Hyperfine Interact
DOI 10.1007/s10751-015-1124-1

Novel protocol for the solid-state synthesis of magnetite for medical practices

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Abstract It is reported a novel approach to prepare nanoparticles of magnetite (Fe_3O_4) by heating a mixture of synthetic commercial maghemite (γFe_2O_3) with sucrose. This solid-state reaction leads to the chemical reduction of part of the Fe^{3+} of the precursor oxide to render Fe^{2+} and Fe^{3+} in octahedral and Fe^{3+} in tetrahedral sites of the Fe-O coordination framework. Powder X-ray diffraction patterns, FTIR and 298 K Mössbauer spectra confirm the conversion of maghemite into magnetite. Based on these results, the optimal sucrose:maghemite rate was found to be 4.

Keywords Biomedicine · Nanotechnology · Sucrose · Hyperthermic material

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Proceedings of the 14th Latin American Conference on the Applications of the Mössbauer Effect (LACAME 2014), Toluca, Mexico, 10-14 November 2014

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1 Introduction

Researches and developments on easier and economically more attractive alternatives to prepare magnetic nanoparticles have been intensively pursued not only for the fundamental scientific interest on their chemical (composition and purity) and physical characteristics (as is their magnetic structure) but also on other intrinsic critical properties, if the material is directed to more specific technological applications [1–4]. For many selected applications, the synthesis and preparation of magnetic powders containing more uniform nanoparticles have been of central importance, in order to allow getting better overall control over their electrical, optical, magnetic, and even biological behaviors. In wider related contexts, uniformly sized magnetic nanoparticles have been attracting special attention because of their broad range of potential applications for which they can be used, including magnetic storage media, ferrofluids, magnetic ferric resonance imaging (MRI), magnetically guided drug delivery, medical diagnosis, and alternating-current (AC) magnetic-field-assisted cancer therapy [1, 5–13].

Certainly due to its remarkably high spontaneous magnetization among the naturally found iron oxides, the magnetite (Fe_3O_4) was very early used in many medical technologies for clinical and laboratorial purposes, as for the magnetic separation of biochemical products [14] and cells [15] and as the magnetic guiding and hyperthermic systems for site-specific drug delivery in mammals [16]. In such applications, the size, charge, and surface chemistry of the magnetic particles could strongly influence their bio-distribution and bio-response in the live body [17, 18]. Their magnetic behavior strongly depends on the mean size and morphology of the magnetite particles in the ferrofluid medium [19].

The use of properly coated magnetite nanoparticles for medical clinical purposes has also been well intensified over the last few decades. All these technological and medical uses basically require that the nanoparticles are superparamagnetic, meaning in practice that their mean diametric dimensions are not bigger than 20 nm. The overall particle sizes distribution should also be expectably narrow, so to get as much as possible uniformly distributed physical and chemical properties.

Producing dispersed magnetite particles with the controlled sizes distribution has been a challengeable practical problem. Innumerous synthesis protocols have been used to produce magnetic nanoparticles [20–23]. Some of those are *via* the co-precipitation of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions in alkaline medium [24–27]. Other synthetic methods include (i) the thermal decomposition of an alkaline solution of an Fe^{3+}-chelate in a medium containing hydrazine, and (ii) the sonochemical decomposition of an Fe^{2+} salt followed by thermal treatment [28, 29]. The synthesis of well-dispersed and size-controlled particles of a magnetic ferrite has been recently reported [30–34]. Youjin et al. reported the synthesis of mono-dispersed nanoparticles of γFe_2O_3 and a cobalt ferrite, which were thought to exempt from requiring further size-selection, in order to be used as homogeneous hyperthermic material potentially destined to medical practices [30, 31]. Alivisatos and co-workers reportedly synthesized γFe_2O_3 nanoparticles from the direct decomposition of $FeCup_3$ (Cup = N-nitrosophenylhydroxylamine) [32]. Uniformly-sized nanoparticles of magnetite were synthesized *via* high-temperature reaction of iron(III)-acetylacetonate [33]. Even though the produced magnetic nanoparticles were highly crystalline and uniformly sized, such procedures are not suitable to be used in large-scale and economic production, as they require expensive and often bio-toxic chemicals, complex synthetic steps, and high temperatures. Reverse micelles, which are surfactant-stabilized water-in-oil emulsions, have been successfully used as nano-reactors for the synthesis of magnetic nanoparticles [34].

