

3-2006

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## Recommended Citation

Uskoković, V., Košak, A., Drogenik, M. and Drogenik, M. (2006), Preparation of Silica-Coated Lanthanum–Strontium Manganite Particles with Designable Curie Point, for Application in Hyperthermia Treatments. *International Journal of Applied Ceramic Technology*, 3: 134–143. doi:10.1111/j.1744-7402.2006.02065.x

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Uskoković, V., Košak, A., Drofenik, M. and Drofenik, M. (2006), Preparation of Silica-Coated Lanthanum–Strontium Manganite Particles with Designable Curie Point, for Application in Hyperthermia Treatments. *International Journal of Applied Ceramic Technology*, 3: 134–143.

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# Preparation of Silica-Coated Lanthanum-Strontium Manganite Particles with Designable Curie Point, for Application in Hyperthermia Treatments

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## Abstract

Silica-coated lanthanum-strontium manganite particles with  $\text{La}_{0.76}\text{Sr}_{0.24}\text{MnO}_{3+\delta}$  stoichiometric formula, exhibiting Curie temperature at  $\sim 40$  °C, were prepared by performing a traditional solid-state method of synthesis of magnetic ceramic particles, followed by milling and low-temperature coating procedure in aqueous-alcoholic alkali medium. The properties of the obtained material establish it as a potential candidate for self-regulated power-absorbing and temperature-controlling materials in hyperthermia treatments. Moreover, core-comprising LaSr-manganites with different stoichiometries, ranging from  $\text{La}_{0.5}\text{Sr}_{0.5}\text{MnO}_{3+\delta}$  to  $\text{LaMnO}_{3+\delta}$ , were synthesized, with magnetic and structural properties thereof examined. Herein reported findings can potentially be employed in the preparation of silica-coated magnetic particles with designable Curie temperature, offering wide range of adapting possibilities of the material to practical instrumental setups in drug delivery and hyperthermia treatments.

## Introduction

Researches related to the development of novel biomedical technologies involving *in vivo* use of magnetic nanoparticles, present relatively young and multidisciplinary attempts to overcome the major chemotherapeutic drawback related to its spatial non-specificity and, in general, to apply the knowledge of science for the medical improvements of life quality<sup>1,2</sup>. Since the interrelation of many apparently separated fields of scientific inquiry (physics, chemistry, biophysical chemistry, molecular biology, medicine, and the sub-branches thereof) becomes an essential precondition for comprehensive and successful researches of this kind, an inter- or even trans-disciplinarity of research methodologies is here clearly called for.

Magnetic particles are today commonly used in biomedicine for MRI contrast enhancement, hyperthermia treatments, drug delivery and targeting<sup>1-3</sup>, magnetic separation, protein detection and purification<sup>4</sup>, magnetic-field-assisted radionuclide therapy<sup>5</sup>, magnetorelaxometrical diagnostics and eye surgery<sup>5</sup>, and the detection of intracellular molecular interactions<sup>6</sup> with the potential of developing gene and/or cellular metabolic therapy<sup>7</sup> in the near future. Since the aim of this work has been the preparation of silica-coated LaSr-manganite with particle sizes within the order of magnitude of 0.1  $\mu\text{m}$ , we will briefly explain the desired: a.) chemical composition, b.) particle size, and c.) coating material in the presented procedure of synthesis.

a.) LaSr-manganite particles, produced by herein presented method, with Curie point ( $T_c$ ) existing in human hyperthermal range, offer numerous possibilities for application in the fields of biology and medicine. For instance, bloodstream injection of the magnetic particles with certain drugs (that could even be water-insoluble or unstable in physiological conditions) attached to their biocompatible surfaces, with providing the release of drugs at a specific site by means of an alternating external magnetic field, might be one way. The other way may be to force the distributed drug-carrying particles to release drugs by essentially the same, heating mechanism, but by involving appropriate local and manually performed temperature increases, probably in the close areas of unhealthy, infected or malignant tissues. Significant magnetoresistance effects of manganites - similarly as large magnetocaloric effects - typically observed in the immediate vicinity of the Curie point of the material<sup>8-11</sup>, and potentially evoking eddy currents as part of the heating mechanism, might be employed in the addition to the ordinary,  $T_c$ -limiting production of controlled heat effects by means of an alternating external magnetic field, with the aim of selective warming of the given areas of an organism. In general, particles that switch certain inherent properties “on/off” in relation to relatively simple parameter of temperature, might open possibilities for many potential designs of biomedical apparatus and useful applications thereof. Although manganites have not been used yet in hyperthermia or any other biomedical treatments, many different materials, exhibiting relatively low  $T_c$ , including Cu-Ni<sup>12,13</sup>, Pd-Ni<sup>14,15</sup>, Fe-Pt<sup>16</sup>, Pd-Co<sup>17,18</sup>, and Ni-Si<sup>19</sup> alloys,  $Co_{1-x}Zn_xFe_2O_4$ <sup>20</sup>,  $Y_3Fe_{5-x}Al_xO_{12}$ <sup>20</sup>,  $Fe_{66}P_{13}C_7Cr_{14}$  amorphous flakes<sup>21</sup> and others have been used, albeit in the majority of cases as stationary, interstitial implants.

