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RESEARCH ARTICLE

Magnetic Nanorings for Biomedical Applications

Fernando Rodrigues, Eduardo A. Volnistem, Gustavo S. Dias, Ivair A. Santos, Luiz F Cotica*

Department of Physics, State University of Maringá. Maringá – PR, Brazil

*Corresponding author email: lfcotica@dfi.uem.br

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ABSTRACT

In this work we investigate the characteristics and feasibility of a new class of magnetic particles that are optimized for possible biological applications as magnetic hyperthermia. These new nanostructures have the nanoring shape, being composed of iron oxides (magnetite or hematite). Such morphology gives the nanoparticles a peculiar magnetic behavior due to their magnetic vortex state. The iron oxide nanorings were obtained using hydrothermal synthesis. X-ray Diffraction confirmed the existence of the desired crystal structure and Scanning Electron Microscopy shows that the magnetite particles had nanometric dimensions with annular morphology (diameter ~250 nm). The nanorings also show intensified magnetic properties and a transition to a vortex state. This study showed that it is possible to obtain magnetic nanorings with properties that can be used in nanotechnological applications (mainly biotechnological ones aimed at the treatment and diagnosis of cancer), in large quantities in a simple synthesis route.

Keywords: magnetic nanorings, hydrothermal synthesis, magnetite.

1 Introduction

Cancer has become one of the leading causes of death and the most important barrier to increasing life expectancy in every country of the world [1]. The number of diagnosed people with this disease grows exponentially. According to Bray *et al.* [1], close to 18 million new cases and 9.5 million cancer deaths occur worldwide in 2018. Facing this scenario, this topic has been the subject of much research, especially with regard to the development of new diagnostic and treatment techniques [2, 3]. New medical techniques and equipment for treating diseases and conducting tests using high definition images have been transforming the way of diagnosing various types of illnesses, including cancer [2].

Considering the search for new techniques and the improvement of existing ones, in recent years considerable attention has been directed to one-dimensional nanostructured materials [4, 5]. This occurs due to their physical properties, mainly in magnetic iron oxide nanoparticles with ring and/or tubular morphology [6, 7, 8]. A significant property of these particles is the ability to release heat when subjected to an alternating magnetic field [9, 10]. Within this field, the studies of magnetic nanomaterials have stood out, mainly, with regard to the study and development of nanoparticles with intrinsic properties adequate to therapeutic purposes. Some of the main applications that have been envisioned for magnetic nanoparticles in the treatment of cancer are [11, 12]: surface functionalization aiming the use in diagnostic imaging; use of nanoparticles as a vector for carrying drugs and the use of treatment techniques for magnetic hyperthermia (overheating) of a tumor tissue.

Nanoparticles, especially those that have a vortex state, such as nanorings and nanotubes, in addition to having numerous therapeutic advantages, can cause a reflection in public health spending.

Faced with a huge range of techniques for the synthesis of nanostructures, the hydrothermal method is widely used for the synthesis of oxides, mainly in obtaining nanomaterials of different kinds and shapes. [13, 14]. A hydrothermal system works at high pressures, allowing the solvent to remain in the liquid state at temperatures above its boiling point. Thus, it is possible to obtain a considerable increase in the solubility of the precursor [6, 15, 16]. Hydrothermal synthesis provides the formation of nanometric particles in an aqueous medium, in reactors or autoclaves where the pressure and temperature can be high. There are two main pathways for particle formation via hydrothermal conditions: hydrolysis and oxidation or neutralization of mixed metal hydroxides. A very interesting possibility for the use of hydrothermal synthesis is the production of ring-shaped magnetic nanostructures to optimize the use of magnetic hyperthermia and for diagnosis that use magnetic properties to produce images [9].

