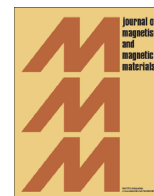




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# Direct synthesis of magnetite nanoparticles from iron(II) carboxymethylcellulose and their performance as NMR contrast agents



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## ABSTRACT

Iron(II) carboxymethylcellulose (CMC) has been successfully employed in the synthesis of hydrophilic magnetite nanoparticles stabilized with a biopolymer coating, aiming applications in NMR imaging. The new method encompasses a convenient one-step synthetic procedure, allowing a good size control and yielding particles of about 10 nm (core size). In addition to the biocompatibility, the nanoparticles have promoted a drastic reduction in the transverse relaxation time ( $T_2$ ) of the water protons. The relaxivity rates have been investigated as a function of the nanoparticles concentration, showing a better performance in relation to the common NMR contrast agents available in the market.

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## 1. Introduction

Nanoparticles (NP), such as biofunctionalized magnetite species (MagNP), have furthered important advances in biomedicine. In special, the magnetite nanoparticles have been preferred because of their good compatibility with the biological environment [1], reflecting their iron oxide constitution also found in the ferritins. Functional MagNPs basically consist of two essential parts: a magnetic core and a surface coating. The magnetic core allows their manipulation by an applied magnetic field, while the surface coating is essential for the nanoparticles stability and performance.

Recently, MagNPs have been used for diagnostic and therapeutic applications [2–4], as drug carriers, active elements in hyperthermia, and in biomedical analysis by nuclear magnetic resonance (NMR) [5,6]. As a matter of fact, MagNPs provide effective contrast agents in NMR imaging, reducing the proton relaxation times ( $T_2$ ) of the water molecules and promoting a darkening effect on the NMR image. For this reason, MagNPs are negative contrast agents. The possibility of modifying the MagNP surface with chemical and biological molecules can greatly

improve their performance in terms of stability and biocompatibility.

In our research group, functionalized MagNPs have been explored in biological catalysis and in environmental remediation, including an interesting process denoted magnetic nanohydrodrometallurgy [7]. This process exploits the magnetic properties and the chemical functionalization of the MagNPs for capturing metal ions, such as  $\text{Cu}^{2+}$ , and then performing their *in situ* reduction at the electrode surface [8–11].

During the development of the present work, Sivakumar et al. [1] have published a remarkable paper on the biomedical applications of folate-tagged carboxymethylcellulose MagNPs, of about 150 nm. From the analysis of toxicological behavior of the MagNPs in three different cell types, they demonstrated a good biocompatibility between the CMC surface and the cellular environment. In a broad sense, CMC based nanomaterials have been successfully applied not only in chemotherapy [1], but also in environmental management for removing organic compounds [12]. It has also been employed in the creation of hybrid magnetic materials [13], and many other materials [14–22].

At the present time, the preparation of functionalized MagNPs involves multi-step procedures, usually based on the co-precipitation method [1,12,13,15]. In this work we are reporting an alternative, fast and convenient one-step method for the production of MagNPs functionalized with CMC (MagNP-CMC). This

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method is based on the use of iron(II) carboxymethylcellulose complex as the starting material. Accordingly, the iron(II) complex with CMC seems to provide a suitable polymeric environment for nucleating the seeds, ensuring a good distribution and uniformity of size for the synthesized MagNPs. In addition, the formation of a stable CMC coating is naturally accomplished in the process.

Besides the nanoparticles synthesis and characterization, we have also investigated their performance as contrast agents in NMR imaging (IMR), which is an essential tool in medicine. This technique explores the spin relaxation processes associated with the water molecules, in order to generate bi and tridimensional images of the internal organisms. For this reason, we carried out a systematic study on the relaxation behavior of the CMC coated MagNPs in low field NMR, at several concentrations, and compared with the relaxivity parameters reported for the main commercial contrast agents. Such comparison revealed a convenient alternative agent, exhibiting excellent contrast performance, good biocompatibility and lower cost.

## 2. Materials and methods

Carboxymethylcellulose sodium salt was obtained from Sigma Aldrich, with an average molecular weight of  $250,000 \text{ g mol}^{-1}$  and a degree of carboxylate substitution (DS) of 0.9. Ferrous sulfate ( $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ), potassium hydroxide (KOH) and potassium nitrate ( $\text{KNO}_3$ ) were obtained from Labsynth. All reactants were analytical grade, and used without any treatment.

Nanoparticles size were analyzed by Dynamic Light Scattering (DLS), using a Nanotracs 252 model instrument, from Microtrac. Infrared Spectra were recorded on a Bruker FTIR, ALPHA model spectrophotometer. DTA/TGA (Thermogravimetric Analysis/Differential Thermal Analysis) measurements were carried out on a Shimadzu DTG 60 equipment, under an inert atmosphere. Scanning Probe Microscopy (SPM) images were obtained using a PicoSPM I equipment, with a PicoScan2100 controller, and a MAC-Mode setup from Molecular Imaging. The hysteresis curves were obtained using a vibrating sample magnetometer manufactured by EG&G Princeton Applied Research-model 4500. Analysis by Transmission Electron Microscopy were carried out at our local Analytical Center, using a JEOL, model JEM 2100 equipment, operating with a  $\text{LaB}_6$  electron emitting filament, allowing a maximum acceleration voltage of 200 kV. The scanning transmission image (STEM) was obtained with a HAADF detector (“High Angle Annular Dark Field”). Evaluation of the iron percentage in the nanoparticles was performed using an ICP OES equipment from Thermo Fisher Scientific, Cambridge, England, constituted by an iCAP 6300 Duo model. The NMR probe used in the analysis consisted of a Bruker Minispec mq20 spectrometer operating at 0.47 T. A 20 MHz frequency was used in the spin echo pulse sequence (CPMG). Magnetic resonance images were obtained using a 500 MHz machine, and a mic500S2/AS probe, attached to the Bruker advance III console.