b.) It has been shown that successful *in vivo* attachment of magnetic particles is - in certain cases of larger entities, such as the cells - not limited to nano-sized particles, but could be even more significant when micron or sub-micron sized magnetic particles are employed<sup>1</sup>, depending largely on the tissue or the organ concerned<sup>22</sup>. Whereas it is said that extracellular maneuvers are limited to particles of less than 50 nm in size<sup>23</sup> (with natural, ferritin particles being 9 nm in diameter and diffusing rapidly through intercellular space<sup>3</sup>), micron-sized particles (wherein, even though the smallest capillaries in the body are 5 – 6  $\mu m$  in diameter<sup>22</sup>, particles as large as 200  $\mu m$  on average were successfully applied<sup>21,24</sup>) are better suited for withstanding the flow dynamics in the circulatory system<sup>1</sup>. Particles of moderate size range ( $\sim 200$  nm)<sup>25</sup>, such as the ones prepared within this work, might therefore be optimally suited for the promotion of *in vivo* drug targeting effects. However, it is important to note that there is no perfect material for drug delivery, but only a potentially perfect compatibility between the host organism, the targeted situation on one side, and the designed biomaterial on the other<sup>26</sup>.

c.) Yet, in order to use magnetic particles for *in vivo* biomedical applications, their surfaces ought to be coated with a given biocompatible and functionalized layer, for several reasons. Coating magnetic particles tends to reduce aggregation and agglomeration of the particles and minimize protein adsorption, which would, otherwise, prevent them from reaching their target. Silica shell, previously prepared within many different systems<sup>27-32</sup>, is also convenient because:<sup>5,23</sup>

- i) unlike polymers, it is not prone to microbial attacks, and does not swell or change porosity in relation to pH changes;

- ii) being chemically inert, it does not affect the redox reactions at the particle surfaces;
- iii) it limits the oxidation of particles surfaces, aging processes and degradation of the coated solid compound into oxides and/or hydroxides of constitutive cations;
- iv) it offers options to covalently bind amino, carboxyl and other functional groups to hydroxyl groups on its surface;<sup>33</sup>
- v) it confers high stability to suspensions of particles at high volume fractions, pH changes or electrolyte concentrations.

All in all, the existence of a  $T_c$ -determined, higher limit of heat production of the magnetic material in an alternating magnetic field of certain intensity, that could potentially overcome the difficulties arising out of the undesired outspreading of extensive heat toward healthy regions of the hyperthermally treated tissues, presents an attractive - although has not been used in medicine practice yet - property of silica-coated manganite particles with relatively low  $T_c$ . Although it has recently been stated that there is currently no suitable magnetic material for the preparation of magnetic fluids with an ideal  $T_c$  for hyperthermia treatments<sup>34</sup>, such biocompatible materials with optimal  $T_c$  required in magnetic fluid hyperthermia treatments (44 – 47 °C) as prepared within this work, that would allow for the auto-regulated power absorption and temperature control in an AC magnetic field, might prove to be of an enormous significance to medical treatments of the future.

## Experimental

Lanthanum-strontium manganite ( $\text{La}_{1-x}\text{Sr}_x\text{MnO}_{3+\delta}$ ) powders with different stoichiometries ( $x = 0, 0.16, 0.24, 0.33, 0.5$ ) were prepared by calcinations (at 1200 °C for 2h in air) of mixtures of  $\text{Mn}_3\text{O}_4$ ,  $\text{La}_2\text{O}_3$  and  $\text{SrCO}_3$ , previously homogenized by milling in a  $\text{YZrO}_2$  planetary ball mill at 300 rpm for 2h. The sample with supposedly optimal  $T_c$ , characterized by its  $x = 0.24$  Sr content in  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_{3+\delta}$  stoichiometric formula, was chosen for further processing. The respective sample was milled under the same conditions as when homogenization had been performed, with and without the addition of NaCl, which was previously proven as an effective dispersing agent<sup>35</sup>. The powder milled for 4h, attaining an average particle size of 100 nm, was subsequently coated with silica by inducing hydrolysis and condensation of tetraethylorthosilicate (TEOS) in the presence of ammonia and 2-propanol. 80 mg of the milled LaSr-manganite powder was, under agitation with a magnetic bar, dispersed in 100 ml of 1.7-M concentrated (25%wt) aqueous ammonia solution in 2-propanol. After the addition of manganite particles in the primary alkali solution, the tightly closed container was thermostated at  $T = 40$  °C for 1 h. When the dispersion reached uniform temperature, TEOS in concentration of 4.5 mmol/l was added in the mixture, with aging continued for 20 h. The resulting solids were separated by performing magnetic decantation, and dried at 70 °C. X-ray diffraction (XRD) analysis (*D4 Endeavor*), magnetic measurements (*Manics DSM10*), specific-surface area measurements (*Micromeritics Gemini II*) and transmission electron microscopy (TEM, *JEOL JEM-2000FX*), were used for the characterization of the prepared, both pure and silica-coated LaSr-manganite powders.