As we can see, the use of nanomaterials in the treatment and diagnosis of cancer is very promising, especially when these systems are designed for use in magnetic hyperthermia. This promising aspect has led to a demand to create new specialized nanoparticle systems. Most of these nanomaterials are based on iron oxide nanoparticles such as magnetite or maghemite, commonly shaped as nanospheres (or shapes close to) in the range of a few tens of nanometers. As a consequence, these materials have a specific magnetic state called superparamagnetic. Thus, the size of these nanoparticles and this specific magnetic state limit the possibilities of using these systems in applications such as magnetic hyperthermia. Therefore, the search for other nanostructured magnetic systems is essential for expanding their use in treatments and diagnoses. The development of nanostructures with new shapes can lead to more efficient treatments using magnetic hyperthermia. For this reason, studies related to the synthesis of magnetic nanostructures with different morphologies and the investigation of the magnetic properties of these new systems are very necessary. Furthermore, studying of the magnetic configuration in these nanoparticles is significant for understanding their properties and future applications' design.

Therefore, in this work we synthesized iron oxide nanorings by hydrothermal synthesis that were subsequently transformed into magnetite nanorings (Fe_3O_4) via redox. The magnetic, morphological and structural properties of the nanorings were studied. Potential applications in nanotechnological applications, mainly biotechnological ones aimed at the treatment and diagnosis of cancer, are discussed.

2 Research Methodology

2.1 Synthesis

In order for the crystallization process to occur via hydrothermal synthesis, it is necessary to use a reactor that allows the system to remain for 48 h in an aqueous medium under high temperature and pressure [10]. The reactor used in our work is composed of an external stainless steel part (cup and lid) and an internal coating of Polytetrafluoroethylene – PTFE, a material that has mechanical and chemical properties suitable for the needs expected during hydrothermal synthesis. To produce iron oxide nanoparticles in a ring-like shape, $FeCl_3$ (0.04 M), Na_2SO_4 (2.2 x 10^{-3} M) and NaH_2PO_4 (10^{-4} M) were dissolved directly in distilled water. The reactor lid was sealed and the solution was mechanically stirred for a few minutes. Afterwards, the reactor was placed in a temperature controlled muffle furnace in order to keep it at 220 ^oC for 48 h. After this period, the reactor was removed from the muffle furnace and the resulting material was washed with distilled water in order to maintain the solution pH close to neutral. After washing, the precipitate was moved to a drying oven for 2 h at 80 ^oC and a reddish powder of nanoparticles was obtained (see Figure 1a). In the next step, the synthesized material was inserted in a tubular oven, which allows the passage of a continuous gas flow to occur the redox reaction. The reddish nanoparticles were subjected to a heat treatment with a progressive temperature increase of 10 °C per minute until 400 °C, remaining at this temperature for 1 h. The entire process took place under a flow of a gas mixture composed of 90% Argon and 10% Hydrogen, at a rate of 120 mL/min. At the end of the reduction process, the nanoparticles changed their color from red to dark gray (Figure 1b). After the oxidation-reduction was completed, the samples proceeded to the characterizations.

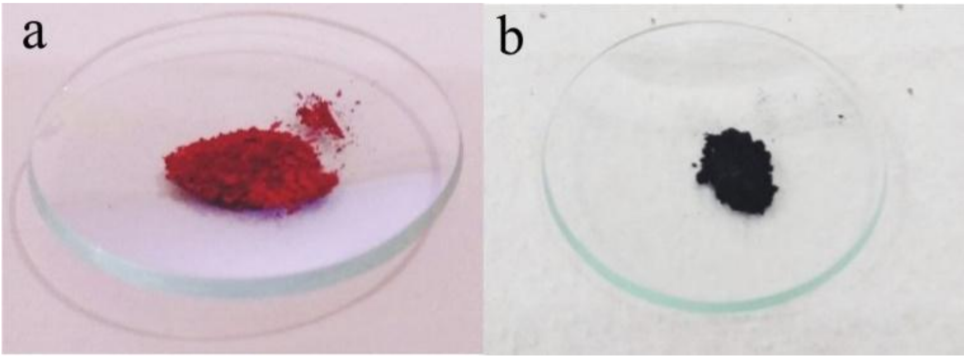

Figure 1: *Images of samples synthesized by hydrothermal reaction (a) before and (b) after oxidation-reduction process performed at 400 °C for 1 h under a flow of a gas mixture composed of 90% Argon and 10% Hydrogen, at a rate of 120 mL/min.*

