Magnetic Properties and Cytotoxicity of Ga-Mn Magnetic Ferrites Synthesized by the Citrate Sol-Gel Method

Javier Sánchez, Laura Elena De León Prado, Dora Alicia Cortés Hernández

Abstract**—**Magnetic spinel ferrites are materials that possess size, magnetic properties and heating ability adequate for their potential use in biomedical applications. The $Mn_{0.5}Ga_{0.5}Fe_2O_4$ magnetic nanoparticles (MNPs) were synthesized by sol-gel method using citric acid as chelating agent of metallic precursors. The synthesized samples were identified by X-Ray Diffraction (XRD) as an inverse spinel structure with no secondary phases. Saturation magnetization (*Ms*) of crystalline powders was 45.9 emu/g, which was higher than those corresponding to $GaFe_2O_4$ (14.2 emu/g) and $MnFe_2O_4$ (40.2 emu/g) synthesized under similar conditions, while the coercivity field (*Hc*) was 27.9 Oe. The average particle size was 18 ± 7 nm. The heating ability of the MNPs was enough to increase the surrounding temperature up to 43.5 °C in 7 min when a quantity of 4.5 mg of MNPs per mL of liquid medium was tested. Cytotoxic effect (hemolysis assay) of MNPs was determined and the results showed hemolytic values below 1% in all tested cases. According to the results obtained, these synthesized nanoparticles can be potentially used as thermoseeds for hyperthermia therapy.

Keywords**—**Cytotoxicity, heating ability, manganese-gallium ferrite, magnetic hyperthermia.

I. Introduction

MAGNETIC nanoferrites are materials that have been extensively studied for the last decade due to their potential as contrast agents for magnetic resonance imaging and thermoseeds for hyperthermia treatment [1]-[4]. A great quantity of synthesis routes, such as microwave [5]-[9], co-precipitation [10]-[17], thermal decomposition [18]-[22], mechano-chemical synthesis [23]-[26], among others [27]-[41], has been developed for obtaining MNPs with desirable magnetic properties for biomedical and technological applications. Among all these synthesis methods, sol-gel is one of the best ways to synthesize pure and mixed magnetic ferrites with appropriate crystalline structure and magnetic properties for their use in biomedical areas [42]-[48]. The sol-gel auto-combustion technique combines the gelification step and the combustion process to obtain crystalline, magnetic and nano-sized simple and mixed ferrites [49]-[61]. Citric acid is one of the three most popular fuels used for the synthesis of fine ceramics such as ferrites by combustion process. This chelating agent can initiate the combustion reaction due to its high negative combustion heat (-2.76 kcal g^{-1}), and at the same time prevents particle agglomeration and undesired spontaneous condensation reactions [62]. However, in this method, important reaction conditions may be considered, such as the type and quantity of organic fuel, pH, combustion source, auto-combustion temperature, etc., which may influence the crystalline structure and properties of synthesized samples [54].

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This work reports the synthesis of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ MNPs by the citrate sol-gel method, evaluating the magnetic properties and crystalline structure of the synthesized samples for their potential use on biomedical applications, without considering the auto-combustion step and the pre-heating of the powder precursor. The heating ability of samples and the hemolytic damage to red blood cells were also studied, taking into account the chemical composition of the magnetic core with the aim to determine the potential utilization of the synthesized particles as thermoseeds in hyperthermia treatment. Paramagnetic gallium was selected as part of magnetic core due to its biological properties and its antineoplastic effect on cancer cells [63]-[65]. In recent years, manganese has been extensively investigated as a component of magnetic ferrites [5], [10], [66]-[69] due to its contribution to the net magnetic moment and the heating capacity of samples. Manganese can also be used in ferrites for magnetic resonance imaging due to its higher relaxivity when it is part of paramagnetic organic molecules and MNPs [41], [70] containing paramagnetic cations such as gallium ions [71]. Gallium ferrites with orthorhombic structure have been extensively studied due to their magnetoelectric properties. However, for the spinel structure, which is necessary for biomedical applications, there is no much research performed.

