

Magnetic studies of iron(III) nanoparticles in alginate polymer for drug delivery applications

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Abstract

Isolated iron ions and iron oxide nanoparticles entrapped in alginate microspheres were studied by ⁵⁷Fe Mössbauer spectroscopy (MS), electron paramagnetic resonance (EPR) and magnetization measurements. Ferric alginate beads were prepared by dropping sodium alginate solution into ferric chloride solution (0.1 and 0.5 M) with stirring under Ar atmosphere.

MS and EPR spectroscopy show that iron is absorbed in alginate as Fe(III). The EPR suggests that isolated Fe(III) substitutes sodium in the polymeric structure (narrow line paramagnetic species at $g=4.23$). This mechanism induces the linking of the alginate units and the formation of the alginate microspheres. During this process, superparamagnetic iron hydroxide particles (broad line species at $g=2.22$) are precipitated inside the polymer network.

MS measurements performed in diluted and concentrated Fe(III) samples displays a paramagnetic doublet at 300 K, and two components at 4.2 K due to a paramagnetic site and blocked superparamagnetic particles.

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1. Introduction

Alginate is a linear copolymer composed of 1–4-linked β-D-mannuronic acid (M) and its *c*-5-epimer α-L-guluronic acid (G), that vary in amount and sequential distribution along the polymer chain depending on the source of the alginate. Soluble sodium alginate can be cross-linked by divalent cations leading to gel formation [1,2]. It has widespread applications in the food, drinks, pharmaceutical and bioengineering industries. Recently, it has been proposed as biomaterial for drug delivery system in which the drug release rates would be activated by external stimuli [3,4]. This activation could be induced by interaction of an external magnetic field with nanostructured magnetic particles previously nucleated in the interior of the alginate.

Two main aspects should be known in order to control the biopolymer release rates: (i) the magnetic response of nanoparticles and (ii) mechanical properties of the polymer matrix. Thus, the development of preparation methodologies of magnetic nanoparticles with controlled dimensions is very important for the success of medical applications.

Many studies were performed using divalent ions such as Ca²⁺, Sr²⁺, Ba²⁺, to cross-link guluronic acids units of alginate [5], but the way alginate interacts with Fe³⁺ is not yet well understood. In addition, because the samples were prepared in an aqueous medium, small iron oxide particle will be nucleated between the alginate polymer chains. Depending on their size and magnetic type, these particles could be in the superparamagnetic state. It has been considered that the alginate polymeric backbone is more conformationally restricted and hence would result in aggregation of iron [6]. Sreeram et al. [6] achieved that the Fe(III) ions are bound to the binding sites in the

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alginate and form spatially separated iron(III) centers on the alginate backbone and not a covering of the backbone with FeOOH precipitates [6]. Nesterova et al. [7] synthesized superparamagnetic clusters of iron(III) complexes in the form of poorly crystalline ferrihydrite in the presence of the polymers polyvinyl alcohol, polyacrylic acid and alginate. They found that these iron particles are superparamagnetic and that the polymer present can exert a significant influence on the stability and organization of the iron(III) hydrolytic products formed.

Polymer-based iron oxide nanoparticles are reported by several authors [8–13]. In general, magnetic properties in nanoparticles are studied using magnetometer measurements, ^{57}Fe Mössbauer spectroscopy (MS) and electronic paramagnetic resonance (EPR). Chatterjee et al. [8] studied maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanoparticles coated with polyethylene; the particles with diameters range between 50–500 nm had a blocking temperature of 60 K. Berger et al. [9] studied the behavior of maghemite nanoparticles formed in a sol–gel silicate glass as a function of sample temperature via the EPR spectra. They found that the blocking temperature of superparamagnetic particles was 90 K. Fiorini et al. [10] investigated the magnetic properties of maghemite nanoparticles dispersed in polyvinyl alcohol by using AC susceptibility and MS. The results showed that interparticle interactions and surface effect controlled magnetic properties. Pardoe et al. [12] used magnetization and Mössbauer spectroscopy to investigate the magnetic properties of magnetite and maghemite particles synthesized in the presence of dextran or polyvinyl alcohol. They verified that superparamagnetic blocking temperature depends on the polymer nature.

