron core, silica layers as well as gold or silver outer layers [3]. Furthermore, investigations have used aptamer-conjugated nanoparticle-based medicine, which are capable of attaching to cancer cells and isolate these cells from the rest of the tissue [4]. Therefore, research pertaining to cancer theranostic applications for nanoparticles are undergoing an explosive development in terms of early diagnosis and more effective therapies.

The aim of this work is to synthesize, and evaluate a theranostic magneto-plasmonic nanoparticle-based as a multitask and multipurpose medicine for cancer treatment, simultaneously enabling magnetic resonance imaging (MRI) and hyperthermia. The final product will have the potential for: (1) using the nanoparticles as contrast agents in noninvasive cancer imaging by magnetic resonance (MR) especially for the tissues that the difference between the time needed for recovery from longitudinal magnetization after removal of the applied radio frequency pulse and the time needed for exponential decay of the transverse magnetization. (2) using them for guidance of biomolecules to tumors sites by applying an external magnetic field gradient, and (3) destroying cancer cells by increasing the temperature of the cells with a laser and/or external magnetic field, where the laser beam is absorbed by the gold shell and magnetic field causes the temperature to increase due to the magnetocaloric effects on magnetic-core of the nanostructure. Also, we will explain and implement a method to synthesize a multimodal phantom of liver as an environmentally safe and well-suited testbed to perform further experiments for magnetic resonance imaging (MRI) using synthesized nanoparticles. The nanoparticles synthesized in this work can provide all the aforementioned properties. They can be used to synthesize semi-hollow nanostructures by subjecting to an etching process using BHF as etching agent. Therefore these nanostructure can also be used for drug delivery applications as well.

*Ya Wang, Assistant Professor, Department of Mechanical Engineering, State University of New York, Stony Brook. Email: ya.s.wang@stonybrook.edu. Phone 631-632-8322.

2. NUMERICAL MODELLING

When a metal nanoparticle is illuminated, some of the photons inside the particle are released in all directions, in a process called “scattering”. At the same time, part of the energy due to the illumination of the light is converted into vibrations of the lattice, referring as *absorption*. In hyperthermia, incident light converts heat to increase the temperature of nanoparticles with the aim of cancer cell ablation. The heat is sufficient to kill cancer cells while the surrounding healthy cells will suffer minimum damages. The absorption/scattering cross-section is a measure for the probability of light or other radiation being absorbed/scattered by a particle. The sum of two absorption and scattering cross sections provides the total light attenuation, characterized by the extinction cross-section [5]:

$$\sigma_{ext} = \sigma_{sca} + \sigma_{abs} \quad (1)$$

The balance between the scattering and absorption depends on the size and shape of the nanoparticle. For spherical nanoparticles, whose diameter, $2R$, are small (~ 25 nm) compared to the wavelength λ of the exciting light, i.e., $\lambda < 2R$, the extinction cross-section can be found from the following equation [6]:

$$\sigma_{ext} = \frac{9V \varepsilon_m^{3/2}}{c} \cdot \frac{\omega \varepsilon_2(\omega)}{\left[\left(\varepsilon_1(\omega) + 2\varepsilon_m \right)^2 + \varepsilon_2(\omega)^2 \right]} \quad (2)$$

where, c , V , and ω are speed of the light, spherical particle volume, and angular frequency of the exciting radiation respectively, and ε_m is the dielectric constant of the surrounding medium. Also, $\varepsilon_1(\omega)$ and $\varepsilon_2(\omega)$ indicate the real and imaginary part of the dielectric function (relative) of the particle material ($\varepsilon(\omega) = \varepsilon_1(\omega) + i\varepsilon_2(\omega)$). From Eq. (2), we see that the resonance occurs when $\varepsilon_1(\omega) \approx -2\varepsilon_m$ if ε_2 is small or only weakly dependent on ω . The absorption cross-section is dependent on the electric field of the incident light