II. Materials and Methods

MNPs of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ were synthesized by the citrate sol-gel method using iron [$Fe(NO_3)_3 \cdot 9H_2O$], gallium [$Ga(NO_3)3 \cdot H_2O$] and manganese [$Mn(NO_3)_2 \cdot 4H_2O$] nitrates and citric acid ($C_6H_8O_7$) as raw materials. For comparison purposes, samples of $GaFe_2O_4$ and $MnFe_2O_4$ were also synthesized under similar conditions. Stoichiometric amounts of metallic nitrates and citric acid, in a molar ratio of 2:1 (Fe_2:Ga_1, Fe_2:$Ga_{0.5}$-$Mn_{0.5}$, Fe_2:Mn_1) and 3:1 ($C_6H_8O_7$:metals), were placed into a 250 mL glass beaker that already contained 20 mL of deionized water. The mixture was magnetically stirred for 2 h at room temperature until a homogenous solution was obtained. The temperature of the solution was slowly increased to promote the formation of a viscous gel and the elimination of both nitric acid and water molecules. The viscous gel was aged for 2 h at room temperature and dried at 95°C for 72 h in a stove obtaining a soluble and brittle gel that was used as magnetic precursor. In accordance to previous results [64], the precursor was heat treated for 1 h at 500°C in air and the powders obtained were characterized by XRD, Vibration Sample Magnetometry (VSM), Infrared Spectroscopy (FT-IR), Transmission Electronic Microscopy and Energy Dispersive Spectroscopy (TEM-EDS). This deep characterization was performed in the aim to identify the crystalline structure and determine the magnetic parameters (magnetization saturation, *Ms*; remanent magnetization, *Mr*; coercive field, *Hc*), the chemical composition and the average core size of synthesized powders. The evaluation of the magnetic properties was carried out at an applied field within a range of -12000 to 12000 Oe. The cell parameter (*a*) of the synthesized samples was calculated using (1), in which the interplanar distance (*d*) and *hkl* planes were acquired from the diffraction patterns. The crystallite size (*D*) and the magnetic moment per molecule (n_B) was also calculated from the most intense diffraction peak and (2), respectively.

$$a = d\sqrt{h^2 + k^2 + l^2} \quad (1)$$

$$n_B = \frac{M_{wt} \cdot Ms}{5585} \quad (2)$$

where M_{wt} is molecular weight, *Ms* is saturation magnetization and 5585 is a magnetic factor. Heating ability of magnetic suspensions (3.0 mg, 4.5 mg, 6.0 mg and 10.0 mg of MNPs per mL of water) was measured by solid state magnetic induction using a field of 10.2 kA/m and a frequency of 354 kHz to determine the potential application of synthesized powders as thermoseeds for hyperthermia treatment. These magnetic conditions are within the range specified for biomedical applications. From these heating curves, the specific absorption rate, SAR [72] (3) was calculated taking into account the mass of MNPs (m_{MNPs}) and carrier liquid (m_{LIQ}), the specific heat of carrier liquid (C_{LIQ}) and the initial slope of the time-dependent temperature curve ($\Delta T/\Delta t$) [73].

$$SAR = \frac{c_{LIQ} m_{LIQ}}{m_{MNPs}} \cdot \frac{\Delta T}{\Delta t} \quad (3)$$

The hemolytic degree of magnetic powders was measured following the experimental procedure described in ASTM E2524-08 (Standard Test Method for Analysis of Hemolytic Properties of Nanoparticles). For these tests, suspensions of 3.0 mg, 4.5 mg, 6.0 mg and 10.0 mg of material per mL of liquid medium and human whole blood were used. Six samples were tested for each suspension and the hemolytic degree was calculated by the quantitative determination of hemoglobin released due to the *in vitro* damage to red blood cells caused by their exposure to nanoparticles.

III. Results and Discussion

The XRD patterns of synthesized samples are presented in Fig. 1. All samples show the characteristic reflections of a cubic spinel structure and the XRD patterns were indexed using the JCPDS card 74-2228 ($Fe_{1.4}Ga_{1.4}O_4$) with good agreement for all *hkl* planes. A reflection displacement was observed in some *hkl* planes (220, 422, 511, 440) for both $Mn_{0.5}Ga_{0.5}Fe_2O_4$ and $MnFe_2O_4$ samples, in comparison to $GaFe_2O_4$, which indicates the correct substitution of Ga^{3+} (ionic radius of 0.62 Å) by Mn^{2+} cations that have a longer ionic radius (0.89 Å). The lattice parameters (*a*) of the samples are presented in Table I. This parameter increases as Mn^{2+} ions are introduced into the oxygen framework, which has high flexibility and tends to modify itself to accept cations with different ionic radii [74]. This may indicate the formation of the mixed ferrite. An increase from 5 nm to 20 nm in the crystallite size was also observed from the XRD diffraction patterns, as an effect of the lattice expansion and the crystallinity of the samples. Unlike both pure $GaFe_2O_4$ and $MnFe_2O_4$ samples synthesized under similar conditions, a cubic spinel phase and a high crystalline structure without secondary products was developed when the magnetic precursor of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ was heat treated at 500°C for 1 h.