## Results and discussion

XRD patterns of the synthesized  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_{3+\delta}$  samples with  $x = 0$ ,  $x = 0.16$ ,  $x = 0.24$ ,  $x = 0.33$ , and  $x = 0.5$  stoichiometries, are presented in Fig. 1. Pure manganite samples are obtained, albeit at different lowest calcination temperatures:  $1000\text{ }^\circ\text{C}$  in cases of  $x = 0$  and  $x = 0.33$  stoichiometries,  $x = 1100\text{ }^\circ\text{C}$  in cases of  $x = 0.16$  and  $x = 0.24$  stoichiometries, and  $1200\text{ }^\circ\text{C}$  in case of  $x = 0.5$  stoichiometry. The transition from doublet to singlet peaks on the corresponding XRD patterns, observed with the increase in parameter “ $x$ ”, is ascribed to the transition of rhombohedral (hexagonal) ( $R\bar{3}c$  (167) space group) towards pseudo-cubic ( $Pm\bar{3}m$  space group) crystal structure<sup>36,37</sup>.

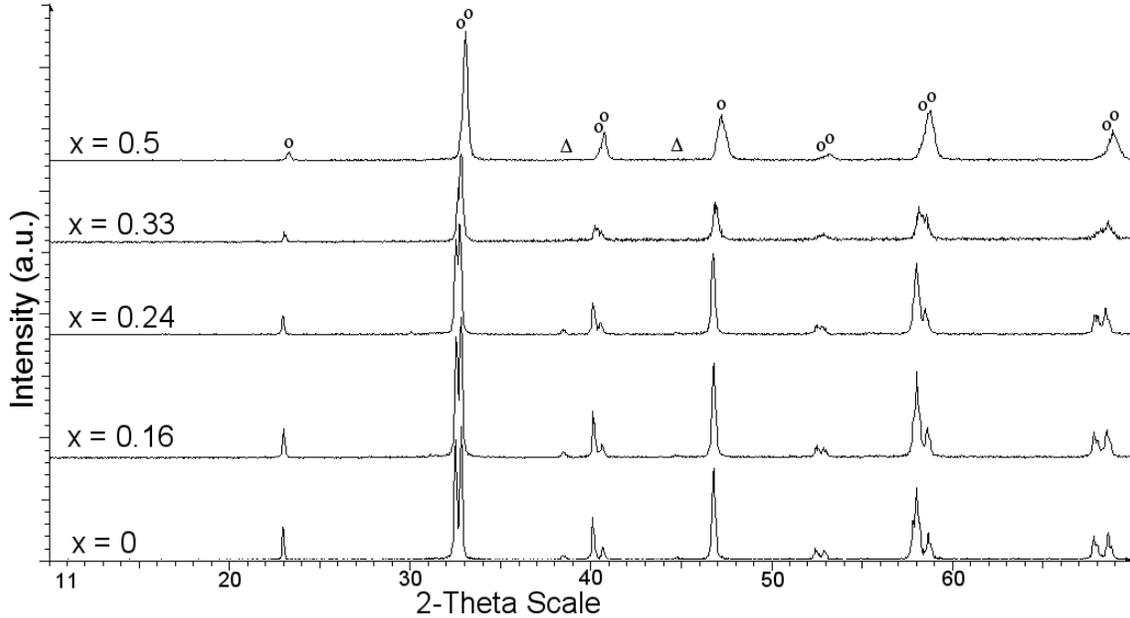


Fig. 1. XRD patterns of the synthesized  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_{3+\delta}$  samples with  $x = 0$ ,  $x = 0.16$ ,  $x = 0.24$ ,  $x = 0.33$ , and  $x = 0.5$  stoichiometries. LaSr-manganite diffraction peaks are denoted with “o”, whereby aluminium reflections from the sample holder are denoted with “ $\Delta$ ”.