In this work, we combined electronic paramagnetic resonance with ^{57}Fe Mössbauer spectroscopy in order to distinguish iron in their different chemical states. The use of EPR is especially suitable because its measuring time is approximately 10^{-10} sec and it is known that the relaxation time in superparamagnetic systems is not greater than 10^{-9} sec. Then, from the EPR measurements, it is possible to observe separately paramagnetic and superparamagnetic signals. On the other hand, MS is a local technique with a measuring time of about 10^{-8} sec which is suitable to study magnetic transitions and chemical states. Thus, with the hyperfine parameters of the Mössbauer spectra at an appropriate temperature, we can identify the magnetic signal of the iron oxide, and, from the paramagnetic component, we could get information about the Fe^{3+} linking the guluronic units. The particle blocking temperature (T_B) is an important parameter that can be obtained directly from MS measurements. T_B is generally also obtained by analyzing the zero field-cooled susceptibility. The factors that determine the blocking temperature are correlation effects influenced by inter particle distance and the particle size anisotropy [5].

2. Sample preparation

Ferric alginate beads were prepared by dropping commercial sodium alginate solution (3%), from Keltone LV, into aqueous ferric chloride solution. Two samples were prepared, sample A with 0.01 M and sample B with 0.5 M ferric chloride solution. Stirring was performed under argon atmosphere at 25 °C. After gelation, samples A and B were allowed to polymerize further for a period of 5 min and 2 h in the FeCl_3 solution, respectively. These beads were washed several times in Milli-Q water and dried in the oven at 35 °C for 12 h.

3. Experimental

The Mössbauer spectroscopy (MS) measurements were performed in the transmission mode using a 25 mCi $^{57}\text{Co}:\text{Rh}$ source moving in a sinusoidal mode. The isomer shift (IS) reported is relative to bcc iron at room temperature (RT). The low-temperature measurements at 4.2 K were performed in a helium bath cryostat where source and absorber are kept at the same temperature; additional MS measurements between 15 and 250 K were performed in a close cycle refrigerator.

Electron paramagnetic resonance (EPR) measurements were recorded with a Bruker ESP-300 spectrometer equipped with X-band 9.5-GHz microwave frequency, several measurements were performed from 300 to 5 K. The sample was cooled down to a given temperature in zero field magnetic field. As is usual the first derivative of the power absorption has been recorded as a function of the applied magnetic field.

X-ray diffraction (XRD) measurements were performed in a conventional diffractometer. AC susceptibility and magnetization measurements at different temperatures were performed using a commercial SQUID magnetometer from Quantum Design.

4. Results and discussion

The EPR measurement at 300 K is displayed in Fig. 1a, the spectrum has a narrowed peak at $g \approx 4.23(1)$ (peak I) and a broad peak at $g \approx 2.22(2)$ (peak II), with peak to peak linewidth (ΔH) ≈ 157 and ≈ 1120 Oe, respectively. Similar lines were observed in earlier studies performed in Fe^{3+} impurities embedded in a number of noncrystalline matrices such as borate, phosphate and silicate glasses [14,15]. The lines typically observed were: a prominent peak at $g=4.3$ and two other major broad lines at $g=9.7$ and $g=2.0$. The conventional attribution is as follow: the peaks at $g>4.0$ are due to isolated Fe^{3+} and the peak at $g=2.0$ arises from oxidic iron particles. Following this description, we can assume that the line close to $g=4.3$ is attributed to isolated Fe^{3+} ions linking the polymer network and suffers

