Journal of Alloys and Compounds 746 (2018) 626–637

Contents lists available at ScienceDirect

Journal of Alloys and Compounds

journal homepage: http://www.elsevier.com/locate/jalcom

Evaluation of $La_{0.7}Sr_{0.3}Mn_{1-x}B_xO_3$ (B=Mo, Ti) nanoparticles synthesized via GNP method for self-controlled hyperthermia

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A R T I C L E I N F O

Article history:
Received 14 November 2017
Received in revised form
25 February 2018
Accepted 26 February 2018
Available online 1 March 2018

Keywords:
Nanoparticles
Magnetic properties
Hyperthermia

A B S T R A C T

This current work deals with the study of the magnetic and biomedical characterization of $La_{0.7}Sr_{0.3}Mn_{1-x}B_xO_3$ (B=Mo, Ti) nanoparticles for hyperthermia applications. Our nanoparticles were prepared through an aqueous combustion process (Glycine Nitrate Process, GNP), and are characterized with a mean crystallite size about 18 nm.

The incorporation of Ti^{4+} and Mo^{6+} in Mn-site induced a structural transition from rhombohedral structure with R-3 C space group for $La_{0.7}Sr_{0.3}MnO_3$ compound to orthorhombic one with *Pnma* space group for $La_{0.7}Sr_{0.3}Mn_{0.95}Mo_{0.05}O_3$ and $La_{0.7}Sr_{0.3}Mn_{0.95}Ti_{0.05}O_3$ compounds. The morphological properties indicated a variation in grain size ranging from 82 to 90 nm with doping extra element in manganese site. All samples exhibit a classical behavior from ferromagnetic (FM) to paramagnetic (PM) state as the temperature increases. A decrease in Curie temperature (T_C) has been remarked from 84 °C to 70 °C and 82 °C for $La_{0.7}Sr_{0.3}MnO_3$, $La_{0.7}Sr_{0.3}Mn_{0.95}Ti_{0.05}O_3$, $La_{0.7}Sr_{0.3}Mn_{0.95}Mo_{0.05}O_3$ respectively. According to the Arrott plots, the slopes of the curves of all the samples are positive, which is a signature of second order transition.

The magnetic heating characteristics in AC field were measured in alternating magnetic fields of 23.89 mT at a fixed frequency of 518.7 kHz. The intrinsic loss power (ILP) has been calculated from SAR values. The different nanoparticles with a high ILP may be useful for the in situ hyperthermia treatment of cancer cells.

1. Introduction

The cancer is still one of the biggest challenges facing the medical research in our time [1]. It is considered as a difficult disease to be treated due to the fact that the available treatment options are limited and, in many cases, the timely diagnosis and the lack of prognosis are difficult. Moreover, the approaches usually used for cancer treatment such as surgery, radiotherapy and chemotherapy present considerable harmful side effects. In this context, a lot of effort has been devoted to find novel approaches for both diagnosis and therapy [2].

Hyperthermia is a therapeutic method for cancer treatment; the term “hyperthermia” is derived from two Greek words, “hyper” and “therme,” meaning “rise” and “heat,” respectively [3]. Busch et al. [4] have reported that cancer cells are sensitive to high temperatures; the growth of these cells can be destroyed at temperatures ranging from 41 °C to 47 °C for at least 20 min to 60 min [5,6].

The hyperthermia treatment includes a list of steps, firstly the magnetic nanoparticles (MNPs) have to be injected into the human body, and once the MNPs are disseminated inside the tumor, then an external AC magnetic field is applied, and the nanoparticles

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https://doi.org/10.1016/j.jallcom.2018.02.302
0925-8388/

transform the electromagnetic radiation into heat [7]. Finally, the generated heat rises the temperature in the tumor area and, in this way, damages or even kills and eradicates cancerous cells with minimally affecting the healthy ones, since healthy cells has a better resistance to high temperature than cancer cells [8,9]. In this manner, the patient can receive a localized and highly efficient cancer therapy, without suffering from the treatments of chemotherapy or radiotherapy.

Another mechanism of heating, which is different from the local magnetic hyperthermia effect, is the magnetocaloric effect (MCE) [10,11].

At the present time, the main research activity in the field of MCE and magnetocaloric materials is directed to magnetic refrigeration. However we try to use another perspective application of these materials in the field of medicine. The MCE occurs as the result of the alignment of magnetic moments with an external applied magnetic field. The alignment reduces the magnetic randomness, or the magnetic component of the total entropy. This reduction of magnetic entropy must be compensated by the increase of another form of entropy and, in the case of magnetocaloric materials, is channeled into phonons, or heat. Since the mechanism of heating in this case is different from that of the conventional magnetic hyperthermia, it is named as "magnetocaloric hyperthermia" [12]. There are three quantities that are usually reported for MCE: the magnetic entropy change (ΔS_M), the refrigeration capacity (RC), and the adiabatic temperature change (ΔT). For a thermodynamic Carnot cycle, the energy observed in one cycle in a magnetocaloric material is calculated as [13,14]: $\Delta Q = \Delta T \cdot \Delta S_M$

Thus, the magnetocaloric contribution to heating in this type of hyperthermia is significant for a material with large MCE parameters.

Magnetic losses in magnetically ordered ferro- and ferrimagnetic materials have a number of advantages as they diminish at the Curie temperature (T_C). As a result, magnetic hyperthermia treatments could be free from external temperature control when T_C is tuned to the therapeutic temperature range. In order to prevent the overheating of normal cells, the development of magnetic materials which are not affected by alternating magnetic field above 318 K (45 °C) has become essential.