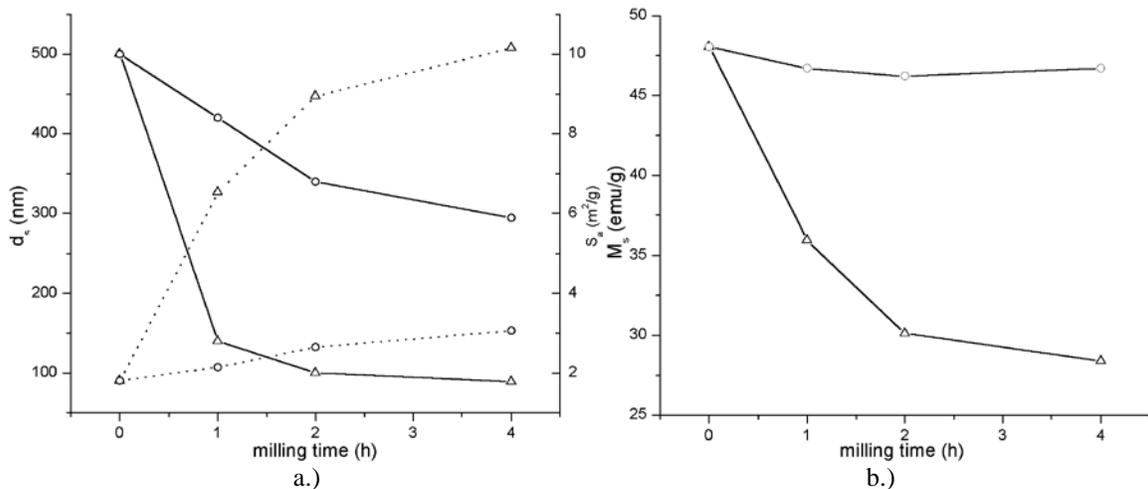


Fig. 2. Specific surface-area (a, -----), average particle size calculated therefrom (a, —), and specific saturation magnetization (b) vs. milling time dependencies for  $x = 0.24$  LaSr-manganite sample, with (-o-) and without (- $\Delta$ -) the addition of NaCl as a dispersing agent.

Increasing specific-surface area and the respective decrease in average particle size, together with the decreasing rate of change in specific-surface area and the average particle size with milling time, are evident from Fig. 2a. Whereas after 1h of milling, average particle size - as calculated from specific-surface area measurements with an approximation of spherical particle shapes and theoretical density of the prepared compound - decreases to ~ 30 % of its initial value, that is from ~ 500 nm to ~ 150 nm, between 1 and 4 h of milling time, average particle size decreases by only ~ 30 %, that is from ~ 150 nm to ~ 100 nm. The dependence of specific saturation magnetization versus milling time follows a similar trend of decreasing rate of decrease in magnetization in relation to milling time - albeit only in the case when milling was performed in the absence of NaCl - as can be seen from Fig. 2b. NaCl is in this case, contrary to its intended function, proven to be effective in retaining initial magnetization values throughout the milling treatment (Fig. 2b), as well as in reducing the number of mechanical contacts that lead to the particles fractures, as can be seen by comparing the the full-lined plots in Fig. 2a.

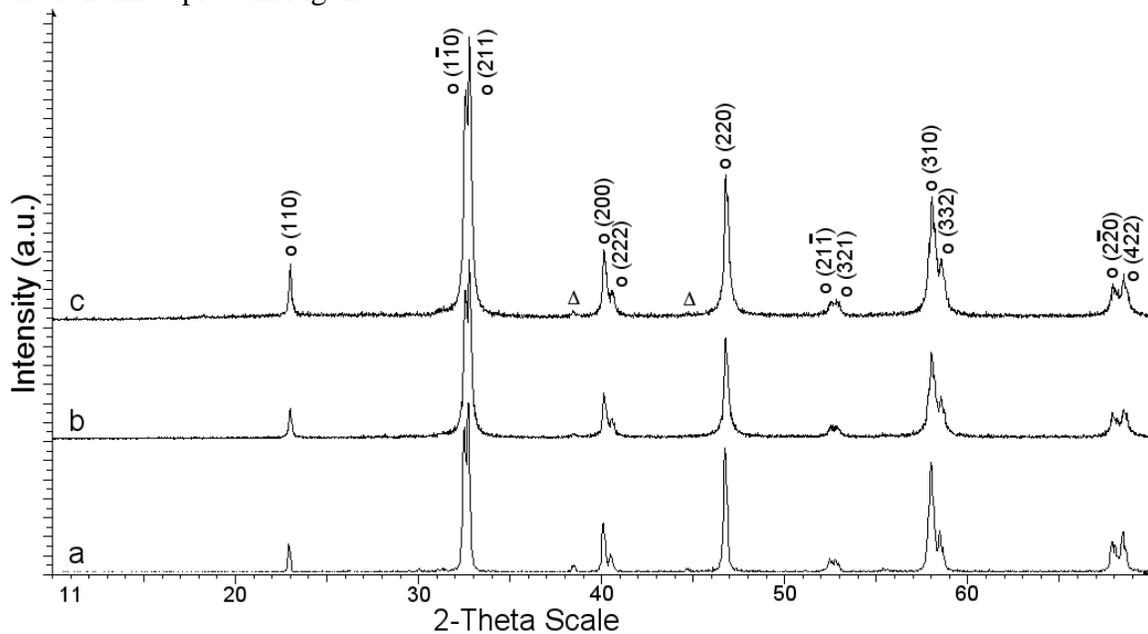


Fig. 3. XRD patterns of LaSr-manganite sample with  $x = 0.24$  stoichiometry (a), of the same sample milled for 4h (b), and of the latter sample coated with silica (c). LaSr-manganite diffraction peaks are denoted with “o”, whereby aluminium reflections from the sample holder are denoted with “ $\Delta$ ”.

X-ray diffractograms of: (a) as-obtained LaSr-manganite sample with  $x = 0.24$  stoichiometry, (b) milled sample of the same stoichiometry and (c) both milled and silica-coated sample of the same stoichiometry, are shown in Fig. 3, wherefrom it is obvious that the initial manganite compound preserves its perovskite crystal structure after milling and coating treatments. The percentage of silica within the coated sample was below the detection limit of the performed XRD analysis, as can be concluded from non-appearance of silica-derived diffraction peaks in Fig. 3c.