The advantage of using the reverse micelles method is that the corresponding particle-sizes and -shapes can be controlled by merely setting the chemical conditions. However, they tend to produce extensively agglomerated nanoparticles. Despite of that there are relatively few reports on the synthesis of highly crystalline nanoparticles using reverse micelles [24–28, 34], most of the nanoparticles that were reportedly obtained through this route were found to be poorly crystalline, as the synthesis is usually performed at relatively low temperatures, and the chemical yields of nanoparticles are often too low. As a corollary, a large amount of solvent is used to synthesize a very small amount of nanoparticles.

The work being here reported was devoted to the simple synthesis of nanosized magnetite through chemically reducing part of the Fe^{3+} of a commercial synthetic maghemite (Mh) to Fe^{2+}, by heating it mixed with sucrose.

2 Materials and methods

2.1 Reagents

All chemicals used in this work, namely iron (III) oxide, with mean particle-sizes $\varnothing < 50$ nm (according to the supplier, Aldrich code # 544884-25), and sucrose (Synth) were analytical grade and used as received.

2.2 Synthesis of magnetite

Magnetite samples were obtained *via* chemical reduction of iron (III) oxide (maghemite; γFe_2O_3) by using sucrose as a carbon source, which upon heating at $400°C$ produces coal that is the chemical reducing agent to convert part of the Fe^{3+} in the cation-vacant spinel structure of the maghemite ($Fe^{3+}_{\frac{8}{3}}O_4$, which stoichiometrically corresponds to γFe_2O_3) precursor into Fe^{2+} ions to produce magnetite ($Fe^{3+}_2Fe^{2+}O_4$). The sample of the commercial iron oxide precursor was labeled Mh.

The synthesis procedure was based on the method described in more details in ref. [20]. Following this procedure, 1 g of the iron (III) oxide was mixed with a predefined amount of sucrose. This mixture was put in a ceramic crucible with lid. The mixture was then heated at a programmed rising temperature, starting from $20°C$ up to 400° C, at a rate of $10°C\ \text{min}^{-1}$, and held at this final temperature so to reach a complete heating time of 20 min. At this temperature of 400° C, the coal particles underwent severe devolatilization and produced solid coke, tar, and light gases [35]:

$$\text{Sucrose} \rightarrow \text{char(coke)} + \text{tar} + \text{gases(e.g., } H_2, CO) \tag{1}$$

It has been shown that hematite (αFe_2O_3) undergoes stepwise reduction by CO, which is represented by (2) [35]. Thus, the same chemical pathway can be assumed for the reaction starting with maghemite:

$$3Fe_2O_3 + CO \rightarrow 2Fe_3O_4 + CO_2 \tag{2}$$

The amounts of sucrose in the mixture were 2, 3, 4, and 5 g; the corresponding powder mixtures were labeled MtS2, MtS3, MtS4, and MtS5, respectively.