$$\sigma_{abs} = \frac{k}{\varepsilon_0 |E_0|^2} \int \varepsilon_2(\omega) |E(r, t)|^2 dr \quad (3)$$

in which, $k = n\omega/c$ is the wave vector, n is the refractive index of the surrounding medium, E_0 is the electric field amplitude of the incoming light, and $E(r, t) = E_0 e^{i(kr + \omega t + \phi)}$ is the electric field. The integral is calculated over the nanoparticle volume [5]. Considering the absorbed light to convert to heat and generate heat power in a specific wavelength, absorption efficiency is given by

$$Q = \sigma_{abs} I \quad (4)$$

where, $I = \frac{nc\varepsilon_0}{2} |E_0|^2$ is the irradiance of the incident light. Substituting Eq. (3) into Eq.(4), we have

$$Q = \frac{n^2\omega}{2} \varepsilon_2(\omega) \int |E(r)|^2 dr = \int q(r) dr \quad (5)$$

where, $q(r) = \frac{n^2\omega}{2} \varepsilon_2(\omega) |E(r)|^2$ is power density of the generated heat.

If the incident light is delivered over a very short duration, as with a short pulse laser having a pulse duration of nanoseconds or less, then conduction and radiation losses from the particle can be neglected. Then the power density can be related to the temperature distribution inside the nanoparticle $T(r)$ as follows

$$K \nabla^2 T(r) = -q(r). \quad (6)$$

Here K is the thermal conductivity of the nanoparticle. In the surrounding medium outside the nanoparticle, it was found that temperature elevation is dependent on the particle radius [5]

$$\Delta T_m = \Delta T_n \frac{R}{r} \quad (7)$$

where, ΔT_m is the temperature changes in the surrounding medium, ΔT_n is the temperature changes inside the nanoparticle, which can be found by

$$\Delta T_n = \frac{Q}{4\pi K_0 r_e} . \quad (8)$$

In Eq. (8) K_0 is the thermal conductivity of the surrounding medium, and r_e is the effective radius of the nanoparticle.

The equations above were obtained for the gold nanospheres. However, for gold nanoshells consist of a gold spherical shell surrounding a dielectric core, we can find the equations as follows. Assuming the dielectric core has a radius R_l and dielectric constant ϵ_c , the gold nanoshell has a thickness $R_2 - R_l$ and dielectric function $\epsilon_{sh} = \epsilon_{1sh} + i\epsilon_{2sh}$, and the embedding medium has a dielectric constant ϵ_m . The absorption cross section can be calculated by deriving the Laplace' equation [7]

$$\sigma_{abs} = \frac{8\pi^2 R_2^3}{3\lambda \epsilon_0} \text{Im} \left(\frac{|E_{loc} - E_0|}{E_0} \right) \quad (9)$$

here, E_{loc} is the local electric field and E_0 is the incident electric field. Assuming that the power absorbed by a single particle is completely converts to thermal energy, the power absorbed by a single particle under the steady-state condition can be found from [8]

$$\dot{Q} = \int_{\lambda_1}^{\lambda_2} \sigma_{abs} I_{\lambda} d\lambda \quad (10)$$

where, I_{λ} is the spectral irradiance of the light source which is constant, λ_1 and λ_2 which are the limiting wavelength of the light over which the light source operates. Finally, the radiated power can be found by knowing the shell temperature [8]:

$$\dot{Q} = h k_B 4\pi R_2^2 (T_{sh}^4 - T_{sur}^4) \quad (11)$$

Figure 1. Scattering cross section of gold nanosphere for different diameter

Figure 2. Scattering cross section for silica gold coated for different gold thickness and silica core diameter of $d=10$ nm

where, h is emissivity of the nanoshell (0.9 for gold nanoshell), k_B is Boltzman's constant, T_{sh} is the shell temperature and T_{sur} is temperature of the surrounding medium.