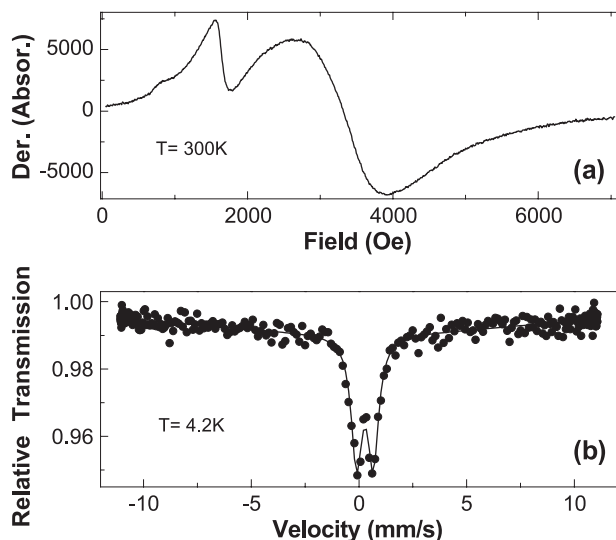


Fig. 1. (a) EPR spectrum measured at 300 K and (b) Mössbauer spectrum measured at 4.2 K of the alginate magnetic composite (0.01 M Fe).

from several degrees of distortion, while the line close to $g=2$ corresponds to iron oxide complexes where Fe ions interact with each other. The last line could be due to FeOOH complexes acting as bridges between the saccharide moieties and to nanoparticles precipitates located among the polymer chains.

Fig. 1b displays the Mössbauer spectrum for the sample A measured at 4.2 K; it shows a broadened superparamagnetic subspectra superimposed with a paramagnetic component with $IS=0.38(1)$ mm/s and $QS=0.76(1)$ mm/s. The superparamagnetic subspectra indicate that the magnetic moment is relaxing at a time less than 10^{-8} – 10^{-9} sec which is related with the Larmor precession τ_L of the ^{57}Fe nuclear magnetic moment.

Fig. 2 shows the temperature dependence of the EPR measurements. The position of the peak at $g \approx 4.23$ and its linewidth showed almost no temperature dependence when the temperature decreases from 300 to 4 K, and the peak at $g \approx 2.2$ showed that as the temperature decreases the linewidth becomes broadened and its position shifts towards lower magnetic fields, see Fig. 2b; it was also observed that the amplitude decreased to smaller values when the sample was cooled down.

The behavior observed for the line at g close to 2 is typically of superparamagnetic particles and has been reported in many works [16].

Fig. 3a shows the room temperature EPR spectrum of the sample B; the resonance peaks are similar to sample A but with the line at 2.22 wider than the observed in sample B. Fig. 3b shows that the Mössbauer spectrum recorded at 300 K is asymmetric: the low-velocity peak being distinctly narrower and having a higher dip than the high velocity peak. The best fit for this spectrum consists of two doublets with different hyperfine parameters. The inner doublet (doublet I) with isomer shift, $IS=0.38$ mm/s and quadrupole

splitting, $QS=0.58$ mm/s, can be related to the doublet observed in the sample A at low temperature. Additional measurements performed at low temperature confirm this assignment.

Thus, it is reasonable to attribute the subspectra I to isolated Fe^{+3} ions in the polymer chain. This site is related to the EPR peak I at $g=4.23$. The outer doublet (doublet II) with $IS=0.38$ mm/s and $QS=1.02$ mm/s is typical of very small particles of FeOOH polymorphs; the observed QS is in agreement with iron oxide hydroxide reported in the literature [17].

