



Structured superparamagnetic nanoparticles for high performance mediator of magnetic fluid hyperthermia: Synthesis, colloidal stability and biocompatibility evaluation

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ABSTRACT

Core-shell structures with magnetic core and metal/polymer shell provide a new opportunity for constructing highly efficient mediator for magnetic fluid hyperthermia. Herein, a facile method is described for the synthesis of superparamagnetic LSMO@Pluronic F127 core-shell nanoparticles. Initially, the surface of the LSMO nanoparticles is functionalized with oleic acid and the polymeric shell formation is achieved through hydrophobic interactions with oleic acid. Each step is optimized to get good dispersion and less aggregation. This methodology results into core-shell formation, of average diameter less than 40 nm, which was stable under physiological conditions. After making a core-shell formulation, a significant increase of specific absorption rate (up to 300%) has been achieved with variation of the magnetization (<20%). Furthermore, this high heating capacity can be maintained in various simulated physiological conditions. The observed specific absorption rate is almost higher than Fe₃O₄. MTT assay is used to evaluate the toxicity of bare and core-shell MNPs. The mechanism of cell death by necrosis and apoptosis is studied with sequential staining of acridine orange and ethidium bromide using fluorescence and confocal microscopy. The present work reports a facile method for the synthesis of core-shell structure which significantly improves SAR and biocompatibility of bare LSMO MNPs, indicating potential application for hyperthermia.

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1. Introduction

Magnetic nanoparticles (MNPs) dispersed in fluid and heated by an alternating magnetic field could be used to treat cancers, in combination with either radiotherapy or chemotherapy or alone [1–3]. The conversion of electromagnetic energy into heat by MNPs has great potential for killing cancer cells by localized heating. By targeting the MNPs at the tumor site with an applied magnetic field (AMF), the temperature at the tumor sites can be increased to 42–46 °C. The increased temperature is responsible for the reduction of viability of cancer cells [4,5]. The transformation of magnetic energy into heat by MNPs is generally measured in terms of specific absorption rate (SAR), which is defined as the rate at which electromagnetic energy is absorbed by a unit mass of a magnetic material. For hyperthermia applications, it is desirable to have higher temperature enhancement rates, i.e. higher SAR by MNPs.

In recent years, there has been a growing interest in the development of La_{1-x}Sr_xMnO₃ (LSMO) MNPs for hyperthermia [6–9]. The increasing attention of LSMO MNPs is due to their tunable Curie temperature (T_c), biocompatibility and superparamagnetic nature. The La_{1-x}Sr_xMnO₃ compounds show wide range of ferromagnetic–paramagnetic transition temperature T_c from 283 to 370 K whereas Fe₃O₄ (ferrites) has T_c ~823 K (550 °C) [5], which is much greater than the therapeutic hyperthermia temperature, but their nanosized particles can have large magnetic moment (50–60 emu/g) and zero coercivity (H_c = 0 Oe) at room temperature. The values of T_c and magnetic moment of the LSMO material are dependent on the compositions of La and Sr. Among the series of LSMO compounds the La_{0.7}Sr_{0.3}MnO₃ shows the highest magnetic moment at room temperature and the transition temperature ~370 K. Hence, it is suitable for magnetic hyperthermia treatment among all doping concentrations.

The use of MNPs for hyperthermia applications in vivo must address issues such as dispersion stability in aqueous and physiological medium, biocompatibility with cells and SAR as high as possible. To meet these challenges surface coating of MNPs with polymer or other organic molecules is necessary for their successful applications in the biomedical

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field. Coating can prevent the leaching of toxic ions and formation of leachable oxide layers of MNPs with surrounding medium during in vivo applications [10]. Additionally, surface coating also provides the option of tailoring the MNP surface with a biological ligand that has the ability to react with certain cell of interest. Capping the surface of MNPs would change their intrinsic physico-chemical properties, like surface functionality, charge, reactivity and dimensions, making them more stable and suitable for in vivo applications. The studies on surface coating of LSMO MNPs need to be evaluated for their safe use in the biomedical field. Very few researchers have used different coatings on LSMO MNPs for improving the biocompatibility of LSMO including SiO_2 [9], citrate ligands [11], dextran [12] and polyethylene oxide [13].

In the present study, we have developed an innovative MNP formulation that consists of an LSMO magnetic core, which is coated with oleic acid (OA) and then stabilized with a block copolymer Pluronic F127 (PF127) to form a polymeric shell, rendering the formulation dispersible in water. This type of formulation on iron oxide MNPs has been extensively studied for biomedical applications [18]. OA plays a dual role in the present case. First it reduces the aggregation of LSMO MNPs and secondly it successfully makes strong binding of PF127 with LSMO MNPs. Oleic acid (OA) is a surfactant that is commonly used to stabilize the MNPs synthesized by different methods. PF127 polymer is approved for food additives, pharmaceutical ingredients, drug delivery carriers and agricultural products by FDA and EPA [14]. PF127 is ABA-type triblock copolymer, in which two A chains consist of hydrophilic polyethylene oxide (PEO) and one B chain of hydrophobic polypropylene oxide (PPO). In this paper, we report OA–PF127 coating on LSMO surface by multistep process. In the first part, optimization of single layer OA content on MNP surface to control aggregation of MNPs is done. The optimized OA coated LSMO sample is used for further PF127 coating. In the second part optimization of PF127 content on OA–LSMO formulation has been done by FESEM, DLS, zeta potential and FTIR techniques. The optimized PF127–LSMO sample is further used for hyperthermia study. The colloidal stability of optimized hyperthermia agents has been examined in phosphate buffer solution (PBS). The effect of ionic strength on colloidal and hyperthermia properties of optimized PF127–LSMO is studied. The biocompatibility of the optimized PF127–LSMO sample is evaluated on L929 cell by MTT assay. The goal of this study is to gain insight into colloidal stability and surface coating on the effect on SAR of LSMO MNPs. In continuation with this we provide a general strategy to optimize the surface coating of LSMO MNPs for high performance hyperthermia agent.