2.2 Characterizations

X-ray diffraction analyzes were performed using the XRD-7000 Shimadzu X-ray diffractometer, with Cu Kα radiation. The scanning electron microscopy images were obtained by using a FEI Scios microscope. The data referring to vibrating sample magnetometry were obtained with a home-made magnetometer at 7 K and 300 K and under magnetic field reaching 5 T.

3 Results and Discussion

X-ray Diffraction measurements were performed on powdered samples synthesized through the hydrothermal technique, before and after oxidation-reduction (see Fig. 1). The analyzes aimed to identify the crystalline phases on these materials. Figure 2a shows the diffractogram obtained for the nanostructures before oxidation-reduction. In the sample with expected ring morphology it is possible to identify that all peaks can be indexed as corresponding to the hematite phase (α-Fe_2O_3, JCPDS: 33-0664 crystallographic file). It is also possible to observe that the diffraction peaks present a typical line broadening of particles with nanometric dimensions. Additionally, an amorphous pattern appears in the background.

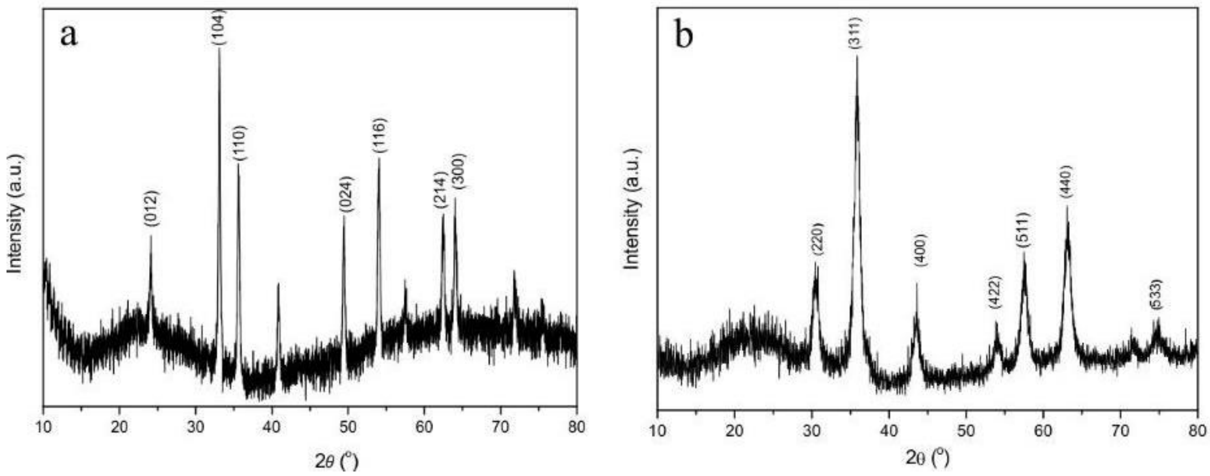

Figure 2: *X-ray diffraction patterns obtained for nanostructures (a) before and (b) after oxidation-reduction process performed at 400 °C for 1 h under a flow of a gas mixture composed of 90% Argon and 10% Hydrogen, at a rate of 120 mL/min.*

The X-ray diffraction patterns for the sample after oxidation-reduction are shown in Figure 2b. It is worth noting the high crystallinity of the material, indexed to the inverse spinel structure of magnetite (Fe_3O_4). The diffraction angle and relative intensities are similar to those des cribed in the JPCDS 11-0614 crystallographic file. It can be seen that the broadening of the diffraction peaks is maintained. It suggests the keeping of nanometric particle sizes after sample reduction treatment.