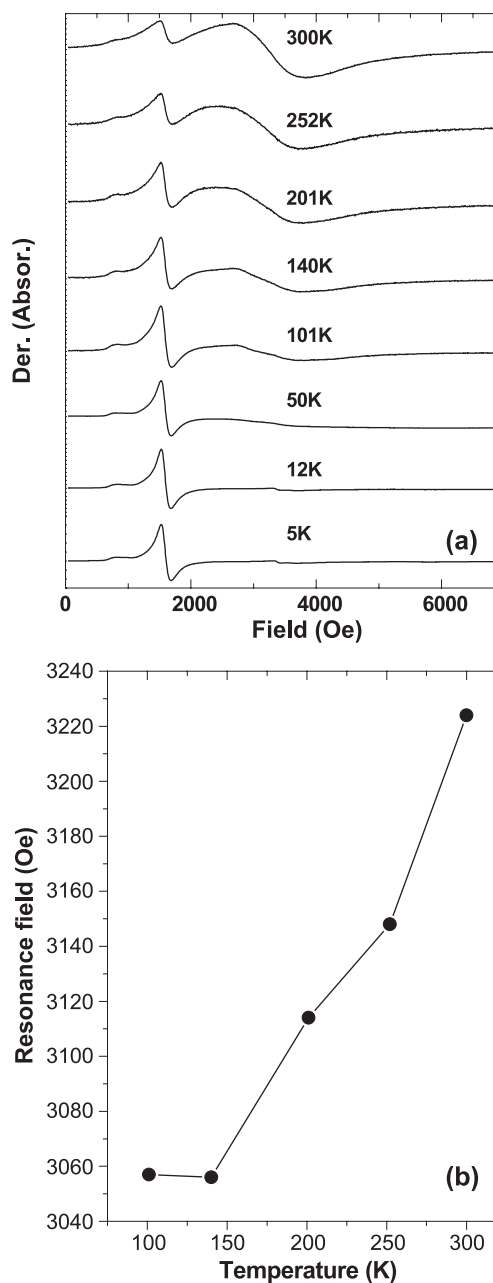


Fig. 2. (a) EPR curves of the alginate magnetic composite (0.01 M Fe) at different temperatures. (b) Temperature dependence of the resonance field obtained from the line at $g=2.2$.

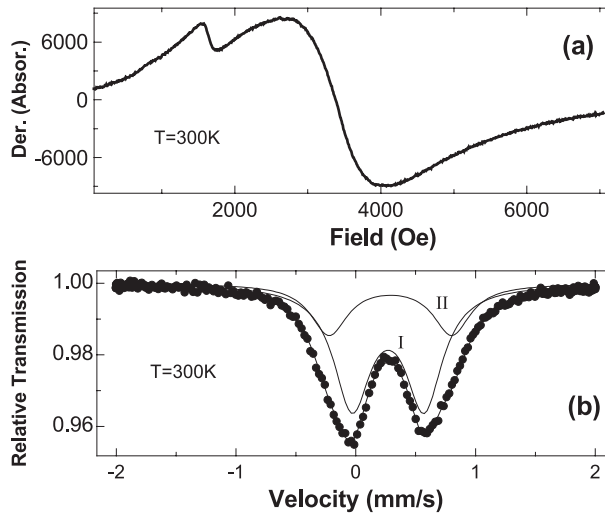


Fig. 3. (a) EPR spectrum and (b) Mössbauer spectrum measured at 300 K of the alginate magnetic composite (0.5 M Fe).

Fig. 4 shows the MS measurements for the sample B recorded at various temperatures. The main features of these spectra are the magnetically split sextet at 4.2 K, with a hyperfine magnetic field of about 47.4 Tesla (T), $IS=0.37$ mm/s and $eQV_{ZZ}/2=-0.2$ mm/s, at 4.2 K, and a paramagnetic component with hyperfine parameters similar to doublet I of the sample A. With increasing temperature from 4.2 to 70 K, there is a gradual collapse of the magnetic component to a doublet. This magnetic behavior is typical for magnetic nanoparticles which exhibit superparamagnetic relaxation and indicates that the sample contains particles with a broad distribution of blocking temperatures.

In the range of temperatures considered in this work, the iron oxide does not show antiferromagnetic behavior because the EPR signal of the superparamagnetic iron particles was observed in the whole temperature range (300–4 K).