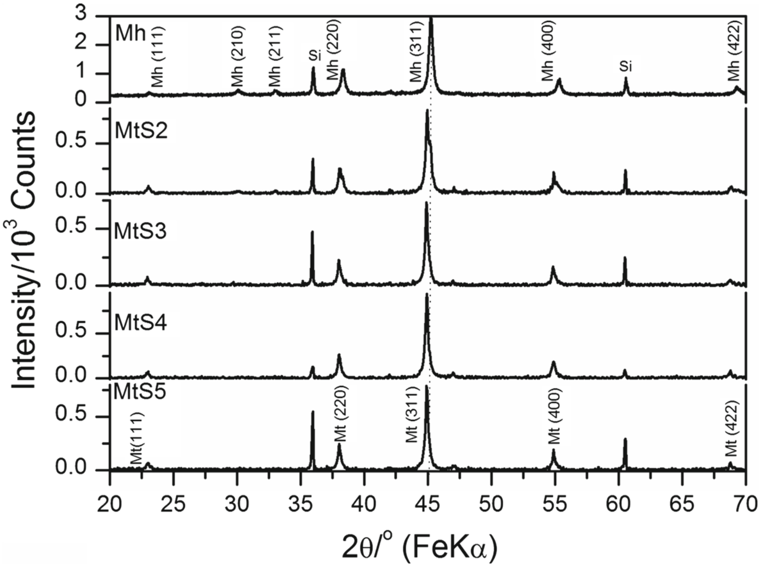

Fig. 1 Powder X-ray diffraction patterns for the prepared samples

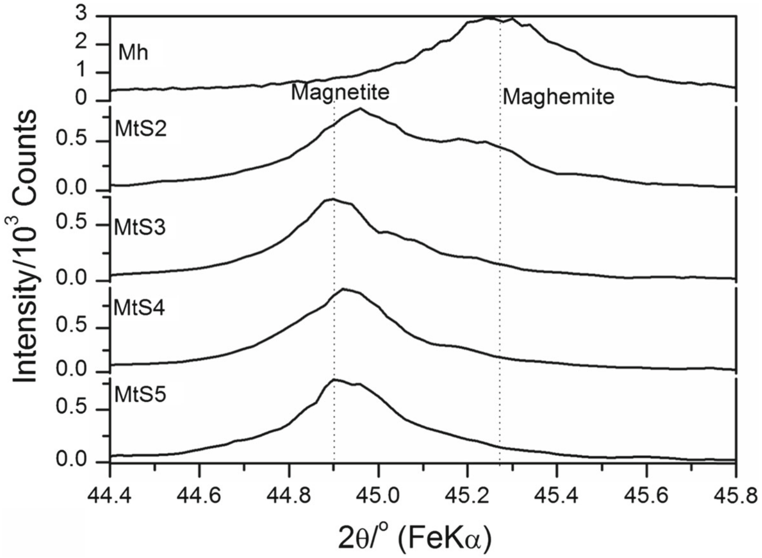

Fig. 2 Expanded (331) reflection of magnetite and maghemite

2.3 Characterization techniques

FTIR spectra were collected with a Perkin Elmer Spectrum GX spectrophotometer. For these analyses, samples were compacted with KBr (approximately 1 mass%) and analyzed in transmission mode. The crystalline structures of the magnetic nanoparticles were assessed

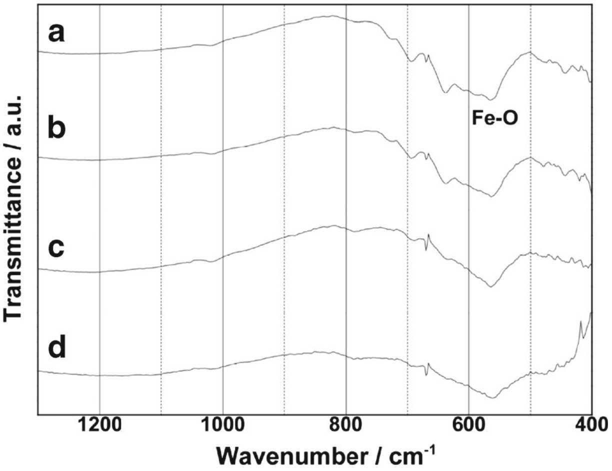

Fig. 3 ATR-FTIR spectra for: **a**) MtS2, **b**) MtS3, **c**) MtS4, and **d**) MtS5

with powder X-ray diffraction (XRD) measurements, using a Shimadzu XRD 6000 diffractometer equipped with an iron tube (40 kV and 30 mA) and a graphite monochromator. The scans were done between 20 and $70° - 2\,\theta$ with a scanning rate of 1°/ min. The assessement of crystalline phases was performed with the Crystallographica Search-Match version 2,0,2,0 (Oxford Cryosystems). Silicon was used as an internal standard. The Mössbauer spectra were collected with a constant acceleration transmission mode setup, with a ~ 50 mCi ^{57}Co/Rh 14 keV-gamma-ray source. Spectra at 298 K were obtained with a spectrometer equipped with a transducer (CMTE model MA250) controlled with a linear function driving (CMTE model MR351). Values of Mössbauer isomer shifts are quoted relatively to αFe. The experimental resonance lines were fitted to Lorentzian functions by least-square fitting with software IGOR Pro 6.36.