Scanning electron microscopy analysis results clearly revealed the morphology of the synthesized nanoparticles and their regularity of growth in the formation of rings. The micrographs obtained by using the secondary electron detector are shown in Figure 3 and show nanoparticles in the form of Fe_3O_4 nanorings with a mean diameter close to 250 nm (outer ring), 150 nm for the inner ring and 100 nm for the ring thickness. As as consequence, the ring shape of nanoparticles can allow atypical magnetic states when external magnetic fields are applied to the sample.

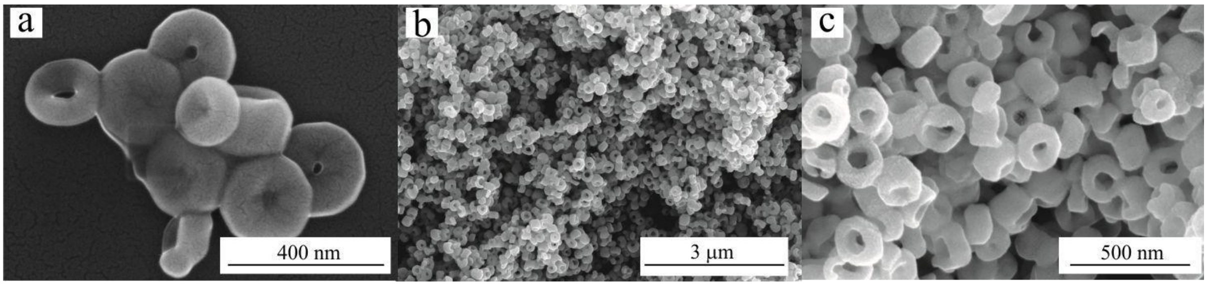

Figure 3: *Scanning electron microscopy images for nanostructures synthesized by hydrothermal reaction, (a) before and (b, c) after oxidation-reduction process performed at 400 °C for 1 h under a flow of a gas mixture composed of 90% Argon and 10% Hydrogen, at a rate of 120 mL/min.*

In addition, the images showed that the oxidation-reduction process did not have negative effects on altering the morphology of the particles (see Figures 3b and 3c), nor was there a significant appearance of porosities on the respective surfaces.

In order to identify the magnetic properties of the processed nanoparticles, vibrating sample magnetometry measurements were performed. Figure 4 shows the magnetic behavior of nanostructures after oxidation-reduction. The magnetization *vs.* applied magnetic field curves were obtained at 7 K and 300 K in a field range up to 20,000 Oe.

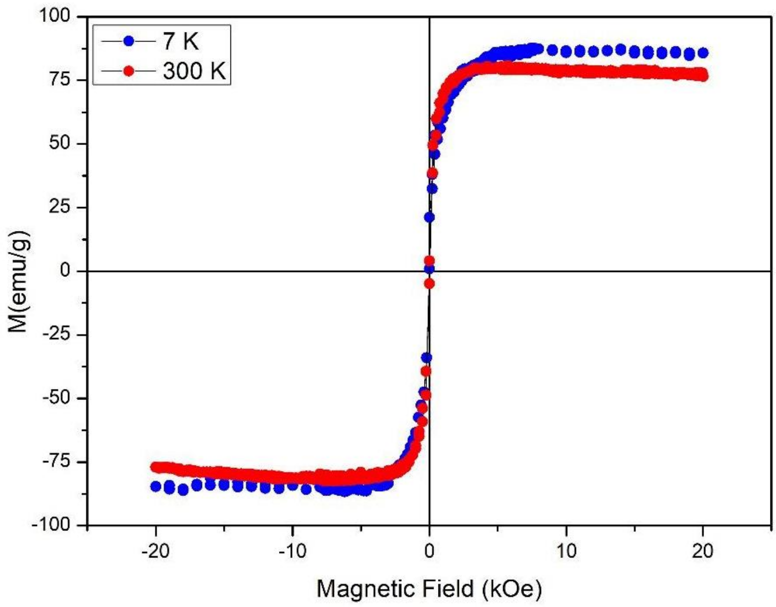

Figure 4: *Magnetization vs. applied magnetic field curves for the Fe_3O_4 nanorings at 7 K and 300 K.*