Scattering cross section of gold nanosphere and also silica nanosphere coated with a gold layer have been studied by using boundary element method as proposed by [9]. Results are shown for gold and goal-coated silica nanoparticles in Figures 1 and 2, respectively. As seen in Figure 1, increasing the diameter of the gold nanosphere results in an increase in scattering cross section, however the wavelength of the maximum scattering does not change. On the other hand, in Figure 2 the maximum scattering wavelength for a silica nanosphere coated with gold can be tuned over a range of roughly 200 nm by changing the thickness of the gold layer.

3. SYNTHESIS PROCESS

3.1 SPIO-Gold Nanoshell Synthesis

Superparamagnetic iron- oxide gold nanoparticles were synthesized with a super paramagnetic iron-oxide core and a silicon layer, followed by the addition of the gold nanoshell. First, silica-coated SPIO (Fe_3O_4) nanoparticles were synthesized according to the Stöber process [10], and then, a gold nanoshell was added by attachment of colloidal gold nanoparticles to an 3-aminopropyltrimethoxysilane (APTMS)-functionalized silica layer. APTMS is used for surface modification of silica to ensure uniform coverage of silica particles surface with aminopropyl groups. This process helps to have a better surface coverage of silica with colloidal gold nanoparticles. Ferrotec EMG 304 SPIOs (average diameter of 10 nm) were stabilized with oleic acid in water. This ferrofluid was chosen because it's biocompatible and has high magnetic affinity due to its aqueous base, high saturation magnetization and high viscosity. The magnetite (Fe_3O_4) magnetic nanoparticles were coated with amorphous silica via the sol-gel process. Gold nanoseeds firmly attach to the amino groups on the silica sphere, which were positively charged at acidic pH, because they have net negative surface charges. The attached gold nanoseeds were used to nucleate the growth of a gold overlayer on the silica surface to form a gold nanoshell. The silica layer served as a dielectric interface for shifting the plasma resonance. 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.

Tetraethylorthosilicate (TEOS), 3-aminopropyltrimethoxysilane (APTMS), ammonia solution (30 wt %), tetrakis (hydroxymethyl) phosphonium chloride (THPC), chloroauric acid (HAuCl_4), potassium carbonate (K_2CO_3), and formaldehyde (37%) were purchased from Sigma-Aldrich. Water-based super paramagnetic iron oxide particles (EMG 304) from Ferrotec were used for its high saturation magnetization and high viscosity. 0.2 mL of water-based SPIO (EMG 304) was diluted with 6 mL of pure water and 80 mL of absolute ethanol. 7mL of an aqueous ammonia solution (30 wt %) and 0.5 mL TEOS were consecutively added into the SPIO solution at room temperature under continuous mechanical stirring. After 30 minutes, silica nanoparticles began to form as the clear solution became murky. 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) groups. These silica nanoparticles were then

treated with 0.04 mL of 3-aminopropyltrimethoxysilane for 6 hours to introduce the amino-terminated silica surface. After the reaction, the SPIO-embedded silica was separated from the reaction medium by centrifugation at 4000 rpm and re-dispersed in 100 mL of absolute ethanol.

Figure 3 (a) SPIO-embedded silica (b) Centrifuging the final solution at 4000 rpm (c) SPIO-Gold nanoshell