3 Results and Discussion

Figure 1 shows the XRD patterns of the prepared samples. The pattern for sample Mh indicates that the iron (III) oxide precursor is constituted of a single phase of cubic maghemite (space group P4132) according to JCPDS card # 39-1346. Upon heating this maghemite mixed with different sucrose contents (samples MtS2, MtS3, MtS4 and MtS5) at 400 °C, the relative intensity of the (311) reflection due to maghemite (Fig. 2) gradually decreases, whereas the relative intensity of the magnetite (311) reflection (space group Fd-3m; JCPDS card # 19-629) increases, confirming that the thermal treatment with sucrose indeed converts maghemite into magnetite. Moreover, the (311) reflection of magnetite (Fig. 2) in the samples MtS3, MtS4 and MtS5 is shifted to lower angle, as compared to the same reflection for the sample MtS2, which suggests that the Fe^{2+} contents in these samples is higher than in the sample MtS2. This indicates that larger amounts of sucrose lead to the formation of increasingly more sctoichiometric magnetite, tending to the limiting ionic ratio Fe^{3+}: Fe^{2+} 2:1.

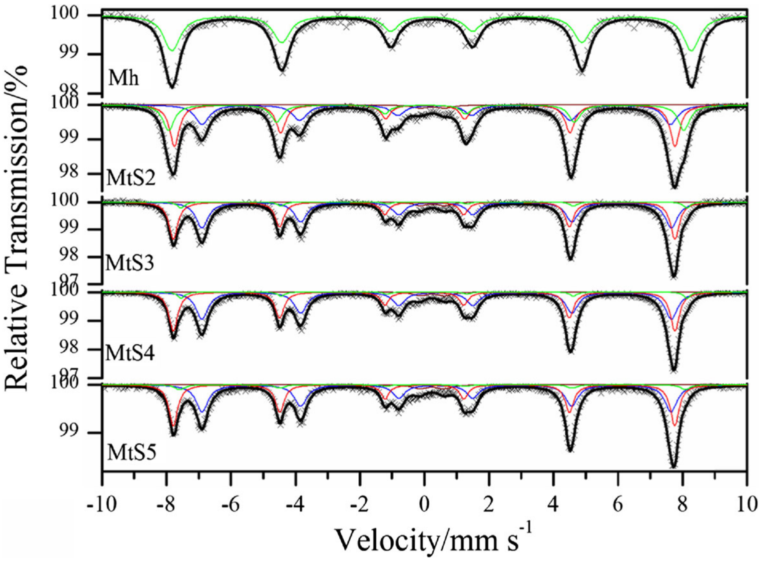

Fig. 4 298 K Mössbauer spectra for the prepared samples

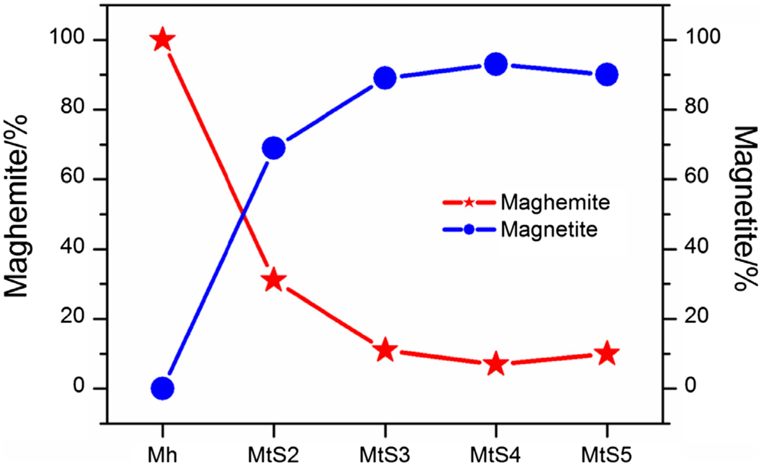

Fig. 5 Maghemite conversion and magnetite formation as a function of the sucrose content

Using the Scherrer equation, the mean crystallite dimension (MCD) of the precursor (sample Mh) was determined as 60 nm, whereas the MCD for magnetite in the samples MtS2, MtS3, MtS4 and MtS5 were 75, 70, 70 and 66 nm, respectively.