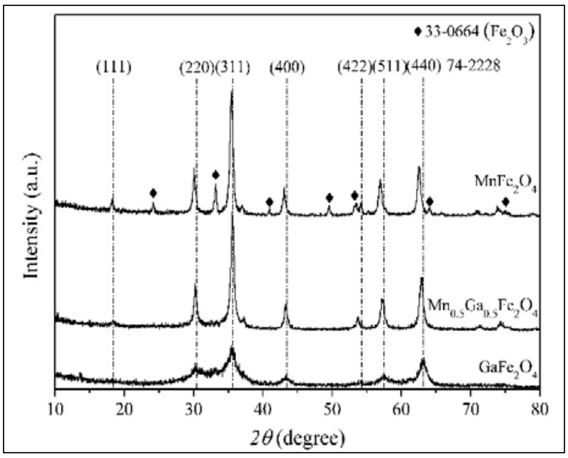

Fig. 1 XRD patterns of $GaFe_2O_4$, $Mn_{0.5}Ga_{0.5}Fe_2O_4$ and $MnFe_2O_4$ samples synthesized by the citrate sol-gel method

The identified crystalline powders showed an *Ms* value of 45.9 emu/g, which was higher than those corresponding to $GaFe_2O_4$ (14.2 emu/g) and $MnFe_2O_4$ (40.2 emu/g), while the *Mr* and *Hc* values were 2.0 emu/g and 27.9 Oe, respectively. This increase in *Ms* has been attributed to the formation of strong exchange interactions among Fe and Mn ions located into both tetrahedral (A) and octahedral (B) sites of the spinel structure [75]. The shape of the hysteresis loop (Fig. 2) indicate a ferrimagnetic behavior, thus the obtained powders can be classified as soft ferrites (high *Ms*, lower *Hc*) [76]. The magnetic moment per molecule increases and it is consistent with the increase of the magnetization values due to the element distribution into the structure, their preferential occupation site and the increase in the Fe-Mn sublattices exchange interactions [50].

TABLE I
MAGNETIC AND CRYSTALLOGRAPHIC PARAMETERS OF GA AND MN FERRITES SYNTHESIZED SAMPLES

Sample	$GaFe_2O_4$	$Mn_{0.5}Ga_{0.5}Fe_2O_4$	$MnFe_2O_4$
Ms **(emu/g)**	14.2	45.9	40.2
Mr **(emu/g)**	1.0	2.0	2.4
Hc **(Oe)**	64.7	27.9	29.0
D**, (nm)**	5.0	18.0	20.0
a, (Å)	8.3290	8.3602	8.3943
n_B **(μ_B)**	0.62	1.96	1.66

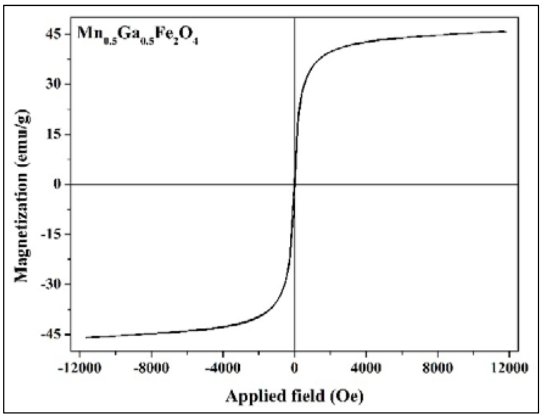

Fig. 2 Hysteresis loop of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ sample at an applied field of 12 KOe

The FT-IR spectrum of synthesized powders is shown in Fig. 3. It was possible to identify the characteristic absorption band (≈550 cm^{-1}) of metal-oxygen bond (Fe-O, Ga-O and Mn-O) due to the intrinsic vibration stretch of A and B sites of the spinel structure. According to Briceño et al. [77], this absorption band indicates the correct formation of the magnetic oxide. Additional absorption bands corresponding to –OH groups (≈3300 cm^{-1}) and C-H bonds (≈2800 and ≈1500 cm^{-1}) were identified as part of the synthesized powders and correspond to water molecules and organic residues from citric acid, not completely burned during heat treatment, respectively. The CO_2 molecules (≈2350 cm^{-1}) may be attributed to the atmospheric conditions at which the analyses were performed.