Addition of 1 mL of SPIO- embedded silica solution to 5 mL of undiluted THPC gold solution led to the attachment of THPC gold nanocrystals onto 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 chlorauric acid (HAuCl_4) with THPC, which affords relatively small gold particles (2nm) with a net negative interfacial charge. Finally, the gold nanoshells were prepared by reduction of K-gold solution with formaldehyde (37%) in the presence of SPIO-embedded silica nanoparticles covered with gold nanoseeds. To prepare K-gold solution, 2mL of 1 wt % HAuCl_4 was added to 100mL of water containing 0.025 grams of K_2CO_3 under magnetic stirring. The nanoparticles were isolated by centrifugation and washed with distilled water to create nanoparticle solutions of less than 0.1 wt % and 0.8 wt % concentrations (Figure 3). After synthesis of the product, Transmission Electron Microscopy (TEM) is utilized to study the formation and structure of the SPIO-Gold nanoshell. These figures provide different views of SPIO coated with silica and gold layer. Looking at these images, we can also identify attached gold nanoseeds on the surface of the nanostructures. Figure 4 (a) and (b) show a group of SPIO covered with silica and gold layers which are attached together and made some kind of a chain. In most cases two or more SPIO particles are attached together during the synthesis process and they share the same silica and gold layers. It can be seen especially in figure 4 (c) that a core of super paramagnetic iron oxide (with the diameter of around 10 nm) is covered with a silica layer and a thin gold layer. The spots that can be observed on the surface of the outer layer are indicating the gold nanoseeds. These nanoseeds available on the surface are evident that, giving more time to grow, would result in a more uniform layer by better conversion of those seeds into the gold layer.

Figure 4 TEM images of synthesized SPIO-Gold nanoshell

3.2 Liver Phantom Synthesis

Ideally, researches regarding to cancer cell imaging and photothermal ablation should be conducted in a phantom that accurately mimics the soft tissue it is intended for. Commercially manufactured phantoms are designed to be used for specific applications and are not easily manipulative. So as to provide a suitable and environment-friendly phantom, the technique proposed by [11] was used to synthesize a multipurpose phantom of liver. The phantom consists of two parts: (1) phantom Parenchyma which acts as the environment and (2) tumor tissue. We synthesized the tumor tissue and phantom Parenchyma and then mixed them to have a final liver phantom. To synthesize agarose gel tumors, 7.5 grams of agarose is mixed with 30 mL of glycerol and 200 mL of distilled water and it is stirred at 250 rpm by using a magnetic stirring. The important step to be noted in this process is that the mixture should not have any bubble. Then, we boil the mixture for 2 minutes and add 4 grams of sephadex in small quantities at high stirring speed. The result is poured into a prepared silicone mold and cooled to 40°C. These tumor tissues can be stored for 1 week for future use.

Figure 5 Tumor tissue manufacturing procedure

The synthesis of liver parenchyma is started by hot magnetic stirring of 1,000 grams of candle gel on a hot plate until it reaches 80°-90° C and melts. Then 4.2 grams of sephadex in small quantities at high stirring speed is added and the mixture is placed in vacuum drying oven at 80-90 °C for 2-12 hours to remove air bubbles. After stirring at 250 rpm for 1 minute, it can be stored in congealed form for months. The material must be reheated until it melts again before using it.

Figure 6 Tissue mold (left) and phantom liver tissue model (right)

Finally, liver parenchyma in liquid form is mixed with tumor tissues to have the phantom liver. First the parenchyma as a layer is poured on the bottom of the tissue mold, which is manufactured using a 3D printer. It is then placed in the refrigerator at 4 °C for 15 minutes. Next two agarose gel tumors are placed onto the first layer of parenchyma. Additional layers of parenchyma 0.2 cm thickness each are successively poured to the top of the mold, each time placing the mold inside the refrigerator for 15 minutes.

4. CHARACTERIZATION THROUGH EXPERIMENTS

4.1 UV Spectroscopy Experiment

Two samples with different volume concentrations were synthesized and then UV spectroscopy was utilized to find the absorbance coefficient of the samples. The purpose of performing such an experiment is to find the wavelength in which the maximum absorbance happens. Then, this wavelength was used to set the frequency of the laser beam in the photothermal experiment. The the following, sample A has a higher volume concentration of nanoparticles than sample B. Figure 7(a) shows the experimental setup and figure 7(c) shows the absorbance for both samples. The spectrometer is a miniature spectrometer preconfigured for general UV-Vis measurements from 200-850 nm manufactured by Ocean Optics Co. It has a signal to noise ratio of 300:1 and the optical resolution of 1.5-2.3 nm FWHM (Full width at half maximum).