The infrared spectra for all samples (Fig. 3) show the characteristic band [36–38] of magnetite at about 570 cm^{-1}. The ATR–FTIR patterns for the samples MtS2, MtS3, and MtS4 also show the characteristic vibrational absorption at 690 cm^{-1} [39–41] due to Fe-O bond in maghemite (γFe_2O_3).

To better investigate the conversion of maghemite into magnetite, Mössbauer measurements were carried out with the sample at 298 K. The collected spectra are shown in

Table 1 Hyperfine parameters of the fitted Mössbauer spectra recorded at 298 K

Sample	δ/mm s^{-1}	2 ε, Δ/mms^{-1}	B$_{hf}$/T	RA/%	Assignment
Mh	0.33	0	49.9	100	Maghemite
MtS2	0.36	0.77	–	4	$\{Fe^{3+}\}$
	0.45	0.04	45.0	37	{Magnetite}
	0.26	−0.02	48.1	32	[Magnetite]
	0.33	0.02	49.5	27	Maghemite
MtS3	0.36	0.76	–	4	{Fe^{3+}}
	0.47	0.02	45.1	49	{Magnetite}
	0.26	−0.01	48.3	40	[Magnetite]
	0.32	0.01	48.9	7	Maghemite
MtS4	0.36	0.76	–	4	{Fe^{3+}}
	0.48	0.02	45.1	56	{Magnetite}
	0.26	0	48.2	37	[Magnetite]
	0.32	0.02	48.6	3	Maghemite
MtS5	0.36	0.76	–	5	{Fe^{3+}}
	0.47	0.01	45.1	54	{Magnetite}
	0.26	−0.02	48.2	36	[Magnetite]
	0.32	0.02	48.6	5	Maghemite

δ = isomer shift relative to αFe; 2ε = quadrupole shift; Δ = quadrupole splitting; B$_{hf}$ = hyperfine field and RA = relative subspectral area. [ ] = tetrahedral coordination, { } = octahedral coordination

Fig. 4 and the hyperfine parameters obtained from the fitting of these spectra are summarized in Table 1. The corresponding hyperfine parameters (Table 1) obtained for the sample Mh indicate that maghemite is actually the single occurring phase. Upon mixing 1 g maghemite with 2 g sucrose and heating the mixture at 400 °C, approximately 69 % of the Mössbauer relative subspectral area correspond to magnetite (Fig. 4). When the amount of sucrose was increased to 3, 4 and 5 g, the Mössbauer subspectral area reached 89, 93 and 90 %, respectively (Fig. 5). It is interesting to note that using sucrose:maghemite ratios higher than 3:1 does not significantly increase the formation of magnetite. Despite of this, the relative subspectral areas due to octahedral and tetrahedral sites in the produced magnetite increase from 1.16 for sample MtS2 to 1.23, 1.51 and 1.50 for samples MtS3, MtS4 and MtS5, respectively. The small (RA ~5 %) Fe^{3+} doublet is assignable to any iron oxide with very small particle size behaving superparamagnetically at 298 K, although further measurements at lower temperature are required to more carefully check this hypothesis. Considering that in magnetite the expected octahedral:tetrahedral subspectral area ratios is 1.88, using sucrose:maghemite ratios higher than 4:1, it may be possible to obtain the Fe^{3+}:Fe^{2+} closer to 2:1, as expected for stoichiometric magnetite.

4 Conclusions

Magnetite was easily and quickly synthesized by mixing maghemite, as an iron source, with sucrose and treating the mixture at 400 °C for 20 min. The optimal amount of sucrose:maghemite was 4:1. This simple and direct method may be further tested in order to prepare magnetic nanoparticles for use in biomedicine and in clinical medical practices.

Acknowledgments Work supported by FAPEMIG (CEX - APQ-00651-11) and CNPq (Brazil). JDF is indebted to CAPES (Brazil) for granting his Visiting Professorship at UFVJM under the PVNS program and to CNPq for the grant # 305755-2013-7.

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