In literature, different MNPs have been reported for magnetic fluid hyperthermia, bio-separations and magnetic resonance imaging including superparamagnetic iron oxides [15] and ferrites of manganese, cobalt, nickel and zinc, etc. [16].

In this field researchers are mainly interested in iron oxides thanks to their low toxicity, however such compounds are limited as application in hyperthermia because they do no exhibit specific physical properties and it is difficult to adjust their properties. Recently, ferrite core-based magnetic nanoparticles are being used for clinical cancer treatment (MagForce Nanotechnologies AG, Berlin, Germany) with a magnetic field strength of up to 0.0225 T at 100 kHz, in combination with radiotherapy, inducing an increase in the median survival time of the patients, but unfortunately no full recovery has been achieved yet [17].

To overcome this challenge, magnetic nanoparticles with perovskite structure were suggested thanks to the ability to control their physical properties and to tune their temperature transition in the desired temperature range. This is due to the fact that this kind of magnetic material provides more heating in the ferromagnetic state (below T_C) and less heating in the paramagnetic state (above T_C). Thus the Curie temperature acts as a temperature control switch and maintains a constant desired temperature in the tumor region.

Strontium doped lanthanum manganite ($La_{1-x}Sr_xMnO_3$) nanoparticles are one of the best candidates for self-controlled hyperthermia applications. Their magnetization is higher than that of most materials for such applications and their Curie temperature can be tuned to be in the range 41.85–46.85 °C (315–320 K) [18].

To underline the fascinating properties of such ferromagnetic material, in physical point of view, the incorporation of atoms into the manganese site of $La_{0.7}Sr_{0.3}MnO_3$ can destroy the long range interaction. Different effects can be produced upon Mn-site doping in ferromagnetic manganites. As reported in the literature, the substitution effect of Mn cations by non-magnetic ions such as Al, Ti, Ga, Sc and Ta [19,20], generally destroys the double exchange ferromagnetism in the samples, leading to a steady decrease of T_C.

The dependence of the physical and chemical properties of magnetic materials on the shape, size of nanoparticles and the thermal history of sample preparation have always motivated the study of new synthetic routes to produce these materials. This is a key factor since the effective morphology, the chemical composition and the grain size distribution deeply affect the physicochemical properties of the materials [21]. Hence the synthesis, sintering, and characterization of the nanoparticles have become a vital part of ceramic research. Particularly, the synthesis of oxides with perovskite crystal structure requires high temperature (≥700 °C). This creates difficulties in terms of shape and individual properties of particles [22]. As a result, soft chemical methods of synthesis will offer some advantages in this regard, in particular the Glycine nitrate process (GNP) 'auto-combustion' presents a considerable asset in comparison with other conventional methods. In fact, it is a low-temperature initiated exothermic and self-propagating process. Combustion reaction is a vigorous exothermic redox reaction between a suitable fuel, which also acts as a complexing agent and an oxidizer. The GNP has the advantage of high temperatures, fast heating rates and short reaction times, thus inhibiting particle size growth and promoting the formation of homogeneous, crystalline nanopowders.

The main goal of this current work is to study the magnetic and biomedical characterization of magnetic nanoparticles for hyperthermia applications of the molybdenum and titanium substitution on manganese site of $La_{0.7}Sr_{0.3}MnO_3$ (LSMO), $La_{0.7}Sr_{0.3}Mn_{0.95}Ti_{0.05}O_3$ (LSM-Ti-O), $La_{0.7}Sr_{0.3}Mn_{0.95}Mo_{0.05}O_3$ (LSM-Mo-O) nanoparticles prepared via auto-combustion process.

The parent compound LSMO exhibits a ferromagnetic-paramagnetic transition with a value of T_C about 357 K. We used (Ti^{4+}) and (Mo^{6+}) ions to partially substitute the manganese site. We expected a decrease of T_C in order to be able to destroy the affected cells by tumor, as a regard to the ionic radius r $\langle Mn^{4+}\rangle = 0.53$ Å and r $\langle Ti^{4+}\rangle = 0.605$ Å. The titanium ion exhibits a valence state (Ti^{4+}). The choice of Ti^{4+} is based on the fact that the substitution of Mn^{4+} reduces the ratio of the Mn^{4+}/Mn^{3+} ions, so the double exchange interactions will be affected. The complete substitution of Mn^{4+} by Ti^{4+} excludes the double exchange interactions Mn^{3+}-O-Mn^{4+} since the 4s state of Ti^{4+} is inaccessible to the conduction electrons due to its low spatial occupation. As a consequence, the Ti^{4+} ions become a site of high dispersion, known as magnetic dilution of the lattice. Among all the substitutions of the Mn site, the Mo effect was considered to be particularly interesting because of its high valence state (Mo^{6+}) and its electronic configuration d^0. Even the slight amount of Mo is expected to induce a large variation in the valence of Mn, since molybdenum (Mo) can exist with different states of valency and may also induce different valences of Mn.

2. Experimental techniques

2.1. Combustion synthesis

$La_{0.7}Sr_{0.3}Mn_{1-x}B_xO_3$ (B=Mo, Ti) (B=Ti and Mo; x = 0.00 and 0.05) samples have been synthesized by the autocombustion