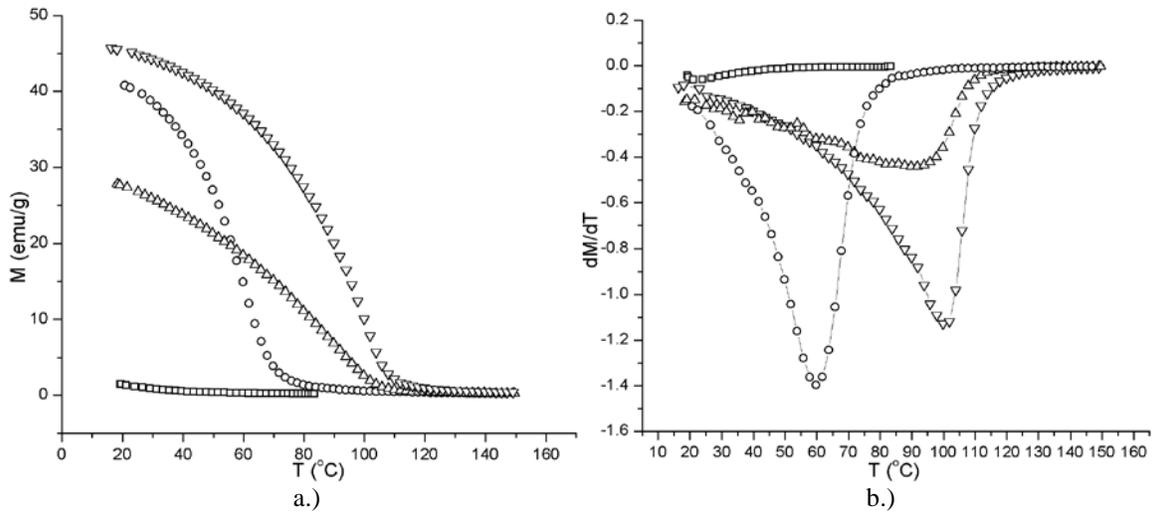


Fig. 4. Specific magnetization at  $H = 0.1$  T (a) and the respective derivatives (b) vs. measuring temperature dependencies for  $x = 0.16$  (□),  $0.24$  (○),  $0.33$  (Δ) and  $0.5$  (▽) samples, all calcined at  $1200$  °C.

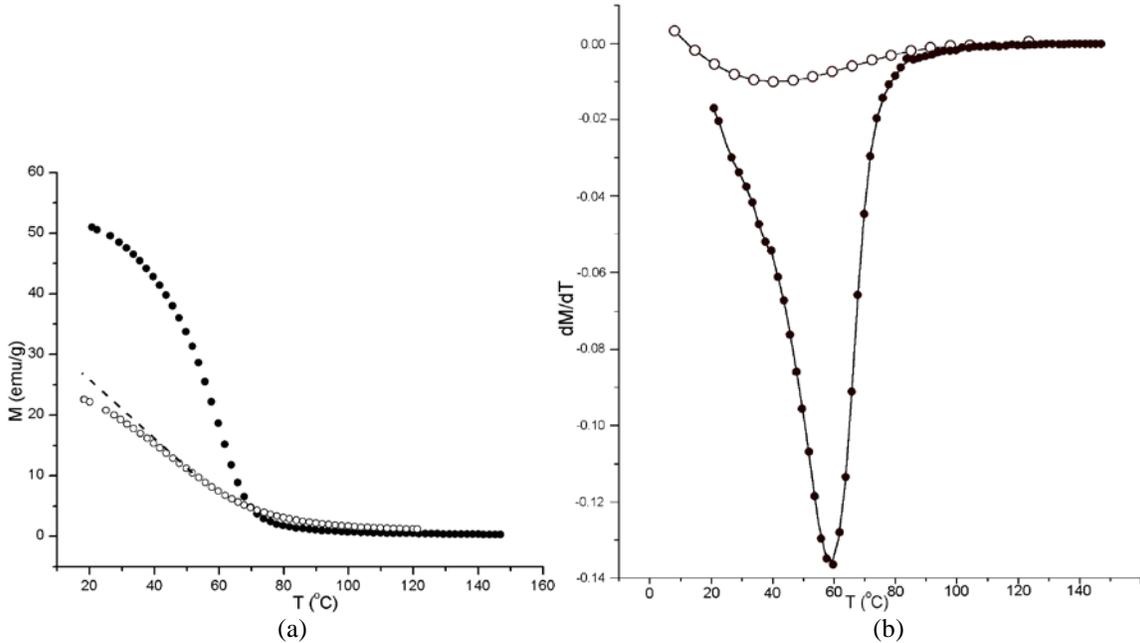


Fig. 5. Specific magnetization at the external field of  $0.5$  T vs. measuring temperature (a) and  $dM/dT$  vs. measuring temperature dependencies (b) of  $x = 0.24$  LaSr-manganite sample (●), and of the same sample, subsequently milled for 4h and coated with silica (○). Dashed line signifies the difference between the milled, silica-coated and non-coated samples.