2. Experimental

2.1. Synthesis of LSMO nanoparticles

The perovskite type $\text{La}_{0.7}\text{Sr}_{0.3}\text{MnO}_3$ (LSMO) MNPs have been prepared by the solution combustion method in which polyvinyl alcohol (PVA) is used as fuel. The advantage of combustion synthesis with PVA as fuel in the biomedical field has been studied well in our recent publication [19].

2.2. Formulations of surface coated LSMO MNPs

Formulations of LSMO MNPs were developed, first optimizing the amount of OA required to form single layer OA coating on MNP surface and then by optimizing the amount of PF127 required to form an aqueous dispersion of OA-coated LSMO MNPs. The synthesis of the OA coated MNPs was performed through a procedure reported elsewhere with modification [20]. The MNPs (100 mg) were dispersed in methanol (100 mL) by sonication for 20 min. During sonication different weight ratios of OA to LSMO MNPs (5, 10, 15 and 20%) are added into the solution. The solution was then heated below the boiling point of methanol ($\sim 80^\circ\text{C}$) with vigorous stirring up to complete removal of methanol

and then cooled to room temperature. The solution was washed with water three times and the particles were collected by filtration. The filtered particles are again redispersed in acetone to remove the excess oleic acid, and the final particles were collected by magnetic decantation. The prepared OA coated LSMO MNPs are dispersed in hexane to identify the OA coating. At each concentration of OA, particle size distribution of OA coated MNPs is measured by dynamic light scattering (DLS) and initially the sample is optimized on the basis of obtained results. The optimized sample is used for further PF127 coating.

In the second step optimization of Pluronic F127 coating on OA coated LSMO MNPs was done. Different amounts of PF127, i.e. 10, 20 and 30% (corresponding to total weight of OA coated LSMO MNPs) are made in Milli-Q water. Optimized sample of OA coated LSMO MNPs is added into the aqueous solutions of PF127. Initially, to disperse OA capped MNPs, the solution is ultrasonicated with light shaking, after well dispersion of OA coated MNPs in solution, the solution is stirred for 48 h in a closed container. After stirring, the particles were separated by ultracentrifugation at 10,000 rpm for 20 min, the supernatant was discarded and the sediment was washed by Milli-Q water three times. The sample prepared with 10, 20 and 30% of PF127 is named as A, B and C respectively and used for further characterizations.

2.3. Characterizations

2.3.1. Physical characterizations

X-ray diffraction (XRD) patterns were recorded to study the structural and phase analysis by Philips PW-3710 diffractometer using $\text{Cu K}\alpha$ radiation in the 2θ range from 20 to 80° . The XRD patterns were evaluated by X'pert HighScore software and compared with JCPDS card (file no. 00-040-1100 and reference code: 00-051-0409). Thermal decomposition behavior of the OA coated and OA–PF127 coated precursors was studied on a DuPont 2100 thermal analyzer on 6–7 mg samples in nitrogen with a scanning rate of $10^\circ\text{C min}^{-1}$. The Fourier Transform Infrared spectroscopy (FTIR) measurements were carried out on a Perkin-Elmer spectrometer (model no. 783, USA) in the range 400 to 4000 cm^{-1} . More distinct surface morphology and particle size have been observed by Field Emission-Scanning Electron Microscopes (FESEM-Model JSM-7600F). The particle size and shape were determined by Transmission Electron Microscopy (TEM, Philips CM200 model, operating voltage 20–200 kV, resolution $2.4\text{ \AA}$). The magnetization measurements were performed on a Quantum Design SQUID magnetometer to investigate the saturation magnetization (M_s), blocking temperature (T_B) and Curie temperature (T_C). The measurements include (i) zero-field cooling (ZFC) and field cooling (FC), which were taken in the range of 5 to 375 K at applied magnetic field of 500 Oe and (ii) field dependent hysteresis loops ($M-H$) at two different temperatures 5 and 300 K with applied field range from 0 to $\pm 2 \times 10^4$ Oe (2 T).

2.3.2. DLS and zeta potential measurements

Zeta potential and dynamic light scattering (DLS) measurements were performed by using a PSS-NICOMP-380 ZLS (USA) particle sizing system. Measurements taken in water as well as in PBS, HCl and NaOH are used to tune the pH of water from 1 to 12. The effect of ionic strength on zeta potential and particle size distribution of PF127 coated MNPs was also studied. For that different weight % NaCl solutions are made and measurements were taken. The reported zeta potential values are an average of three measurements, each of which was obtained over 30 electrode cycles.

2.3.3. Magnetic fluid hyperthermia

Induction heating of LSMO MNPs for hyperthermia application was performed in plastic microcentrifuge tube (1.5 mL) by using an induction heating unit (Easy Heat 8310, Ambrell, UK) with 6 cm diameter (4 turns) heating coil. A provision of water circulation in the coil was made to keep the temperature of the coil at ambient temperature.

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