A clear hysteresis cycle is easily identified in the magnetization *vs.* magnetic field curve, suggesting a superparamagnetic type behavior of magnetic nanoparticles. However, the particles are 250 nm in diameter and have a ring shape. These conditions do not indicate a superparamagnetic behavior. As seen, the remnant magnetization and coercivity are very small in the absence of an external magnetic field [17]. It is also observed (Figure 4) that the saturation magnetization reached 85.6 emu/g at 7 K and 78.3 emu/g at 300 K, in a close agreement with what is expected (92 emu/g at room temperature) for macroscopic *(bulk)* Fe_3O_4 particles [6].

Among the possible atypical magnetic states presented by magnetic nanorings are the vortex and onion states [18, 19]. The magnetic moments are aligned circumferentially along the ring in the vortex state. In the onion state, the moments align symmetrically in different hemispheres of the ring, creating a domain wall structure. The onion state is metastable, and a step in the hysteresis loop would attend a vortex-onion state transition [18].

Regarding the shape of the hysteresis curve, no signal of a vortex-onion transition could be observed. The shape of the curve closely resembles that of a superparamagnetic system, but due to the size and microstructure of nanoparticles, it can be decrypted that the magnetic state is the vortex. The configuration of a vortex state is presented in some works reported in the literature [19, 20, 21]. Interestingly, even with a considerable temperature variation, in our case from 7 K to 300 K, there is no evidence of a change in the magnetic state of the ring-shaped nanoparticles.

Therefore, we conclude that the magnetic state present when an external magnetic field is applied is the vortex state in the samples produced in this work. However, more detailed studies are required to conclude whether the state present in the nanorings produced in this work is the vortex state or the onion state or in a state of coexistence of these two magnetic orientations.

In summary, the nanoparticles synthesized through the hydrothermal method, after the oxidation-reduction process, have magnetic properties that allow the obtained nanorings to be controlled through a magnetic field and, possibly, to be applied in magnetic hyperthermia and drug delivery processes. Precisely, this configuration can be used to facilitate the preparation of magnetic nanorings suspensions. Nanostructures with vortex-like states offer new opportunities to obtain stable magnetic suspensions and high saturation magnetizations simultaneously [21, 22]. Also, compared to superparamagnetic nanoparticles, nanorings with the vortex-like magnetic state are larger and have a much higher saturation magnetization. Thus, the nanoparticles obtained in this work have microstructural and magnetic properties necessary to be controlled/guided by a magnetic field, enabling the delivery of drugs to specific targets [12, 23]. These features of our nanoparticles also allow the absorption of energy transmitted via an alternating magnetic field, a fundamental property for using this material in cancer treatments via magnetic hyperthermia [10, 24].

4 Conclusions

In this paper, the characteristics and potentialities to synthesize a new class of magnetic nanostructures (nanorings) with adequate properties for applications such as magnetic hyperthermia and drug delivery. The obtained iron oxide nanorings (magnetite - Fe_3O_4, 250 nm of diameter) showed a peculiar magnetic response, reaching magnetizations (85.6 emu/g) close to those observed for micrometric magnetic particles without coercivity. The shape of the magnetization curve closely resembles that of a superparamagnetic system, but due to the size and microstructure of nanoparticles, it can be decrypted that the magnetic state is the vortex. The intensified magnetic properties of the hydrothermally processed iron oxide nanorings reveal their potential for biotechnological applications in magnetic assisted diagnosis and treatment, such as hyperthermia and drug delivery protocols.

5 Declarations

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5.3 Competing Interests

There exists no potential conflict of interest.

5.4 Publisher's Note

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