Journal of Magnetism and Magnetic Materials 427 (2017) 241–244

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Synthesis, characterization and hemolysis studies of $Zn_{(1-x)}Ca_xFe_2O_4$ ferrites synthesized by sol-gel for hyperthermia treatment applications

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ARTICLE INFO

Keywords:
Nanoparticles
Ferrites
Magnetic hyperthermia

ABSTRACT

The synthesis of $Zn_{(1-x)}Ca_xFe_2O_4$ nanoparticles, x=0, 0.25, 0.50, 0.75 and 1.0, was performed by sol-gel method followed by a heat treatment at 400 °C for 30 min. These ferrites showed nanometric sizes and nearly superparamagnetic behavior. The $Zn_{0.50}Ca_{0.50}Fe_2O_4$ and $CaFe_2O_4$ ferrites presented a size within the range of 12–14 nm and appropriate heating ability for hyperthermia applications. Hemolysis testing demonstrated that $Zn_{0.50}Ca_{0.50}Fe_2O_4$ ferrite was not cytotoxic when using 10 mg of ferrite/mL of solution. According to the results obtained, $Zn_{0.50}Ca_{0.50}Fe_2O_4$ is a potential material for cancer treatment by magnetic hyperthermia therapy.

1. Introduction

Magnetic nanoparticles have potential applications in biomedicine such as agents for magnetic resonance imaging (MRI), systems for drug delivery and thermoseeds for magnetic hyperthermia [1–3]. Magnetic hyperthermia treatment consists of using magnetic nanoparticles for destroying cancer tumor cells by raising their temperature within the range of 41–46 °C [1]. In order for nanoparticles to be used in medicine, specific characteristics are required: biocompatibility, heating ability, particle form, size and distribution, a ferrimagnetic/superparamagnetic behavior, hemocompatiblity, dispersibility in water and suspensions stability [4–6]. Magnetite nanoparticles, with an inverse spinel structure, are the most studied ferrites for biomedical applications [7,8]. However, research has been focused on developing mixed ferrites by partial substitution of Fe ions with other cations such as Zn, Ca, Mg, Mn, Co, Cu, Ga and Ni [9–16].

In this work, the magnetic behavior, heating ability and hemocompability of $Zn_{(1-x)}Ca_xFe_2O_4$ ferrites (x=0, 0.25, 0.50, 0.75 and 1.0), synthesized by sol-gel followed by a heat treatment at 400 °C for 30 min, were studied. The general hypotheses behind this investigation are the following: i) the incorporation of Zn cations may promote antimicrobial activity, ii) Zn may act as heating regulator for magnetic hyperthermia [15,17,18] and, iii) the incorporation of Ca into the ferrite structure may favor biocompatibility of nanoparticles.

2. Materials and methods

Reagent grade chemicals of metallic nitrates ($Fe(NO_3)_2{\cdot}9H_2O$, 99.99%, $Zn(NO_3)_2{\cdot}6H_2O$, 98% and $Ca(NO_3)_2{\cdot}4H_2O$, 99%) and ethylene-glycol ($C_2H_6O_2$, 99%), were used for the nanoparticles sol-gel synthesis. Stoichiometric amounts of nitrates were dissolved into $C_2H_6O_2$ under vigorous stirring for 2 h at 40 °C, then this mixture was heated up to 80 °C and kept at this temperature until obtaining a brown gel. This gel was aged for 2 h and then dried at 95 °C for 72 h. After drying, the precursors were heat treated at 400 °C for 30 min.

The materials obtained were characterized by X-ray diffraction (XRD, Philips 3040) and vibrating sample magnetometry at room temperature (VSM, Princeton Measurements Co, MicroMag™ 2900). Samples with more appropriate magnetic properties were analyzed by transmission electron microscopy (TEM, FEI Titan 80–300). The heating capacity of selected nanoparticles was evaluated under an appropriate magnetic field [4,19,20] for located body regions (10.2 kA/m and frequency of 354 kHz) using a solid state induction heating equipment (Ambrell, EasyHeat, 0224). These tests were performed during 15 min; suspensions of 20 mg of ferrite/2 mL of water were used. Hemolysis test was carried out according to the ASTM E2524-08 [21] standard using suspensions of 10 mg of ferrite/mL of solution.