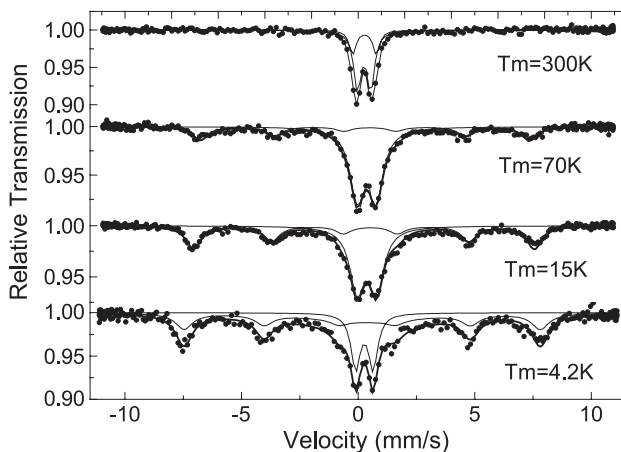


Fig. 4. Mössbauer spectroscopy measurements of alginate magnetic composites (0.5 M Fe) measured at different temperatures.

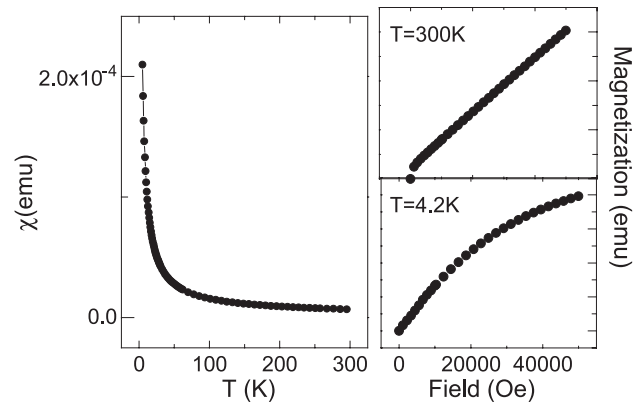


Fig. 5. Susceptibility and magnetization measurements of the alginate composite (0.5 M Fe), measured at temperatures as indicated in the figure.

Magnetization measurements were performed and are shown in Fig. 5. In the zero field cooling measurement, the curve shows a peak with its center at temperatures lower than 4.2 K; from this measurement, we can say the blocking temperature is lower than 4.2 K. The magnetization curve measured at 5 K shows an unsaturated regime up to 5 T, indicating that some particles are already blocked at this temperature. At 300 K, the curve shows only a paramagnetic behavior because all magnetic iron nanoparticles are unblocked and the isolated iron ions bound to the polymer structure are paramagnetic.

In order to identify the type of iron oxide, we performed X-ray diffraction (XRD) measurements, Fig. 6, which showed very small and broad peaks typical of a system containing small crystallites, although the line broadening could be due to internal strain. The XRD pattern is characteristic of an iron oxide hydroxide but is not in agreement with an antiferromagnetic phase such as a goethite, which would support the MS and EPR results.

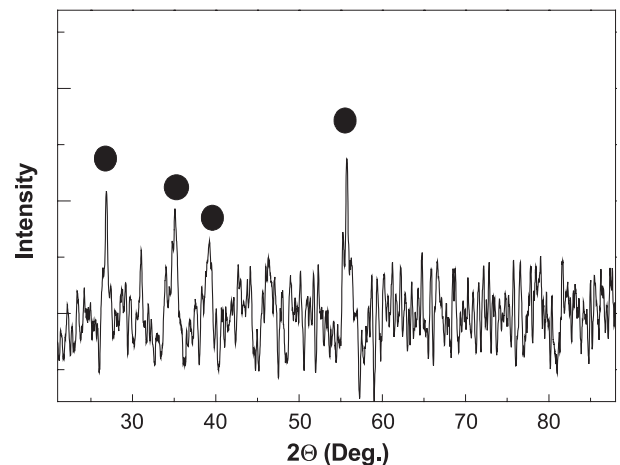


Fig. 6. X-ray diffraction pattern of the sample B: (•) principal peaks positions of the iron hydroxide.

5. Conclusions

It was possible to synthesize an alginate polymer with entrapped superparamagnetic iron hydroxide particles. Using EPR and MS, we showed that structural Fe^{3+} ions are linked to the guluronic acid units. From the low-temperature MS measurements, we have characterized the magnetic behavior of iron oxide hydroxide particles. We found blocking temperature corresponding to particles with nanometric dimensions. This composite system, alginate–iron oxide particles, has a potential use for controlled drug delivery applications.

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