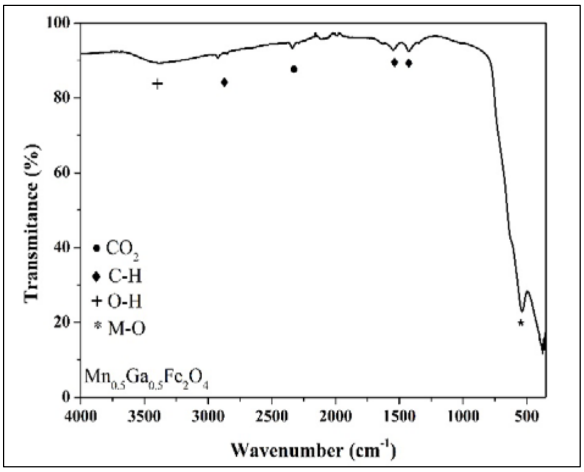

Fig. 3 FT-IR spectra of synthesized powders

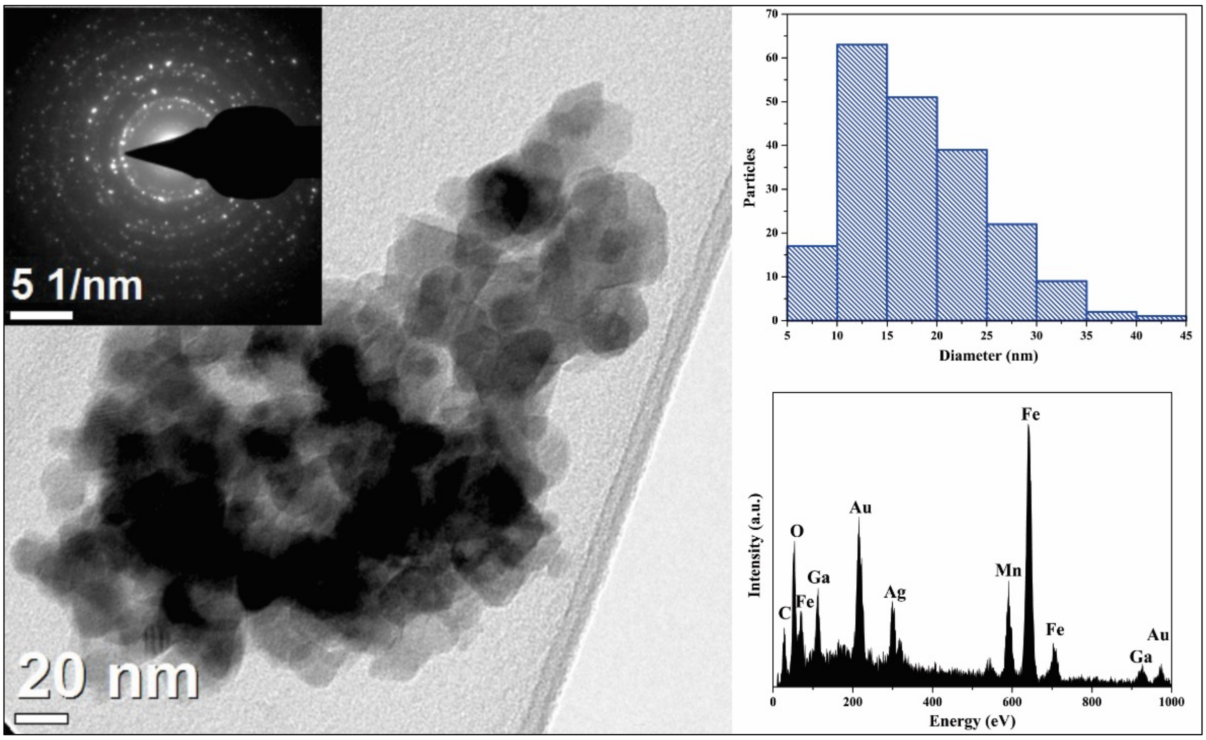

Fig. 4 TEM and SAED images, EDS spectrum and calculated size of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ MNPs