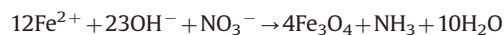
### 2.1. Synthesis of magnetic nanoparticles (MagNP-CMC)

Stock solution of CMC was prepared by solubilizing 7.5 g of the polymer in 1.0 L of distilled water. For the production of magnetic nanoparticles coated with CMC (MagNP-CMC), 200 ml of the stock solution was transferred to a flask (1 L) equipped with condenser and mechanical stirrer. The solution was heated to  $85^\circ\text{C}$  under stirring (600 rpm) and then, a solution containing 6.8 mmol of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  in 80 ml of water was added to the reaction medium, generating the yellow Fe(II)-CMC complex. In a separate flask, 30 mmol of KOH and 0.35 mmol of  $\text{KNO}_3$  were solubilized in 20 ml of water and then heated to  $85^\circ\text{C}$ . The hot solution was quickly

transferred to the reaction medium containing the Fe(II)-CMC complex, keeping the stirring rate (600 rpm) for 30 min. Finally, the suspension was cooled to room temperature, and the black magnetic nanoparticles were precipitated with acetone and confined at the bottom, with an external magnet. After removing the solution, the magnetically confined solid was redispersed in acetone, and the same procedure was repeated three times. The isolated solid was kept dried at room temperature.

## 3. Results and discussion

A very simple way of obtaining MagNPs involves the direct reaction of iron(II) sulfate with nitrate ions in strongly alkaline medium. In this process, the initially formed iron(II) hydroxides get partially oxidized with the nitrate ions according to the reaction



The role of the nitrate ions in this process is quite unusual, since the reduction seems to proceed up to the formation of  $\text{NH}_3$ , instead of  $\text{N}_2$ . As a matter of fact, the formation of  $\text{NH}_3$  in this process can be readily perceived from its characteristic smell [23].

Because of its simplicity, this method has been successfully adopted in our experimental undergraduate courses, but leading always to very large nanoparticles ( $> 400 \text{ nm}$ ), displaying strong magnetization response. For this reason, if CMC were added at the end of the process, the generated products would not be suitable for applications in nanobiomedicine. In contrast, by starting with the iron(II)-CMC complex, a controlled growth of nanoparticles can be performed, leading to smaller superparamagnetic nanoparticles. Presumably, the CMC matrix is providing a special polymeric environment for the nucleation process.

After the synthesis, the size distribution of MagNP-CMC was probed by dynamic light scattering (DLS), as shown in Fig. 1, revealing 65% hydrodynamic radius distribution, in the range of 45–75 nm, encompassing the nanoparticles core and the polymer coating, with a maximum distribution rate at 63 nm (35%).

FTIR spectrum of MagNP-CMC, in KBr pellets, is shown in Fig. 2, in comparison with the spectrum of pure CMC. The sharp peak at  $618 \text{ cm}^{-1}$  coincides with the characteristic  $\nu(\text{Fe}-\text{O})$  stretching vibrational peak of the  $\text{Fe}_3\text{O}_4$  core, but its shape reveals the presence of some  $\text{SO}_4^{2-}$  ions employed in the process. The CMC peaks are consistent with the literature [24]. The most relevant peaks are associated with the carboxylate group, corresponding to the symmetric ( $\nu_{\text{symCOO}}$ ) and asymmetric ( $\nu_{\text{asymCOO}}$ ) stretching vibrations observed at  $1604$  and  $1422 \text{ cm}^{-1}$  for free CMC and  $1590$  and  $1417 \text{ cm}^{-1}$  for MagNP-CMC, respectively. In general, the difference between the symmetric and asymmetric frequencies increases

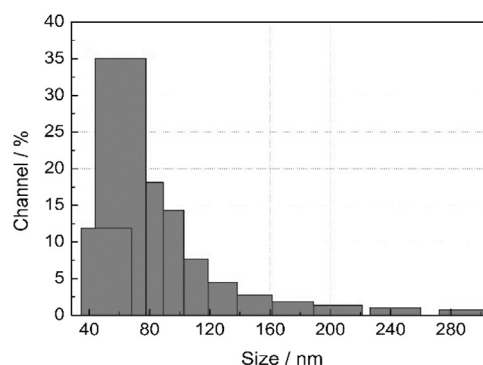


Fig. 1. Typical size distribution of MagNP-CMC probed by DLS, showing the predominant hydrodynamic radius around 63 nm, in aqueous solution.

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