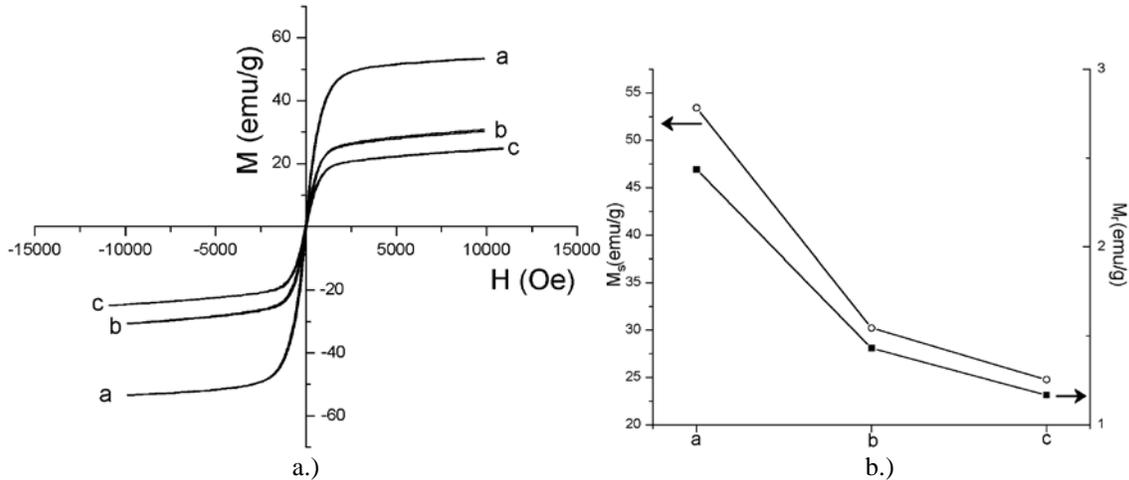


Fig. 6. Hysteresis loops, saturation (-o-) and remanence (-■-) magnetizations of the prepared  $x = 0.24$  LaSr-manganite sample (a), and of the same sample, subsequently milled for 4h (b) and then coated with silica (c).

Specific magnetizations and the respective derivatives vs. measuring temperature dependencies for all the synthesized samples, are presented in Figs. 4 and 5. Hysteresis loops of the synthesized  $x = 0.24$  LaSr-manganite sample, and of the same sample subsequently milled and coated, are presented in Fig. 6a, whereas the corresponding decrease in both magnetization of saturation and remanence with milling and coating treatments, is presented in Fig. 6b. With an increase of parameter “x”, that is of strontium content in LaSr-manganite stoichiometric formula,  $T_c$  determined as  $dM^2/dT^2 = 0$  point in the corresponding  $M = f(T)$  diagram, increases as well (Fig. 4), which is consistent with similar findings from literature<sup>38</sup>. Thus,  $x = 0.16$  sample has  $T_c = 25$  °C,  $x = 0.24$  sample has  $T_c = 60$  °C,  $x = 0.33$  sample has  $T_c = 90$  °C,  $x = 0.5$  sample has  $T_c = 100$  °C, whereby  $x = 0$  sample exhibits  $T_c$  below room temperature.

Acknowledging the observed facts that  $T_c$  decreased when silica or polymer coatings were introduced in the system<sup>12,39</sup>,  $x = 0.24$  sample was chosen for further processing with an aim to obtain  $T_c$  in a typical temperature range used in hyperthermia treatments (42 – 47 °C). This presumption has been indeed observed in reality, and can be evidenced by comparing  $dM/dT$  versus  $T$  dependencies of pure, non-milled and milled, silica-coated  $x = 0.24$  LaSr-manganite samples in Fig. 5b. Whereas the former sample has  $T_c \sim 60$  °C, the silica-coated sample, albeit with less narrow Curie transition, has  $T_c \sim 40$  °C. However, a negligible difference in  $T_c$  between silica-coated and non-coated milled  $x = 0.24$  LaSr-manganite powder (Fig. 6), bears the fact that despite previously evidenced structural modifications of the surrounding-dependent particle surfaces with the addition of silica coatings<sup>40</sup> – with the knowledge of the fact that any chemical modification of the surface alters the magnetic properties of the system – that might potentially influence the Curie point of a sample, the reduction in interparticle and interdomain interactions caused by the milling treatment is in our case seen as the major reason for the observed reduction in  $T_c$  between the as-prepared  $x = 0.24$  LaSr-manganite powder and the same, afterwards milled and coated sample. The most significant influential part in the decrease in saturation magnetization during the coating treatment, obvious from Fig. 6a, belongs to the effect of decreasing average particle size with milling treatment, as was evidenced from Fig. 2, whereby only a small part of  $\sim 20$  % belongs to the weight contribution of

silica coating. That it is weight contribution being most decisive here, is obvious from the close correlation between the decrease slopes of saturation and remanence magnetizations with treatment steps, whereby coercivity remains unchanged throughout the milling and coating procedures, at  $\sim 40$  G.