3. Results and discussions

Fig. 1(a) shows the XRD patterns of $Zn_{(1-x)}Ca_xFe_2O_4$, x=0, 0.25,

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http://dx.doi.org/10.1016/j.jmmm.2016.10.099
Received 13 June 2016; Received in revised form 17 October 2016; Accepted 19 October 2016
Available online 20 October 2016
0304-8853/

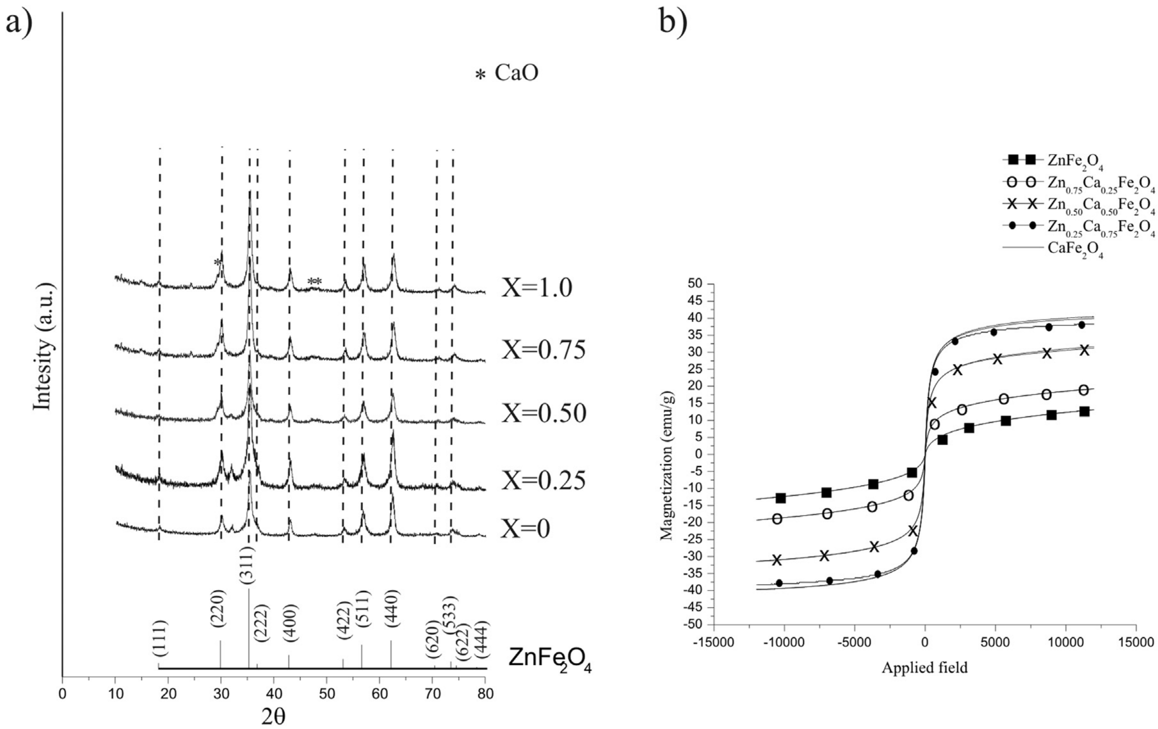

Fig. 1. XRD patterns (a) and magnetization curves (b) of $Zn_{(1-x)}Ca_xFe_2O_4$ ferrites.

0.50, 0.75 and 1.0. The indexing of these XRD patterns was performed according to the JCPDS 22–1012 card for zinc ferrite. The $ZnFe_2O_4$ ferrite possesses a spinel structure, nevertheless due to the method used, an inverse spinel structure was obtained. This may be due to the partial migration of Zn ions to the octahedral sites [1,15]. As it can be observed, the patterns corresponding to mixed ferrites show a slight displacement of reflections in comparison to those of the pattern corresponding to the sample with x=0. This may indicate the incorporation of Ca ions into the inverse spinel crystalline structure. The pattern corresponding to $Zn_{(1-X)}Ca_XFe_2O_4$ ferrite with x=1 shows a subproduct of calcium oxide (JCPDS 28-0775).