The average size, morphology and the semi-quantitative chemical composition of particles were determined by TEM analysis (Fig. 4). The corresponding EDS spectrum, SAED and histogram are also shown in Fig. 4. Synthesized MNPs showed an average particle size of 18 ± 7 nm. The observed agglomeration is due to magnetic interactions among particles (Van der Waals forces and dipole-dipole interactions) [78]. According to the EDS spectrum, Ga, Fe, O and Mn were the only elements present in the powders, while Au and Ag elements correspond to the conductive metallic layer applied on the samples for their semi-quantitative characterization. NPMs have a non-spherical morphology as an effect of the reaction medium used (citric acid) and the heat treatment conditions, which was not observed for synthesized MNPs under different conditions [63]-[65].

The heating ability of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ is shown in Fig. 5. As expected, temperature increases as the suspension concentration is increased. From these results, it is possible to demonstrate that, under these testing conditions (10.2 kA/m and 354 kHz), the suspensions of 4.5 mg, 6.0 mg and 10.0 mg of MNPs per mL of water are able to increase their medium temperature up to 43.5°C in less than 10 min.

The SAR values are shown in Table II; these are lower than those reported by other authors [10], [70], [79]. This difference is mainly due to the calculations, which involve only the overall weight fraction of magnetic elements (Fe, Mn) without considering the mass of oxygen and paramagnetic gallium present in the mixed ferrites.

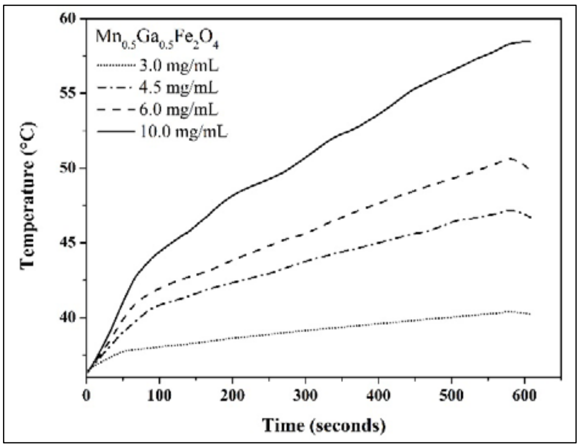

Fig. 5 Heating ability of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ under an AC magnetic field of 10.2 kA/m and 354 kHz

TABLE II
HEMOLYTIC DEGREE AND SAR VALUES OF $MN_{0.5}GA_{0.5}FE_2O_4$ MNPS SYNTHESIZED BY THE CITRATE SOL-GEL METHOD

Sample	Quantity of MNPs (mg/mL)	Hemolytic value (%)	SAR Values (W/g)
1	3.0	0.01	7.5
2	4.5	0.27	14.3
3	6.0	0.10	14.4
4	10.0	0.66	13.8

The results of the red blood cells damage caused by MNPs are shown in Table II. In all cases, the hemolysis values were lower than 1% and according to ASTM E2524-08; the tested MNPs are nonhemolytic materials.

IV. CONCLUSION

MNPs of $Mn_{0.5}Ga_{0.5}Fe_2O_4$ were successfully synthesized by the citrate sol-gel method. Powders showed an inverse spinel crystalline structure with no other secondary phases. Saturation magnetization increases as gallium ions are replaced by manganese ions due to the net magnetic moment between A and B sublattices, while *Mr* and *Hc* values decrease as an effect of the super-exchange interactions among Mn cations. The synthesized MNPs showed an average size of 18 ± 7nm and a homogeneous chemical composition. A quantity of 4.5 mg of MNPs per mL of deionized water was enough to increase the medium temperature at the required range for hyperthermia treatment (43.5 °C) in less than 10 min. In all the cases, the hemolysis percentage was below 1%. According to the results obtained, $Mn_{0.5}Ga_{0.5}Fe_2O_4$ has adequate properties for its potential use in hyperthermia therapy.

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