The relatively low slope of  $M = f(T)$  curve in the range of the Curie transition, might have already stood as an indication of negligible decrease in the limiting temperature of material with the addition of silica component, since it is known that the sharpness of the Curie transition, being the measure of the quality of temperature control, is limited by the asymptote of the power absorption<sup>41</sup>. It can be calculated from Fourier's law that even in case of an infinite thickness of the coated silica layer, the expected decrease in the resulting  $T_c$  would be, due to relatively small, nano-sized cores of the particles and thus small magnitude of energy absorption per particle, in the range of mK. However, as has already been said, the decreases in Curie temperature by  $\sim 30$  K were noticed when the original magnetic particles were encapsulated either with silica<sup>39</sup> or polyethylene glycol<sup>12</sup>.

If  $T_c$  would have been determined by the point of intersection of extrapolated tangents of  $M = f(T)$  curve below and above the critical transition, higher obtained value would not restrict the material from the intended usage. In this context, it is worth noting that ferromagnetic implants (Fe-Pt alloy) with  $T_c \sim 70$  °C were successfully used for preoperative interstitial hyperthermia<sup>42</sup>, as well as that a finite element heat-transfer model (although relatively poor level of experimental correlations with theoretical heating predictions is generally acknowledged in this field<sup>18</sup>) of ferromagnetic thermoseeds and catheters developed for simulating hyperthermia, suggested Curie point of  $\sim 63$  °C as an optimal value over nearly all the analyzed blood perfusion cases<sup>43</sup>. In fact, it is known that due to unsteady vascular and neural structures within malignant tissues, tumors are much more easily heated than healthy tissues, receding at  $\sim 43$  °C, whereas healthy cells - due to better oxygen supply and more developed and flexible both inner, molecular metabolic networks and higher-level organization of multi-cellular networks that incorporate them - can survive much higher temperatures without significant damage<sup>44</sup>. Magnetic thermoblation that uses temperatures of up to 55 °C is therefore sometimes preferred over magnetic hyperthermia that normally involves temperatures of up to 44 °C.<sup>3</sup>