Fig. 1(b) shows the magnetization curves of $Zn_{(1-x)}Ca_xFe_2O_4$ ferrites. These ferrites have the following saturation magnetization values (Ms): 13.11, 19.24, 31.31, 38.30 and 40.02 emu/g for x=0, 0.25, 0.50, 0.75 and 1.0, respectively. As observed, Ms increases as the Zn content is decreased. According to the literature [1], zinc has a strong effect on the magnetic properties of some mixed ferrites; substitution with a non-magnetic cation such as zinc, which has a preference for tetrahedral sites occupancy, results in the reduction of the exchange interaction between cations occupancy in both the tetrahedral and octahedral sites. Remanence and coercivity were close to zero. Due to their magnetic properties, the ferrites $Zn_{0.50}Ca_{0.50}Fe_2O_4$, $Zn_{0.25}Ca_{0.75}Fe_2O_4$, and $CaFe_2O_4$ were selected for further investigation.

Fig. 2(a–c) shows TEM images, electron diffraction patterns and particle size distribution of selected ferrites. All ferrites are polycrystalline and show high agglomeration due to their high magnetization. The average particle size of $Zn_{0.50}Ca_{0.50}Fe_2O_4$, $Zn_{0.25}Ca_{0.75}Fe_2O_4$ and $CaFe_2O_4$ are 14, 12 and 13 nm, respectively. By sol-gel method, it is possible to obtain a narrow nanoparticle size distribution [1,22]. However these particles agglomerate, which can be a problem in biomedical applications [23,24].

Fig. 2(d) shows the heating ability of selected nanoparticles, where temperature increases continuously as a function of time during the test. In these tests the starting temperature was 28 °C. The maximum temperature reached was 41.2, 38 and 46.5 °C for $Zn_{0.50}Ca_{0.50}Fe_2O_4$, $Zn_{0.25}Ca_{0.75}Fe_2O_4$ and $CaFe_2O_4$, respectively. Two of these samples are able to heat at a temperature within the appropriate range for hyperthermia (41–46 °C). The heating efficiency, specific absorption rate, (SAR) was calculated by direct calorimetric measurement according to equation [25,26]:

$$SAR=\frac{C}{m}*\frac{\Delta T}{\Delta t}$$

Where C is the specific heat of the medium in which the particles are suspended (H_2O=4.18 J g^{-1}), $\Delta T/\Delta t$ is the initial slope of the time-dependent temperature curve and m is the ferrite mass in the fluid per unit mass of fluid. These values are shown Table 1. The maximum SAR value (24.5 W/g) was observed for the $CaFe_2O_4$ ferrite.

The $Zn_{0.50}Ca_{0.50}Fe_2O_4$ and $CaFe_2O_4$ ferrites were selected for hemolysis testing. For $Zn_{0.50}Ca_{0.50}Fe_2O_4$ the value was 0.2% ± 0.0004, indicating that this material is not hemolytic. On the other hand, for $CaFe_2O_4$ the value was 14.4% ± 0.007, which shows that this material is hemolytic. According to the ASTM E2524-08 standard, samples with values higher than 5% can be considered as hemolytic.

4. Conclusions

It was possible to synthesize a calcium ferrite ($CaFe_2O_4$) and a mixed zinc and calcium ferrite ($Zn_{0.50}Ca_{0.50}Fe_2O_4$) by sol-gel method which show an appropriate heating ability for hyperthermia applications and nanometric sizes (12–14 nm). The $Zn_{0.50}Ca_{0.50}Fe_2O_4$ ferrite demonstrated to be no hemolytic with a value of 0.2%. According to the results obtained, this ferrite is a potential material for cancer treatment by magnetic hyperthermia therapy.

Acknowledgements

The authors gratefully acknowledge CONACYT, México for the provision of the Rosario Argentina Jasso-Terán scholarship and SEP-CONACYT (127815) for the financial support of this research.