Figure 7 (a) UV Spectroscopy experimental setup (b) Schematic diagram of the experiment (c) absorbance of two different samples with different particle concentrations

From figure 7(c), one can notice that the maximum absorbance for these samples happen to be around the wavelength of 500~550 nm. Therefore, to heat up these samples and measure the maximum temperature, the efficient way is to set our high-power pulsed laser frequency close to this wavelength range. A frequency doubled Nd:YAG (532 nm wavelength) or Nd:YLF 527 nm wavelength) laser is ideally suited for such experiments.

4.2 Photothermal Experiment

One of the purpose of synthesizing these nanoparticles is to be used as practical medicines for hyperthermia. We performed an experiment to investigate the light-induced thermal feature of the synthesized nanoparticles for killing cancer cells. So as to study the temperature increment of the SPIO-Gold nanoparticles induced by irradiation, a high-power Nd:YLF pulsed laser beam with a wavelength of 527 nm was chosen, as it overlaps well with the absorption peak found by UV spectroscopy (Figure 7). The laser has a pulse duration of 200 ns, pulse energy adjustable from 0-30 mJ, and a pulse repetition rate ranging from single shot 3,000 Hz. Samples were laser heating while the temperature was measured over the time.

Figure 8 (a) Photothermal experiment setup (b) Schematic diagram of the experiment and (c) Temperature elevation for samples with different particle concentrations

The temperature increase versus time is shown in Figure 8. Sample A is seen to exhibit a larger temperature increase, since it has a higher volume concentration of nanoparticles than sample B. The temperature for Sample A reaches 45°C in about 10 minutes. This temperature is high enough to kill cancer cells, but does not substantially affect other cells of the body.

5. CONCLUSIONS AND REMARKS

A multilayered and multipurpose SPIO-Gold nanoshell was numerically modeled, synthesized and experimentally studied to explore its structure and characteristics in terms of light absorption and temperature elevation, when it is under the influence of an incident laser beam. A multimodal phantom of liver was synthesized separately to have a custom-

fitted environment for the further experiments of the synthesized nanoparticle-based drugs. First, a numerical procedure was explained to model the nanoparticle with two layers, having silica as the core and gold as the coating layer. Then, SPIO-Gold nanoshell synthesis process was demonstrated along with TEM images of the final nanostructure. After explaining the phantom liver synthesis procedure, UV-spectroscopy and photothermal experiments were performed to analyze and characterize the resulting synthesized samples. Two different samples with different volume concentrations of nanoparticles were investigated. Their absorbance properties were measured, then the samples were exposed to light from a Nd:YLF laser at 527 nm, and the sample temperature recorded as a function of time. As expected, the sample with the higher concentration of nanoparticles resulting in a faster heating rate. For the future work, these samples will be used and injected into the synthesized tumor tissues residing inside the phantom of liver. Then, the phantom containing nanosamples will be studied by using an MRI machine to investigate the magnetic properties as well as explore the possibility of magnetic guidance to reach to tumor sites. In sum a method to synthesize a multilayer nanostructure so as to provide a basis for further synthesizing a semi-hollow nanostructure for drug delivery has been presented. The semi-hollow nanostructure can be synthesized from the current nanosamples by an etching process and the final structure has the advantages of hyperthermia use and magnetic guidance possibility as well as a high-capacity drug delivery mechanism, due to the hollow portion of the particle that enables the structure to carry drugs inside the body and then release the drug in the vicinity of the tumor.

ACKNOWLEDGMENT

The authors would like to express their gratitude towards Emma Dong and Phil Smith from Stony Brook University for assisting Nanoparticle synthesis. Research carried out in part at the Center for Functional Nanomaterials, Brookhaven National Laboratory, which is supported by the U.S. Department of Energy, Office of Basic Energy Sciences, under Contract No. DE-SC0012704.

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