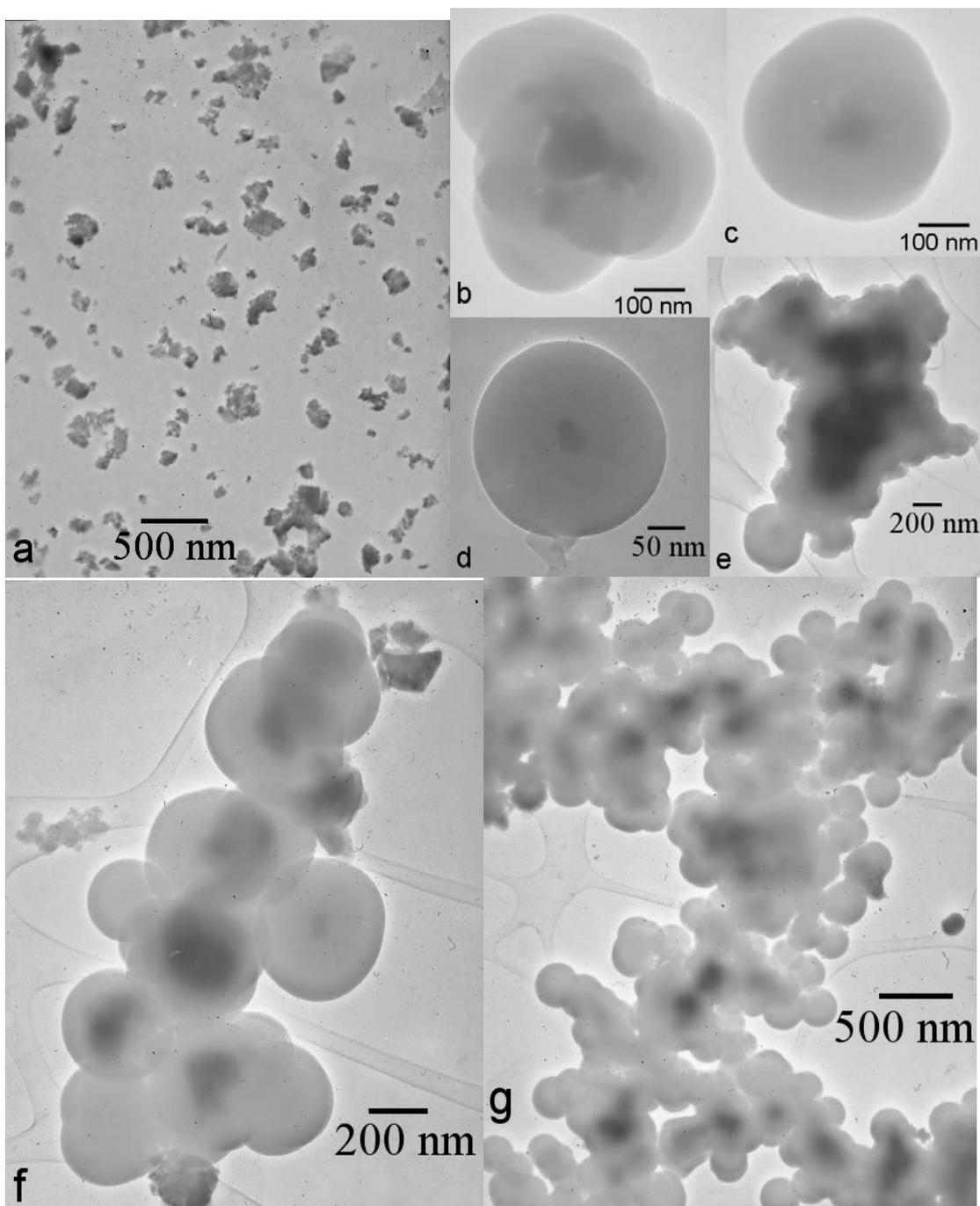


Fig. 7. TEM images of the milled (a) and subsequently coated with silica (b – g), LaSr-manganite sample with  $x = 0.24$  stoichiometry.

From the TEM image of the milled  $x = 0.24$  LaSr-manganite powder, presented in Fig. 7a, finely dispersed particles with relatively wide distribution of sizes, ranging from few tens to few hundreds of nanometers, together with irregular shapes thereof, typical for milling treatments in general, can be discerned. TEM images of silica-coated LaSr-manganite particles are presented in Figs. 7b-g, with darker areas within the particle images indicating the presence of manganite phase and lighter spherical contours

belonging to silica coatings. Manganite cores of the particles in the size range of 20 – 100 nm, consistent with the results obtained from specific-surface area measurements, are visible on the corresponding images, whereby spherical silica coatings possess radii of ~ 120 nm, with narrow, almost monodisperse distribution of sizes thereof. Single and few overlapping silica-encapsulated LaSr-manganite particles are presented in Figs. 7c,d and Fig. 7b, respectively, whereas a typical agglomerate of precursor, milled manganite particles, surrounded with uniformly thick silica layer, is shown in Fig. 7e. Most of the manganite particles are observed as coated with silica, which is a favourable precondition for eliminating antigenic effects related to the potential recognition of manganite surfaces - but not of silica surfaces as well - by macrophages of mononuclear phagocyte system, once the particles are injected in the bloodstream. Furthermore, since thoroughly coated with silica, the manganite particles could be conjunctioned with biomolecules (enzymes, antibodies, DNA, etc.) and sugars (dextrans, starch, albumin, poly(ethylene glycol), etc.) for the production of more complex magnetically-guided site-specific drug delivery systems<sup>45</sup>. However, a relatively large percentage of hollow silica spheres can be discerned from Fig. 7f,g. The reason for the presence of different morphological patterns within the finally synthesized samples can be found in the roots of traditional, solid-state approach to materials synthesis, coupled with milling treatments, that in general leaves final products with wide distribution of most properties per particle, subsequently in our case reflecting on a similar non-uniformity of particle shapes and a variety of the obtained nano-structures. However, high temperatures of calcination, as well as complex pathways of the formation of mixed rare-earth manganites, significantly decrease or even fundamentally limit the space of possible reaction conditions that lead to certain uniformities, regarding both morphologies and magnetic characteristics. Wet methods of synthesis, although they may not overcome such limits, could drastically widen such probability spaces, as has already been in many occasions proven in practice, wherein many novel sets of limiting conditions within specific procedures of synthesis, are daily discovered in laboratories world-wide. Future researches concerning the preparation of biocompatibly coated LaSr-manganites might be directed in such a way.

## Conclusions

A successful pathway for the preparation of silica-coated lanthanum-strontium manganite particles with  $\text{La}_{0.76}\text{Sr}_{0.24}\text{MnO}_{3+\delta}$  stoichiometric formula, exhibiting resulting Curie temperature at ~ 40 °C, was presented. Calcination in air at 1200 °C for 2 h, followed by 4h milling treatment, and the subsequent wet procedure for encapsulating the produced particles with silica, comprised the basic synthesis steps towards the final material. The produced pure manganite particles were sized in the range of 10 – 200 nm, whereas the final, silica-coated manganite spheres had almost uniformly ~ 250 nm in diameter. Larger agglomerates of the milled precursor manganite particles were mostly coated with amorphous silica layers, enabling complete potential elimination of antigenic effects upon *in vivo* functional implementation of the prepared material. Investigated dependencies of Curie temperature on stoichiometry of LaSr-manganite particles that comprise cores of the eventual core-shell structures, enables potential preparation of silica-coated and therefore biocompatible LaSr-manganite particles with tunable Curie point within the broad range of temperatures used in hyperthermia

treatments: 40 – 70 °C. In general, the presented investigation contributes to the large body of knowledge, related to the contemporary attempts of using nanoscience and nanotechnologies for improvements of human life.

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