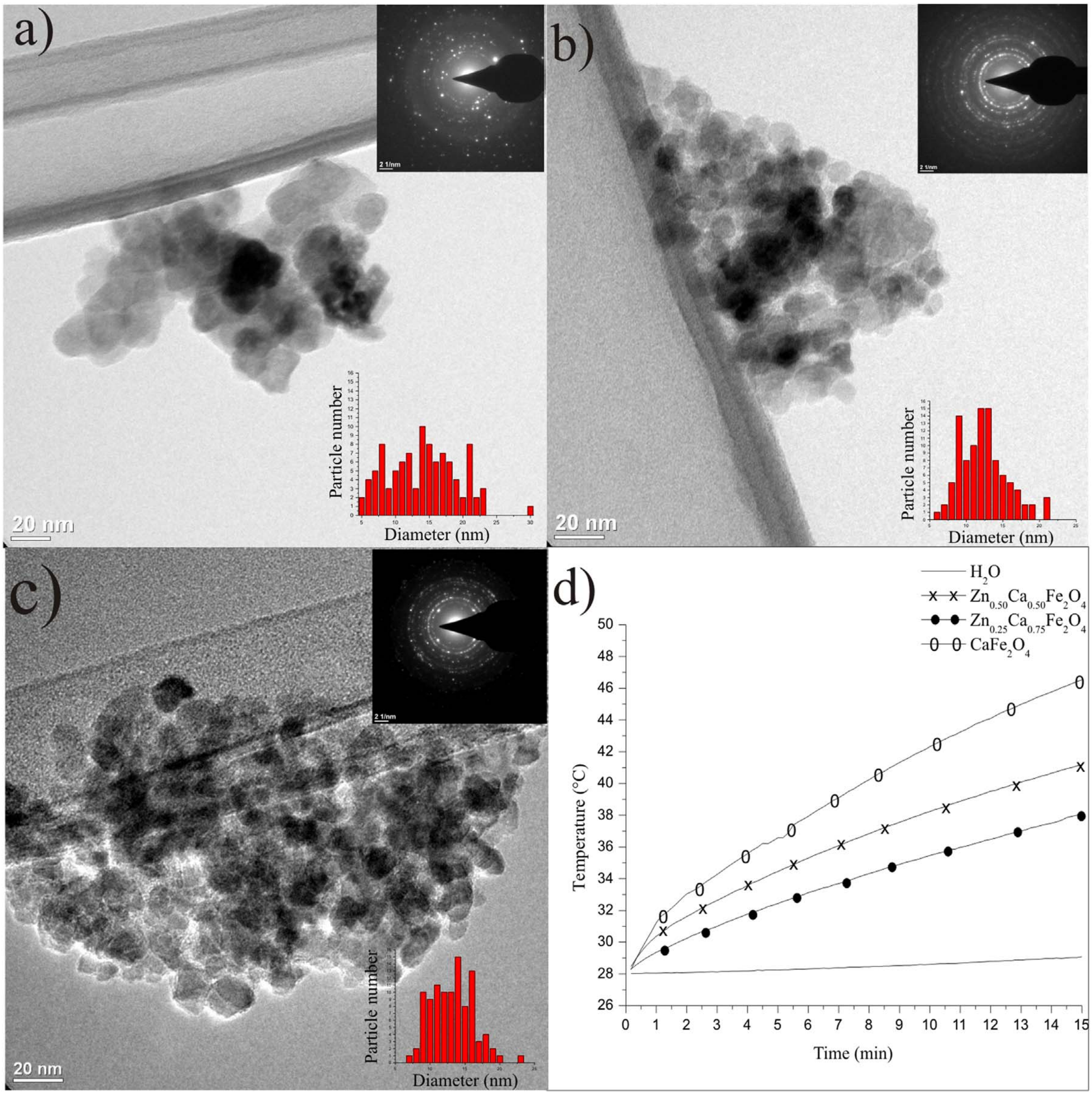

Fig. 2. TEM images of $Zn_{0.50}Ca_{0.50}Fe_2O_4$ (a), $Zn_{0.25}Ca_{0.75}Fe_2O_4$ (b), $CaFe_2O_4$ (c) with corresponding electron diffraction pattern, particle size distribution and heating ability of selected ferrites (d).

Table 1
Maximum temperature reached and SAR values of selected ferrites.

Sample	T (°C)	ΔT/Δt (°C/s)	SAR (W/g)
$Zn_{0.50}Ca_{0.50}Fe_2O_4$	41.2	0.0353	14.8
$Zn_{0.25}Ca_{0.75}Fe_2O_4$	38.0	0.0201	8.4
$CaFe_2O_4$	46.5	0.0584	24.5

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